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Expanding the speech and language phenotype in Koolen-de Vries syndrome: late onset and periodic stuttering a novel feature

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Speech and language impairment is core in Koolen-de Vries syndrome (KdVS), yet only one study has examined this empirically. Here we define speech, language, and functional/adaptive behaviour in KdVS; while deeply characterising the medical/neurodevelopmental phenotype in the largest cohort to date. Speech, language, literacy, and social skills were assessed using standardised measures, alongside an in-depth health and medical questionnaire. 81 individuals with KdVS were recruited (35 female, mean age 9y 10mo), 56 of whom harboured the typical 500–650 kb 17q21.31 deletion. The core medical phenotype was intellectual disability (largely moderate), eye anomalies/vision disturbances, structural brain anomalies, dental problems, sleep disturbance, musculoskeletal abnormalities, and cardiac defects. Most were verbal (62/81, 76.5%), while minimally-verbal communicators used alternative and augmentative communication (AAC) successfully in spite of speech production delays. Speech was characterised by apraxia (39/61, 63.9%) and dysarthria (28/61, 45.9%) in verbal participants. Stuttering was described in 36/47 (76.6%) verbal participants and followed a unique trajectory of late onset and fluctuating presence. Receptive and expressive language abilities were commensurate with one another, but literacy skills remained a relative weakness. Social competence, successful behavioural/emotional control, and coping skills were areas of relative strength, while communication difficulties impacted daily living skills as an area of comparative difficulty. Notably, KdVS individuals make communication gains beyond childhood and should continue to access targeted therapies throughout development, including early AAC implementation, motor speech therapy, language/literacy intervention, as well as strategies implemented to successfully navigate activities of daily living that rely on effective communication.

European Journal of Human Genetics (2023) 31:531–540; https://doi.org/10.1038/s41431-022-01230-7

INTRODUCTION

Koolen-de Vries syndrome (KdVS) is a chromatin-related disorder caused by the haploinsufficiency of the *KANSL1* gene. It is caused by a variant in *KANSL1* or a deletion of chromosome 17q21.31 that encompasses *KANSL1* [1–4]. There is uncertainty about the true prevalence of KdVS; although the prevalence of a 17q21.31 deletion is estimated at 1 in 55,000 individuals. The prevalence of *KANSL1* variants cannot be determined due to limited cases in the literature [5, 6].

Core features of KdVS are developmental delay and intellectual disability (ID, largely mild to moderate), early childhood hypotonia, characteristic facial dysmorphism, and behavioural characteristics, including a friendly and amicable disposition [2]. Other recurrent features are congenital heart defects, structural brain anomalies, kidney and urogenital concerns, vision issues, and epilepsy [2].

A striking speech and language profile is a key component of the KdVS phenotype. A study of speech and language in 29 individuals with KdVS documented markedly delayed speech, with first words not achieved until 2–7 years of age [7]. Speech acquisition is slow and effortful, with a core early diagnosis of childhood apraxia of speech (CAS), alongside oromotor hypotonia. Once CAS resolves, dysarthric features become more prominent with poor intelligibility (ability to be understood) extending into the teenage and adult years [7]. Stuttering was noted in 3/18 participants by Morgan et al. [7] but was not systematically explored.

Morgan et al. [7] attempted to systematically investigate language, showing that receptive and expressive language abilities are typically equivalent. Whilst linguistic development is slow, such skills do continue to develop, and most children can form sentences by the middle school years. Literacy impairment was also noted in 6 individuals, but most ($n = 22$) could not be assessed with standardised tools (i.e. too young, no access to assessment tools). Further, most of the cohort were under 5 years of age and unable to be assessed [7], and thus, early reading and writing abilities remain relatively unexplored. Social skills have been noted as a relative strength in KdVS, yet have only been empirically examined in $n = 3$ individuals using standardised measures [8].

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Received: 4 July 2022 Revised: 18 October 2022 Accepted: 31 October 2022
Published online: 19 December 2022

Given the critical involvement of speech and language within the KdVS phenotype, here we conduct a comprehensive study of speech, language, literacy, and social skills using standardised tools, in a large cohort of individuals with KdVS. Considering the complex medical and neurodevelopmental features that are often present, we explore these features, and how they interact with and impact the speech and language profile of the condition. In addition, we utilise adaptive functioning and behaviour measures to provide an understanding of how the communicative abilities in KdVS affect activities of daily living.

MATERIALS AND METHODS

Participants

Participants were recruited via study flyers posted on Koolen-de Vries Syndrome Foundation social media pages (i.e. website, Facebook, newsletter), study advertising at the KdVS Patient Advocacy Summit, and via the Australian Association of Clinical Geneticists. Inclusion criteria were (a) confirmed genetic diagnosis of KdVS (either a causative variant in *KANSL1* or 17q21.31 deletion inclusive of *KANSL1*) and (b) aged 6 months or older. Exclusion criteria were the presence of any other confirmed genetic variant or syndrome likely to impact the clinical phenotype.

Measures

Caregivers/participants completed assessments, either via online (REDCap-administered) survey and/or videoconference interview, and/or in-person (when possible) as detailed below using our previously validated approach. Caregivers began by completing an in-depth health and medical survey [9, 10] and provided relevant clinical reports for medical or developmental diagnoses previously received to confirm survey responses (i.e., ID, autism). Participants completed verbal or minimally-verbal assessment protocols according to their abilities.

Language, literacy, and adaptive behaviour

The Vineland Adaptive Behaviour Scales Parent/Caregiver Rating Form — Third Edition [Vineland-3; [11]] provided standard scores for Communication, Daily Living Skills, Socialisation, and Motor abilities, as well as an overall Adaptive Behaviour Composite (ABC, an average of Communication, Daily Living Skills, and Socialisation). Scaled scores were calculated for the subdomains: 'expressive', 'receptive', and 'written' (denoting Communication); 'personal', 'domestic', and 'community' (denoting Daily Living Skills); 'interpersonal relationships', 'play and leisure', and 'coping' (denoting Socialisation); and 'gross motor' and 'fine motor' (denoting Motor). Normative data for Motor subtests are only available up to age 9y 11m (as all motor skills are expected to be achieved by this age), and so chronologically-older individuals were compared against the oldest age data available to estimate the level of motor delay. The Children's Communication Checklist-2 (CCC-2) was used to assess specific communication domains in verbal participants aged 4–16 years [12]. Individuals who were chronologically older than the assessment age range ($n = 12$), but with linguistic abilities seen in younger persons were compared against the oldest age data available to estimate the level of language delay. The Communication and Symbolic Behaviour Scales—Developmental Profile was used to assess early language and social development in those younger than 4 years of age [13].

