

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

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24 **Abstract**

25 Speech and language impairment is core in Koolen-de Vries syndrome (KdVS), yet only one
26 study has examined this empirically. Here we define speech, language, and
27 functional/adaptive behaviour in KdVS; while deeply characterising the
28 medical/neurodevelopmental phenotype in the largest cohort to date. Speech, language,
29 literacy, and social skills were assessed using standardised measures, alongside an in-depth
30 health and medical questionnaire. 81 individuals with KdVS were recruited (35 female,
31 mean age 9 y 10mo), 56 of whom harboured the typical 500-650 kb 17q21.31 deletion. The
32 core medical phenotype was intellectual disability (largely moderate), eye anomalies/vision
33 disturbances, structural brain anomalies, dental problems, sleep disturbance, musculo-
34 skeletal abnormalities, and cardiac defects. Most were verbal (62/81, 76.5%), while
35 minimally-verbal communicators used alternative and augmentative communication (AAC)
36 successfully in spite of speech production delays. Speech was characterised by apraxia
37 (39/61, 63.9%) and dysarthria (28/61, 45.9%) in verbal participants. Stuttering was
38 described in 36/47 (76.6%) verbal participants and followed a unique trajectory of late onset
39 and fluctuating presence. Receptive and expressive language abilities were commensurate
40 with one another, but literacy skills remained a relative weakness. Social competence,
41 successful behavioural/emotional control, and coping skills were areas of relative strength,
42 while communication difficulties impacted daily living skills as an area of comparative
43 difficulty. Notably, KdVS individuals make communication gains beyond childhood and
44 should continue to access targeted therapies throughout development, including early AAC
45 implementation, motor speech therapy, language/literacy intervention, as well as strategies
46 implemented to successfully navigate activities of daily living that rely on effective
47 communication.

48 **Introduction**

49 Koolen-de Vries syndrome (KdVS) is a chromatin-related disorder caused by
50 haploinsufficiency of the *KANSL1* gene. It is caused by a variant in *KANSL1* or a deletion of
51 chromosome 17q21.31 that encompasses *KANSL1* [1-4]. There is uncertainty about the true
52 prevalence of KdVS; although the prevalence of a 17q21.31 deletion is estimated at 1 in
53 55,000 individuals. The prevalence of *KANSL1* variants cannot be determined due to limited
54 cases in the literature [5-6].

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

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

68 Morgan et al. [7] attempted to systematically investigate language, showing that
69 receptive and expressive language abilities are typically equivalent. Whilst linguistic
70 development is slow, such skills do continue to develop, and most children can form
71 sentences by the middle school years. Literacy impairment was also noted in 6 individuals,

72 but most (n=22) could not be assessed with standardised tools (i.e., too young, no access to
73 assessment tools). Further, most of the cohort were under 5 years of age and unable to be
74 assessed [7], and thus, early reading and writing abilities remain relatively unexplored.
75 Social skills have been noted as a relative strength in KdVS, yet have only been empirically
76 examined in n=3 individuals using standardised measures [8].

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

84 **Materials & Methods**

85 *Participants*

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

93 *Measures*

94 Caregivers/participants completed assessments, either via online (REDCap-administered)
95 survey and/or videoconference interview, and/or in-person (when possible) as detailed

96 below using our previously validated approach. Caregivers began by completing an in-depth
97 health and medical survey [9-10] and provided relevant clinical reports for medical or
98 developmental diagnoses previously received to confirm survey responses (i.e., ID, autism).
99 Participants completed verbal or minimally-verbal assessment protocols according to their
100 abilities.

101 *Language, literacy, and adaptive behaviour*

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

119 *Speech*

120 Speech was assessed for verbal communicators, including a differential diagnosis across
121 speech conditions (articulation disorder, phonological disorder, dysarthria, CAS, and
122 stuttering). All speech assessments were video- and/or audio-recorded. For non-English
123 speaking families, clinical reports were collected to confirm speech diagnoses. Articulation
124 (i.e., motor act of producing sounds) and phonological (i.e., understanding the sound
125 contrasts in a given language) abilities were assessed with the Diagnostic Evaluation of
126 Articulation and Phonology (DEAP, [14]). This is a single-word test with stimuli designed to
127 assess all phonemes of English. The presence of dysarthria was determined from rating a
128 five-minute conversational speech sample using the Mayo Clinic dysarthria classification
129 system [15-17]. CAS was diagnosed by examining connected speech samples, DEAP scores,
130 and production of multisyllabic words (when indicated, using the Single Word Test of
131 Polysyllables, [18]) [17]. Individuals were considered to meet criteria for a CAS diagnosis if
132 they met the three main diagnostic criteria: (1) inconsistent errors, (2) lengthened and
133 disrupted coarticulation between sounds and syllables, and (3) inappropriate prosody [19].
134 The presence of stuttering was assessed via an in-depth fluency questionnaire, regarding
135 onset, progression, and triggers (See Supplemental material). Once identified and rated by a
136 parent, the presence and severity of stuttering was then rated utilising connected speech
137 samples. Stuttering was rated using a 10-point stuttering severity rating scale [20].

138 *Statistical Analyses*

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

142 **Results**

143 *Medical and neurodevelopmental characteristics*

144 Eighty-one individuals (35 female, 46 male) were recruited. Participants were aged 1 year 6
145 months to 40 years 2 months (mean 9y 10mo, SD 7y 0mo), with a spread across age
146 groupings as follows: n=24 pre-schoolers \leq 4 years; n=35 children aged 5-12 years; n=13
147 adolescents aged 13-19 years; n=9 adults aged \geq 19 years. Most participants and their
148 families were English-speaking (n=73, 90.1%), with smaller proportions of Dutch (n=4, 4.9%),
149 German (n=2, 2.5%), French (n=1, 1.2%) and Portuguese speakers (n=1, 1.2%), Table 1. Most
150 presented with typical 500- to 650-kb deletions of 17q21.31 encompassing five genes
151 (*CRHR1*, *IMP5*, *MAPT*, *STH*, *KANSL1*) (n=56, 69.1%), while n=4 had larger deletions of
152 17q21.31 with additional genes deleted (see Table 2). 19 individuals had genetic variants
153 that affected only *KANSL1* (n=11 truncating variants; n=7 splice site variants; n=1 intragenic
154 deletion, exons 5-7). For summary and analysis, intragenic deletions of *KANSL1* were
155 classified within the category of “*KANSL1* variants”. Two individuals had small deletions
156 (72kB and 51kB), not large enough to equate to “typical deletions” but affecting more than
157 *KANSL1* alone. Sequence variants were deposited to Decipher
158 (<https://decipher.sanger.ac.uk/>).

159 Dysmorphic facial features were noted in 73/81 participants (90.1%), including pear-
160 shaped nose with bulbous tip (48/81, 59.3%), ear anomalies (32/81, 39.5%), hypertelorism
161 (25/81, 30.9%), lip/tongue tie (11/81, 13.6%), macroglossia (11/81, 13.6%), narrow
162 mouth/thin lips (7/81, 8.6%), high-arched palate (7/81, 8.6%), and underbite (6/81, 7.4%).
163 Two individuals had submucous cleft palates. Medical and neurodevelopmental features are
164 summarised in Table 1, Figure 1. 87.5% (49/56) had a diagnosis of ID, most moderately
165 impaired (29/56, 51.8%). 9/56 (19.6%) had severe ID. 30.9% (25/81) were too young or had