Speech

Speech was assessed for verbal communicators, including a differential diagnosis across speech conditions (articulation disorder, phonological disorder, dysarthria, CAS, and stuttering). All speech assessments were video- and/or audio-recorded. For non-English-speaking families, clinical reports were collected 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, [14]). This is a single-word test with stimuli designed to assess all phonemes of English. The presence of dysarthria was determined from rating a five-minute conversational speech sample using the Mayo Clinic dysarthria classification system [15–17]. CAS was diagnosed by examining connected speech samples, DEAP scores, and production of multisyllabic words (when indicated, using the Single-Word Test of Polysyllables, [18]) [17]. Individuals were considered to meet the criteria for a CAS diagnosis if they met the three main diagnostic criteria: (1) inconsistent errors, (2) lengthened and disrupted coarticulation between sounds and syllables, and (3) inappropriate prosody [19]. The presence of stuttering was assessed via an in-depth fluency questionnaire, regarding onset, progression and triggers (See Supplemental material). Once identified and rated by a parent, the presence and severity of stuttering was then rated utilising connected speech samples. Stuttering was rated using a ten-point stuttering severity rating scale [20].

Statistical analyses

Non-parametric analysis (Kruskal–Wallis and Wilcoxon sign-rank tests) were used to compare the mean scores across Vineland-3 domains to determine the relative impact on communication, as well as to compare across individual subdomains.

RESULTS

Medical and neurodevelopmental characteristics

Eighty-one individuals (35 female, 46 male) were recruited. Participants were aged 1 year 6 months to 40 years 2 months (mean 9y 10mo, SD 7y 0mo), with a spread across age groupings as follows: $n = 24$ pre-schoolers aged ≤4 years; $n = 35$ children aged 5–12 years; $n = 13$ adolescents aged 13–19 years; $n = 9$ adults aged ≥19 years. Most participants and their families were English-speaking ($n = 73$, 90.1%), with smaller proportions of Dutch ($n = 4$, 4.9%), German ($n = 2$, 2.5%), French ($n = 1$, 1.2%) and Portuguese speakers ($n = 1$, 1.2%), Table 1. Most presented with typical 500- to 650-kb deletions of 17q21.31 encompassing five genes (*CRHR1, IMP5, MAPT, STH, KANSL1*) ($n = 56$, 69.1%), while $n = 4$ had larger deletions of 17q21.31 with additional genes deleted (see Table 2). Nineteen individuals had genetic variants that affected only *KANSL1* ($n = 11$ truncating variants; $n = 7$ splice site variants; $n = 1$ intragenic deletion, exons 5–7). For summary and analysis, intragenic deletions of *KANSL1* were classified within the category of '*KANSL1* variants'. Two individuals had small deletions (72kB and 51kB), not large enough to equate to 'typical deletions' but affecting more than *KANSL1* alone. Sequence variants were deposited to Decipher (https://decipher.sanger.ac.uk/).

Dysmorphic facial features were noted in 73/81 participants (90.1%), including a pear-shaped nose with a bulbous tip (48/81, 59.3%), ear anomalies (32/81, 39.5%), hypertelorism (25/81, 30.9%), lip/tongue tie (11/81, 13.6%), macroglossia (11/81, 13.6%), narrow mouth/thin lips (7/81, 8.6%), high-arched palate (7/81, 8.6%) and underbite (6/81, 7.4%). Two individuals had submucous cleft palates (2.5%). Medical and neurodevelopmental features are summarised in Table 1 and Fig. 1. 87.5% (49/56) had a diagnosis of ID, most moderately impaired (29/56, 51.8%). 11/56 (19.6%) had severe ID. 30.9% (25/81) were too young or had never been assessed for ID. A diagnosis of developmental delay (DD) by a paediatrician was taken as a comparable measure of ID and was present in 78/81 (96.3%) of individuals. There was a high incidence of eye anomalies and vision disturbances (48/81, 59.3%), most commonly strabismus and hyperopia; structural brain anomalies in those with brain imaging results (33/62, 53.2%), most commonly changes to or agenesis of the corpus callosum; dental problems (36/72, 50.0%) including too few teeth and complex orthodontics; sleep disturbances (33/81, 40.7%) often frequent and early waking; musculoskeletal problems (32/81, 39.5%) including scoliosis and joint laxity; cardiac defects (32/81, 39.5%) commonly atrial septal defects; and epilepsy and seizures (29/81, 35.8%). To a lesser extent but still highly prevalent were skin conditions (26/81, 32.1%) i.e., eczema; renal/urogenital complications (25/81, 30.9%) including hydronephrosis and vesicoureteral reflux; gastrointestinal concerns (24/81, 29.6%), often constipation; and mental health problems (23/81, 28.4%), often anxiety. 21/46 (45.7%) males had cryptorchidism. 29.6% (24/81) had hearing loss (HL), most often moderate (i.e., 40–69 dB HL) and conductive in nature. A complete and detailed list of individual patient comorbidities can be found in Supplemental Table 1.

Table 1. Medical and neurodevelopmental characteristics of individuals with KdVS in this cohort.

Characteristic	*n/total* (%)
Age, years (mean, SD)	9y10m, 7y0m
Sex	
Male	45/81 (55.6%)
Female	36/81 (44.4%)
Primary language	
English	73/81 (90.1%)
Dutch	4/81 (4.9%)
German	2/81 (2.5%)
French	1/81 (1.2%)
Portuguese	1/81 (1.2%)
Developmental delay	78/81 (96.3%)
Intellectual Disability	49/56 (87.5%)
Mild	9/56 (16.1%)
Moderate	29/56 (51.8%)
Severe	11/56 (19.6%)
Too young/not assessed	25/81 (30.9%)
Eye anomalies/vision disturbance	48/81 (59.3%)
Structural brain anomalies	33/62 (53.2%)
Dental problems	36/72 (50.0%)
Sleep disturbance	33/81 (40.7%)
Musculoskeletal abnormalities	32/81 (39.5%)
Cardiac malformations	32/81 (39.5%)
Epilepsy/seizures	29/81 (35.8%)
Allergies	29/81 (35.8%)
Skin conditions	26/81 (32.1%)
Renal/urogenital complications	25/81 (30.9%)
Gastrointestinal concerns	24/81 (29.6%)
Hearing impairment	24/81 (29.6%)
SNHL	6/81 (7.4%)
Conductive	13/81 (16.0%)
Mixed	5/81 (6.2%)
Mild	11/81 (13.6%)
Moderate	12/81 (14.8%)
Severe	1/81 (1.2%)
Profound	0/81 (0.0%)
Mental health problems (i.e., anxiety, depression)	23/81 (28.4%)
Asthma	16/81 (19.8%)
Behavioural concerns	15/81 (18.5%)
Endocrine disorders	14/81 (17.3%)
Blood/immune disorders	9/81 (11.1%)
Sensory processing disorder	9/81 (11.1%)
Developmental coordination disorder	8/81 (9.9%)
ADHD	8/81 (9.9%)
Movement disorders	6/81 (7.4%)
Autism	5/81 (6.2%)
Tremor	4/81 (4.9%)
Cerebral palsy	2/81 (2.5%)
Chronic pain	2/81 (2.5%)
Cancer	1/81 (1.2%)
Arthritis	1/81 (1.2%)

ADHD attention deficit hyperactivity disorder, *SNHL* sensorineural hearing loss.

Language, literacy, and adaptive behaviour

Adaptive functioning was impaired across all participants (mean 71.6, SD 10.2) on the Vineland-3, compared to a population mean 100, SD 15, and no participant performed within the average range across all subdomains. Four participants (ID23, ID29, ID26 and ID51) scored within the average range on the ABC; however, even these individuals scored below average on at least one subdomain. Daily Living Skills were most severely affected (mean 67.4, SD 12.4), followed by Communication (mean 70.2, SD 15.2) (Table 3). Socialisation was a relative strength (mean 79.1, SD 14.3) across the group. Motor skills were also impaired (mean 72.8, SD 11.0). A Kruskal–Wallis test found a significant difference across Communication, Daily Living Skills and Socialisation Scores ($p < 0.005$). A Wilcoxon signed-rank test revealed that Socialisation scores were better than Daily Living Dkills ($p < 0.005$) and Communication ($p < 0.005$). Communication and Daily Living Skills did not differ from one another ($p = 0.16$).

Individuals with KdVS were impacted across all subdomains of the Vineland-3 (Table 3). The most affected domains were in the 'Written' subdomain, i.e., reading and writing skills (mean 8.3, SD 3.5), and the 'Community' subdomain, i.e., functioning in the world outside the home, including safety and using money (mean 8.6, SD 2.5). Individuals showed relative strength across all Socialisation subdomains, including 'Interpersonal Relationships' i.e., responding and relating to others (mean 11.5, SD 2.9), 'Play and Leisure' i.e., engaging in play and activities with others (mean 11.1, SD 3.3) and 'Coping' i.e., behaviour and emotional control (mean 11.3, SD 2.7).

In regard to subdomain differences, Wilcoxon signed-rank tests revealed that in the Communication domain, 'Written' language scores were poorer than 'Receptive' ($p < 0.005$) and 'Expressive' ($p < 0.005$) language scores; in the daily living skills domain 'Domestic' skills were better than 'Community' skills ($p < 0.005$) and 'Personal' skills ($p = 0.008$); and in the Socialisation domain 'Interpersonal Relationships' scores were better than 'Play and Leisure' scores ($p = 0.024$). 'Gross Motor' scores were higher than 'Fine Motor' scores ($p < 0.003$)

Scores were compared for those with larger deletions versus typical 500–650 kb deletions versus those with *KANSL1* variants (Table 3). No group differences were observed across scores and no statistical differences were found across genetic groupings across any domain or subdomain assessed (Fig. 2). Considering deletion breakpoints are not always precisely defined, we also performed group comparisons comparing all deletions (larger *and* typical) with *KANSL1* variants to ensure no subtle differences were missed. No group differences were observed with this dichotomous split.

Across the 42 verbal patients who completed the CCC-2, the average General Communication Composite (GCC) scores were low (mean 31.2, SD 16.2) (Table 4). Average scaled scores across all subdomains were markedly low, in particular for 'Speech' (mean = 2.0), 'Syntax' (mean = 4.0) and 'Use of context' (mean = 3.2). Individuals had relative strengths in 'Interests' (mean = 5.7), 'Social relations' (mean = 5.5) and 'Non-verbal communication (mean = 5.1). Scaled scores 6 and above (i.e., greater than 15th percentile) indicate skills within normal limits. The average was not above 6 for any subdomain. No group differences were observed across scores when comparing deletions with *KANSL1* variants.

Speech disorder profile

CAS and dysarthria. 19/81 individuals (23.5%) were classified as non-verbal or minimally-verbal at the time of assessment, however, $n = 2$ of these were younger than 2 years of age. The remainder of the non-verbal or minimally-verbal individuals were aged 2 years 1 month to 6 years 9 months. All individuals classified as minimally-verbal utilised alternative and augmentative communication (AAC) options or multimodal strategies to communicate, including

Table 2. Genetic data of individuals with KdVS in this cohort.

ID/s	Genetic anomaly	Variant details incl. minimum deletion, est. breakpoints	Genes affected
20	17q21.31 deletion	1114kB; 43,685,925-44,800,046	*CRHR1, IMP5, MAPT, STH, KANSL1, LRRC37A, LRRC37A2, NAPA*
56	17q21.31 deletion	1019kB;43,706,895-44,725,843	*CRHR1, IMP5, MAPT, STH, KANSL1, LRRC37A, LRRC37A2, NAPA*
49	17q21.31 deletion	699kB; 43,513,643-44,212,416	*PLEKHM1, CRHR1, IMP5, MAPT, STH, KANSL1*
1	17q21.31 deletion	638kB; 43,574,907-44,212,416	*PLEKHM1, CRHR1, IMP5, MAPT, STH, KANSL1*
2, 3, 4, 5, 8, 10, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 37, 40, 41, 43, 45, 48, 50, 51, 53, 55, 57, 58, 59,65, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81	17q21.31 deletion	Typical KdVS deletion, 500-650-kB; 43,700,000-44,250,000 range	*CRHR1, IMP5, MAPT, STH, KANSL1*
64	17q21.31 deletion	72kB; 44,047,215-44,119,098	*KANSL1, MAPT, STH*
26	17q21.31 deletion	51kB; 44,094,241-44,145,588	*MAPT, KANSL1*
61	Truncating variant	c.2066 G > A, p.Trp689*	*KANSL1*
44	Truncating frameshift variant	c.2659_2660insGA, p.Thr887Argfs*13	*KANSL1*
66	Truncating frameshift variant	c.540delA, p.Lys180Asnfs*22	*KANSL1*
46	Splice site variant	c.1652 + 1 G > A	*KANSL1*
52	Splice site variant	c.2830_2837 + 13del21	*KANSL1*
67	Truncating variant	c.1532delT, p.Leu511*	*KANSL1*
9	Splice site variant	c.2837 + 1 G > A	*KANSL1*
42	Truncating frameshift variant	c.930delC, p.Lys311Serfs*19	*KANSL1*
47	Truncating variant	c.1816C > T, p.Arg606*	*KANSL1*
11	Splice site variant	c.1289 + 1 G > A	*KANSL1*
54	Truncating variant	c.1042 C > T, p.Arg348*	*KANSL1*
39	Deletion exons 5-7	18kB; 44,127,593-44,145,131	*KANSL1*
60	Truncating frameshift variant	c.808_809delCT, p.Leu270Valfs*11	*KANSL1*
38	Splice site variant	c.2837 + 2 T > A	*KANSL1*
62	Splice site variant	c.2837 + 4 A > G	*KANSL1*
7	Truncating frameshift variant	c.647delA, p.Asp216Valfs*2	*KANSL1*
63	Truncating variant	c.2470 C > T, p.Arg824*	*KANSL1*
36	Truncating frameshift variant	c.611dupG, p.Met205Tyrfs*9	*KANSL1*
6	Splice site variant	c.1652 + 5 G > C	*KANSL1*

RefSeq: NM_001193466, Genome assembly: GRCh37/hg19.

non-verbal gestures and sign language, low-tech options such as picture communication systems, or high-tech options such as iPads with dedicated communication applications and speech-generating devices. Verbal speech was assessed for the remainder of the participants (62/81, 76.5%). Differential diagnoses revealed CAS and dysarthria profiles were most prominent. 39/62 (62.9%) had CAS, many alongside mild articulation errors (e.g., interdental lisp) (20/39; 51.3%) and phonological impairment (10/39; 25.6%). 27/62 (43.5%) had clinical features of dysarthria. 68/80 (85.0%) had a history of delayed communication milestones, and 63/80 (78.8%) reported the use of AAC options prior to their child's verbal speech development, and as a facilitator to this development. Most utilised multiple AAC forms and systems to support communication, with 39/80 (48.8%) using sign language, 32/80 (40.0%) using low-technology visual communication systems like communication boards, and 24/80 (30.0%) using high-technology visual communication systems (e.g., Proloquo2Go on an iPad).

Stuttering. The speech fluency questionnaire was completed by 47 families. Individuals who did not complete this questionnaire were either non-English-speaking, non-verbal at the time of assessment, or did not finish all questionnaires in their entirety.

Stuttering was observed in 36/47 (76.6%). Individuals had an average stuttering rating of 4.36 across the ten-point severity rating scale (Fig. 3a). Stuttering behaviours were varied, with the most common being sound repetitions ($n = 17$, 47.2%), whole word repetitions ($n = 17$, 47.2%), syllable repetitions ($n = 16$, 44.4%), and phrase repetitions ($n = 16$, 44.4%) (Fig. 3b).

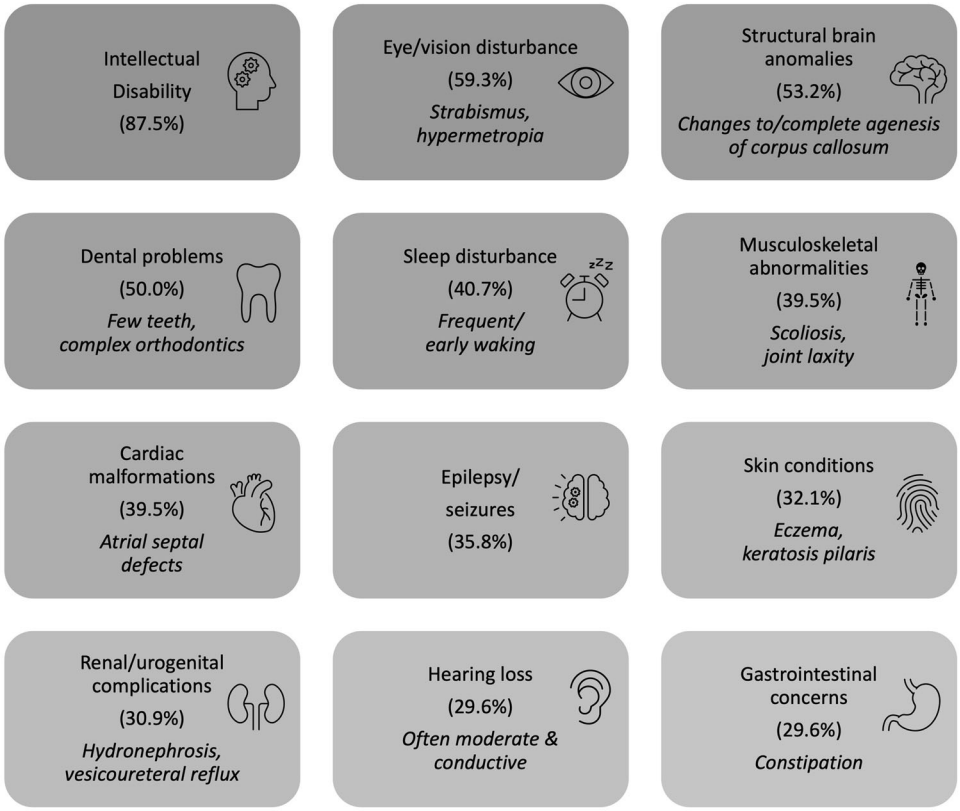

Fig. 1 Core medical and neurodevelopmental comorbidities of individuals with KdVS in this cohort.

Table 3. Adaptive behaviour scores of individuals with KdVS in this cohort based on Vineland-3.

	All		Larger deletions		Typical deletions		*KANSL1* variants	
Adaptive behaviour domain/subdomain	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Communication	**70.2**	**15.2**	**73.5**	**10.1**	**69.6**	**16.2**	**70.3**	**9.9**
Receptive	*10.4*	*3.5*	*11.0*	*1.8*	*10.4*	*3.6*	*10.4*	*3.1*
Expressive	*10.4*	*3.7*	*9.3*	*1.7*	*10.4*	*4.1*	*10.5*	*2.9*
Written	*8.3*	*3.5*	*9.0*	*4.4*	*8.2*	*3.6*	*8.3*	*2.6*
Daily Living Skills	**67.4**	**12.4**	**73.5**	**4.5**	**65.7**	**12.5**	**67.1**	**8.2**
Personal	*9.0*	*3.1*	*9.3*	*1.5*	*8.7*	*3.2*	*9*	*2.7*
Domestic	*9.8*	*2.3*	*10*	*1.0*	*9.7*	*2.4*	*9.8*	*1.7*
Community	*8.6*	*2.5*	*10*	*1.0*	*8.4*	*2.4*	*8.6*	*1.7*
Socialisation	**79.1**	**14.3**	**81.3**	**5.0**	**79**	**14.8**	**79.2**	**10.2**
Interpersonal relationships	*11.5*	*2.9*	*12.0*	*1.6*	*11.5*	*3*	*11.5*	*2.4*
Play and leisure	*11.1*	*3.3*	*11.0*	*0.8*	*11.3*	*3.3*	*11.1*	*3.0*
Coping	*11.3*	*2.7*	*11.0*	*1.0*	*11.3*	*2.7*	*11.4*	*2.2*
Adaptive Behaviour Composite	**71.6**	**10.2**	**74.5**	**3.4**	**71.0**	**10.7**	**71.6**	**6.3**
Motor	**72.8**	**11.0**	**72.5**	**3.7**	**71.7**	**9.6**	**71.7**	**7.7**
Gross motor	*10.7*	*2.5*	*9.8*	*1.0*	*10.5*	*2.3*	*10.6*	*2.3*
Fine motor	*9.1*	*2.7*	*9.3*	*1.5*	*8.9*	*2.8*	*8.9*	*2.1*

Domain population mean 100, SD 15; subdomain population mean 10, SD 3.

16/36 did not display accompanying physical behaviours alongside their stutter (44.4%), although for those who did, the most common physical behaviours were facial grimaces (including groping) ($n = 18$, 50.0%), head movements ($n = 8$, 22.2%), and trunk or limb movements ($n = 7$, 19.4%) (Fig. 3d).

Stuttering onset occurred most often during the ages of 5–6 years ($n = 13$, 36.1%) and <4 years ($n = 11$, 30.6%), however, stuttering onset was also reported into the adolescent years for others (ID63, ID69, ID71, ID77) (Fig. 3c). For most individuals ($n = 22$, 61.1%) stuttering had not resolved at the time of assessment and remained a current and significant challenge. For others ($n = 10$, 27.8%), parents reported their child's stuttering 'comes and goes' significantly over time, often characterised by blocks of time (i.e., months) with consistent stuttering followed by blocks of time

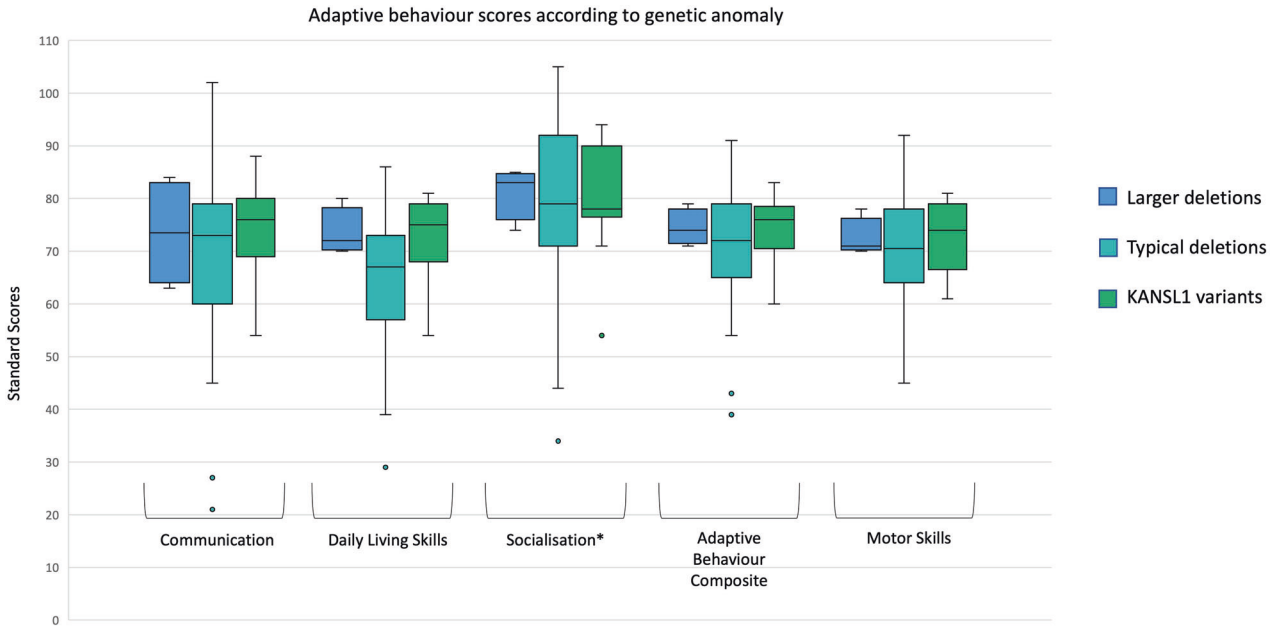

Fig. 2 Box and whisker plot of Vineland-3 adaptive behaviour domain standard scores according to genetic anomaly (i.e., comparing typical 17q21.31 deletions, larger 17q21.31 deletions, and *KANSL1* variants) for individuals with KdVS in this cohort. Lower and upper box boundaries are 25th (Q1) and 75th (Q3) percentiles, respectively. Line inside box indicates median (Q2). Lower and upper whiskers indicate 10th and 90th percentiles, respectively. Filled circles indicate data falling outside either the 10th or 90th percentiles. *Socialisation scores are significantly higher than other domains ($p < 0.05$).

Table 4. Children's Communication Checklist (CCC-2) scores for individuals with KdVS in this cohort.

	All		Larger deletions		Typical deletions		*KANSL1* variants	
Communication subdomain	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
a. Speech	2.0	2.6	0.0	0.0	2.2	2.5	2.2	3.1
b. Syntax	4.0	3.8	1.7	2.1	4.3	3.7	4.7	4.2
c. Semantics	3.7	2.8	4.3	4.0	3.9	2.8	3.6	2.8
d. Coherence	4.0	2.4	3.7	2.1	4.1	2.4	4.2	2.3
e. Inappropriate initiation	4.3	2.8	5.3	3.1	4.1	3.1	4.3	0.8
f. Stereotyped language	5.0	2.6	4.0	2.6	4.9	2.7	5.5	2.2
g. Use of context	3.2	2.9	3.7	4.0	3.1	2.9	3.1	3.0
h. Non-verbal communication	5.1	3.0	4.3	5.1	4.9	2.7	6.1	3.1
i. Social relations	5.5	2.5	3.3	4.2	5.8	2.6	5.4	1.3
j. Interests	5.7	2.3	4.7	2.1	5.9	2.4	5.5	1.9
GCC	**31.2**	**16.2**	**27.0**	**19.2**	**31.4**	**16.3**	**33.7**	**16.0**

GCC general communication composite, GCC population mean 100, SD 15; subdomain population mean 10, SD 3.

without any stuttering at all, with ongoing cycles of this pattern. Individuals who experienced this fluctuating presence of stuttering were aged between 4 years 6 months and 24 years 3 months (mean 12y 7mo; SD 6 y 11mo). At the point of assessment, only $n = 4$ (11.1%) reported that their stuttering had resolved; this occurred at the ages of 5 years, 7 years, 12 years, and 14 years respectively (Fig. 3e).

9/36 (25.0%) reported that their stuttering is brought on by specific situations (e.g., under pressure, nervous or tired), however, the majority (27/36, 75.0%) did not report any such triggers. Most parents reported their children were aware of their stutter (28/36, 77.8%), and in turn, the majority reported some degree of anxiety due to their stuttering (25/36, 69.4%) (Fig. 3f). Of these, parents report that 'specific situations' caused the most anxiety (13/27, 48.2%) (Fig. 3g).

Although $n = 36$ reported a history of stuttering, only $n = 24$ (66.7%) had sought speech pathology services for this, and only $n = 16$ (44.4%) had received a diagnosis of 'stuttering' or 'stammering' from a trained speech-language professional. 12/36 (33.3%) had received some form of therapy or intervention, yet only $n = 4$ (11.1%) had undergone a formal, evidence-based stuttering intervention. One individual completed the Lidcombe Programme in a one-to-one setting [20] and had also trialled a smooth speech intervention. Three others had completed a smooth speech intervention alone. All others did not follow any set therapy programme but had speech-language pathologists using their own 'techniques'. Almost always, the specific therapeutic techniques for addressing stuttering were not made explicit or shared with parents.

Analysis of factors potentially associated with stuttering development. Several phenotypic and genotypic factors were analysed to identify any associations with the presence of stuttering. Statistically and qualitatively, we saw no association between

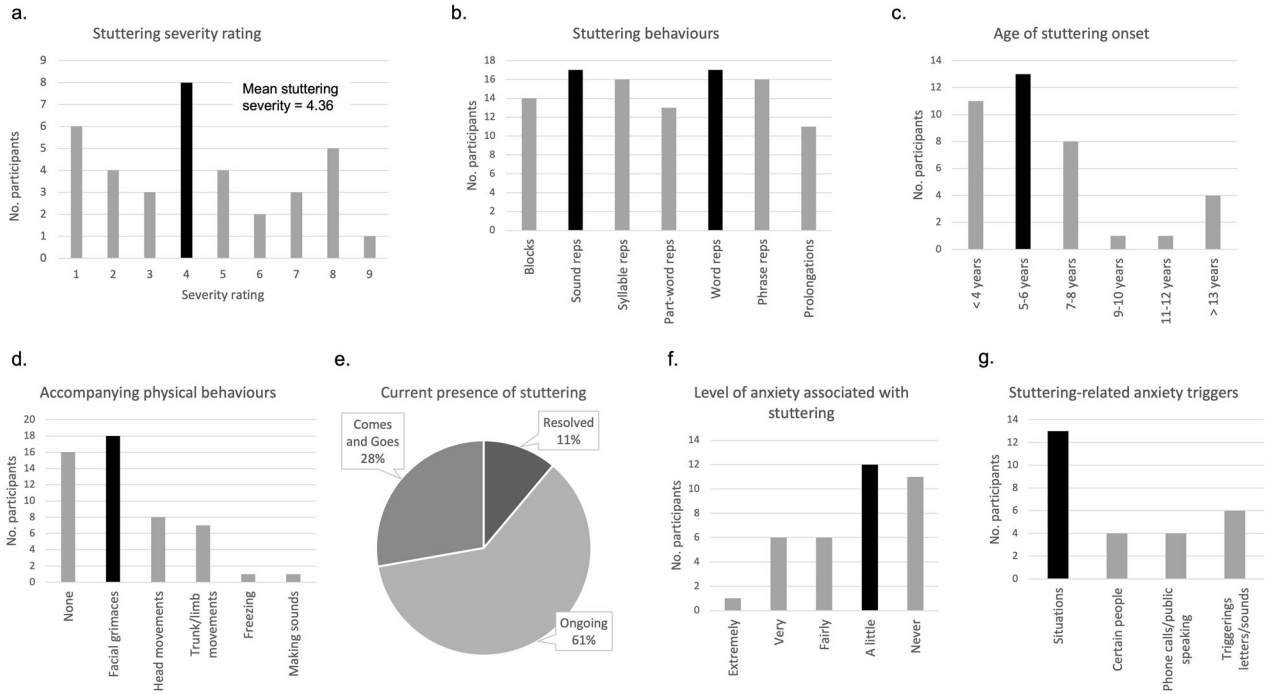

Fig. 3 Stuttering related characteristics in individuals with KdVS in this cohort. a Number of participants with each level of stuttering severity. **b** Number of participants presenting with various stuttering behaviours. Reps, repetitions. **c** Onset of stuttering according to age bandings. **d** Number of participants presenting with accompanying physical behaviours. **e** Current presence of stuttering. **f** Number of participants with anxiety associated with stuttering and the level of anxiety. **g** Number of participants reporting individual stuttering-related anxiety triggers.

stuttering and the following factors: history of seizures or epilepsy, medication is taken for a neurological condition (i.e., ADHD, epilepsy), or in those with 17q21.31 deletions (as opposed to smaller *KANSL1* variants).

Co-occurrence of diagnoses

The co-occurrence of ID with core speech and language diagnoses, and between speech and language diagnoses, were calculated across the group. The percentage of each possible combination of ID, expressive language impairment, receptive language impairment, motor speech disorder, and functional speech disorder were plotted onto a heatmap to show those with higher incidences of co-occurring features (Fig. 4). ID was most commonly seen alongside receptive language impairment (65%), CAS (60%), and stuttering (68%).

DISCUSSION

Here we provide the most comprehensive study of speech, language, and adaptive functioning in individuals with KdVS. Novel features of the study include a detailed analysis of stuttering in the context of the broader medical and neurodevelopmental profile, a characterisation of literacy development, and a direct comparison of social skills relative to other domains of functional communication and daily living skills.

A consistent observation [i.e., 7, 8] that has not been comprehensively quantified within a cohort, are the strong social skills of those with KdVS. Only one study has examined this systematically in $n = 3$ [8]. Our data confirmed that social skills are a relative strength for individuals with KdVS. Although standard scores for social skills do sit below the population average, those with KdVS show relative strengths in their development of play skills and ability to form interpersonal relationships with others, in comparison to their overall communication skills and daily living skills. In addition, their higher scores in the 'Coping' subdomain, confirm previous reports of resilience and high frustration tolerance [8]. Such relative strength in coping is perhaps a positive predictive factor for why individuals with KdVS persist with therapies (e.g., speech and physical) so successfully, and key in their continued functional gains over many years.

Although communication impairment is key to the KdVS profile, daily living skills were most impaired across the group, with almost all individuals presenting with relative weakness here. Considering the heavy reliance on communication ability (such as reading and talking) in activities of daily living, it is unsurprising that individuals with KdVS have particular struggles around personal care tasks (e.g., dispensing medication correctly), domestic jobs (e.g., reading a recipe) or community activities (e.g., reading street signs or using words to ask for directions). These findings emphasise that, although traditional motor speech therapies and receptive/expressive language therapy (e.g., regarding vocabulary, syntax) are fundamental in KdVS, it is of equal importance that speech-language pathologists (and other professionals, i.e., occupational therapists, educators) pay close attention to how communication difficulties are affecting the wider activities of daily living at school and in the community, and provide strategies to successfully navigate the world, particularly into adolescence.

Previous research suggested receptive language skills were more intact in comparison to expressive language [5], yet these were commensurate with one another across our group. Reading and writing were, however, more severely impacted in comparison to receptive language. Considering strikingly delayed early speech milestones in KdVS, and the known impact of such delays on later literacy, this is unsurprising but warrants emphasis, as literacy skills should remain a therapy focus. It is important to note that the literacy subdomain used within our measures includes reading and writing as one score, however it was noted, descriptively, that poor fine motor skills were a significant factor in lowering the literacy scores overall. This is important, as individuals should be provided with other means of developing written communication skills that

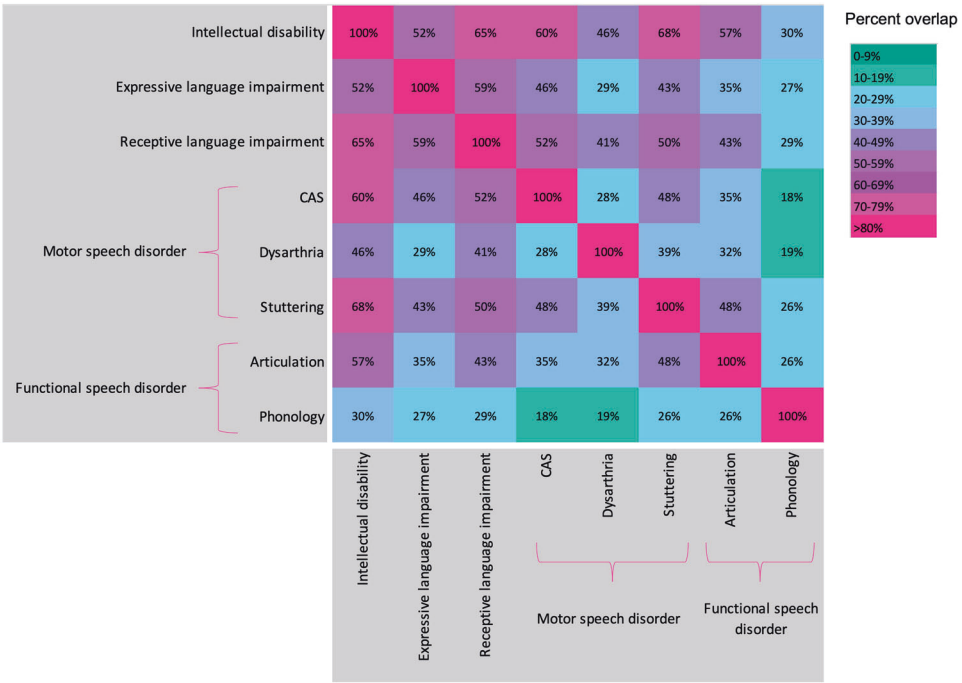

Fig. 4 Prevalence of comorbidities. Heatmap showing the co-occurrence of intellectual disability, expressive language impairment, receptive language impairment, motor speech diagnoses, and functional speech diagnoses. At each intersection, the percentage indicates the proportion of individuals who had both diagnoses (of those with results for both). Colour closer to magenta indicates a higher percentage; colour closer to teal indicates a lower percentage. Based on $n = 54$ with ID results; $n = 68$ with language results; $n = 60$ with speech results ($n = 47$ with stuttering results).

do not rely so heavily on precise fine motor control (e.g., using a keyboard rather than pen and paper).

Previous work described the speech and language profile of KdVS as distinct and largely homogeneous [7], which is emphasised here. Of specific importance is the finding that communication and functional behaviour outcomes do not appear at all influenced by the specific genetic anomaly (i.e., whether an individual has a 17q21.31 deletion or *KANSL1* variant). Our differential diagnosis of speech disorders confirms previous reports of an early apraxic profile; many are diagnosed with CAS alongside delayed speech milestones and early hypotonia. In addition, those in later childhood and adolescence often displayed a dysarthric profile, significantly impacting the clarity and intelligibility of speech for familiar and unfamiliar listeners. Such data emphasises, once again, the continued need for motor speech therapies in these individuals, even when the initial development of phonemic repertoire is slow, and as CAS begins to resolve.

Previous reports indicate around 17% of individuals with KdVS present with stuttering [5], however, the prevalence appears to be considerably higher than originally reported, such that it is one of the key and distinctive speech features of KdVS; not only in comparison to the typical population but also relative to other neurodevelopmental disorders. Half of the sample from Morgan et al. [7] were under 5 years of age, so it is not surprising that the true prevalence has not been previously captured, as here we saw many individuals develop persistent dysfluency beyond 5 years of age. Past research indicates that stuttering prevalence in individuals with ID and in typically developing individuals is 5% and 1%, respectively [21, 22], and so a prevalence of 76.6% in our sample is striking. Across the general population, previous research consistently reports the onset of stuttering between 2–4 years of age, with very few reporting onsets of stuttering beyond 9 years [22–25]. Yet stuttering in KdVS appears to emerge later; most often between 5–8 years, and sometimes even in adolescence. Stuttering onset is thought to coincide with preschool linguistic development, i.e., when children begin combining words and producing longer sentences. Considering the delayed communication milestones in KdVS, it is unsurprising that stuttering onset would also be delayed; however, this does not explain such high prevalence. Stuttering in KdVS is distinct, not only in onset but in presentation. Typically, stuttering severity is negatively correlated with age, and is characterised by blocking as the most common behaviour [23]. In KdVS, we found stuttering severity to be higher on average in adults and most often characterised by sound and word repetitions. Interestingly, those with KdVS described lower levels of anxiety associated with their stutter (i.e., 'a little anxious'/'never anxious') compared to those who typically experience stuttering, who more often report being 'fairly'/'very anxious' [23].

For most individuals in the wider population who have a persistent stutter (i.e., longer than 6 months), variability in severity across time and situations is common. In other words, individuals may have times where certain words, sounds, or situations prove more challenging for speech fluency, and other times when they experience a different combination of triggers, a different level of severity, or a different frequency in stuttering moments [26]. Our preliminary data suggest that individuals with KdVS have a unique presentation, in that for a significant proportion of the group, stuttering is completely present or completely absent for extended periods of time (e.g., 3 months with absolutely no stuttering, followed by three months with daily stuttering moments, followed by no stuttering again, etc). Whilst we provide a sizable sample size in the context of a rare population, we did not follow individuals longitudinally over time and our data did not reveal any trends as to why stuttering presents this way in KdVS. Further longitudinal research is needed in this area.

Only a handful of children had received an evidence-based stuttering intervention, and amongst these, none saw a complete resolution of their stutter. Yet considering many individuals had co-occurring speech and language diagnoses, speech pathologists may be conflicted in choosing therapy targets. That is, most

children also present with CAS where speech development is hard-won in the early years, with individuals needing to acquire individual sounds, sound combinations, and early words with repetitive therapy. Hence stuttering may be seen to be of secondary importance. For some individuals, there may also be difficulty clearly delineating CAS from stuttering, as these diagnoses can share perceptual characteristics (e.g., revisions/repetitions/perseverations of sounds or syllables) [27]. Into the future, quantitative brain imaging studies may help pinpoint underlying neurobiological mechanisms of the condition, and provide further insights into the speech phenotypes, leading to better-targeted therapies.

CONCLUSION

In summary, those with KdVS present with a relatively homogenous profile of speech development with slowed communication milestones, childhood apraxia of speech, and dysarthria, impacting heavily on intelligibility in the early years. Early AAC options are key during early development, yet we emphasise that the vast majority begin to rely more on verbal speech by early childhood (6–7 years). In addition, stuttering is a core feature in KdVS, following a unique onset pattern compared to idiopathic stuttering in the general population. Evidence for stuttering management in complex genetic disorders is lacking (let alone in KdVS specifically). Speech therapists should utilise the best evidenced-based stuttering therapies applicable in the typical population (i.e., Lidcombe programme, Demands and Capacities Model) and modify these according to age and cognitive ability [20, 22, 28–30]. Well-developed social skills, behaviour, and emotional control across situations are a relative strength in KdVS, as shown here with standardised measures, and such social competence and resilience should be utilised in therapy plans. Literacy (reading, spelling) and writing are challenging for those with KdVS, however, written communication is often complicated by poor fine motor development. Alternative options should be used to develop such skills. Individuals with KdVS should continue to access speech therapy throughout development, as the therapeutic focus shifts from motor speech control and language understanding, to successful literacy acquisition, and to the development of more complex communication skills required for life beyond school and into the community.

DATA AVAILABILITY

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

REFERENCES

1. Koolen DA, Vissers LE, Pfundt R, de Leeuw N, Knight SJ, Regan R, et al. A new chromosome 17q21.31 microdeletion syndrome associated with a common inversion polymorphism. Nat Genet. 2006;38:999–1001.
2. Koolen DA, Sharp AJ, Hurst JA, Firth HV, Knight SJ, Goldenberg A, et al. Clinical and molecular delineation of the 17q21.31 microdeletion syndrome. J Med Genet. 2008;45:710–20.
3. Koolen DA, Kramer JM, Neveling K, Nillesen WM, Moore-Barton HL, Elmslie FV, et al. Mutations in the chromatin modifier gene KANSL1 cause the 17q21.31 microdeletion syndrome. Nat Genet. 2012;44:639–41.
4. Zollino M, Orteschi D, Murdolo M, Lattante S, Battaglia D, Stefanini C, et al. Mutations in KANSL1 cause the 17q21.31 microdeletion syndrome phenotype. Nat Genet. 2012;44:636–8.
5. Koolen DA, Pfundt R, Linda K, Beunders G, Veenstra-Knol HE, Conta JH, et al. The Koolen-de Vries syndrome: a phenotypic comparison of patients with a 17q21.31 microdeletion versus a KANSL1 sequence variant. Eur J Hum Genet. 2016;24:652–9.
6. Koolen DA, Morgan A, de Vries BBA. Koolen-de Vries syndrome. [Updated 2019 Jun 13]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington; 2010.
7. Morgan AT, Haaften LV, van Hulst K, Edley C, Mei C, Tan TY, et al. Early speech development in Koolen de Vries syndrome limited by oral praxis and hypotonia. Eur J Hum Genet. 2018;26:75–84.
8. Egger JI, Wingbermühle E, Verhoeven WM, Dijkman M, Radke S, de Bruijn ER, et al. Hypersociability in the behavioral phenotype of 17q21.31 microdeletion syndrome. Am J Med Genet A 2013;161A:21–6. https://doi.org/10.1002/ajmg.a.35652
9. Morgan A, Braden R, Wong MMK, Colin E, Amor D, Liégeois F, et al. Speech and language deficits are central to SETBP1 haploinsufficiency disorder. Eur J Hum Genet. 2021;29:1216–25. https://doi.org/10.1038/s41431-021-00894-x
10. Morison LD, Braden RO, Amor DJ, Brignell A, van Bon BWM, Morgan AT. Social motivation a relative strength in DYRK1A syndrome on a background of significant speech and language impairments. Eur J Hum Genet. 2022; 30:800–81.
11. Sparrow SS, Cicchetti DV, Saulnier CA. Vineland adaptive behaviour scales. 3rd ed. Bloomington, IN: Pearson; 2016.
12. Bishop DV. Children's communication checklist (CCC-2). London: Pearson; 2003.
13. Wetherby AM, Prizant BM. Communication and symbolic behavior scales: developmental profile. Baltimore, MD: Paul H. Brookes; 2002.
14. Dodd BH, Hua Z, Crosbie S, Holm A, Ozanne A. Diagnostic evaluation of articulation and phonology. London: The Psychological Corporation; 2002.
15. Duffy JR. Motor speech disorders: substrates, differential diagnosis and management. St. Louis, MO: Mosby; 2013.
16. Braden RO, Boyce JO, Stutterd CA, Pope K, Goel H, Leventer RJ, et al. Speech, language, and oromotor skills in patients with polymicrogyria. Neurology. 2021;96:e1898–e1912.
17. Mei C, Fedorenko E, Amor DJ, Boys A, Hoeflin C, Carew P, et al. Deep phenotyping of speech and language skills in individuals with 16p11.2 deletion. EJHG. 2018;26:676–86.
18. Gozzard H, Baker E, McCabe P. Children's productions of polysyllables. ACQuiring Knowledge in Speech, Language and Hearing. 2006;8:113–6.
19. American Speech-Language-Hearing Association (ASHA). *Childhood Apraxia of Speech* [Internet]. Rockville, MD: ASHA; 2021.
20. Onslow M, Webber M, Harrison E, Arnott S, Bridgman K, Carey B, et al.The Lidcombe Program Treatment Guide. Lidcombe Program Trainers Consortium (2017).
21. Van Borsel J, Tetnowski JA. Fluency disorders in genetic syndromes. J Fluen Disord. 2007;32:279–96.
22. Yairi E, Ambrose N. Epidemiology of stuttering: 21st century advances. J Fluen Disord. 2013;38:66–87. https://doi.org/10.1016/j.jfludis.2012.11.002
23. Boyce JO, Jackson VE, van Reyk O, Parker R, Vogel AP, Eising E, et al. Self-reported impact of developmental stuttering across the lifespan. Dev Med Child Neurol. 2022;64:1297–306.
24. Kefalianos E, Onslow M, Packman A, Vogel A, Pezic A, Mensah F, et al. The history of stuttering by 7 years of age: follow-up of a prospective community cohort. J Speech Lang Hear Res. 2017;60:2828–39. https://doi.org/10.1044/2017_JSLHR-S-16-0205
25. Howell P, Davis S, Williams R. Late childhood stuttering. JSLHR. 2008;51:669–87.
26. Tichenor SE, Yaruss JS. Variability of stuttering: behavior and impact. Am J Speech Lang Pathol. 2021;30:75–88.
27. Morgan A, Liégeois F, Vargha-Khadem F. Motor speech profile in relation to site of brain pathology: a developmental perspective. In Maassen B, van Lieshout P, editors. Speech motor control: new developments in basic and applied research. Oxford: Oxford Academic; 2010).
28. Brignell A, Krahe M, Downes M, Kefalianos E, Reilly S, Morgan A. Interventions for children and adolescents who stutter: a systematic review, meta-analysis, and evidence map. J Fluen Disord. 2021;70:105843 https://doi.org/10.1016/j.jfludis.2021.105843
29. Brignell A, Krahe M, Downes M, Kefalianos E, Reilly S, Morgan AT. A systematic review of interventions for adults who stutter. J Fluen Disord. 2020;64:105766 https://doi.org/10.1016/j.jfludis.2020.105766
30. Franken MC, de Sonneville-Koedoot C, Stolk E, Rietveld ACM, Bouwmans-Frijters C. Comparing a demands and capacities model approach and the Lidcombe program for pre-school stuttering children: the restart randomised trail. Procedia-Soc Behav Sci. 2015;193:287–8.

ACKNOWLEDGEMENTS

We would like to thank all individuals with Koolen-de Vries syndrome and their families who took part in this research study. Provided by National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Speech and Language #1116976 (AM, DA).

AUTHOR CONTRIBUTIONS

MSJ: collected data, analysed data, interpreted data and wrote/edited manuscript. OvR, DAK and BBAdV: collected data, analysed data and edited manuscript. DJA and ATM: designed and conceptualised the study, interpreted data, directed the project and wrote/edited manuscript.

ETHICAL APPROVAL

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/legal guardian in the case of minors or adults with intellectual disabilities.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41431-022-01230-7.

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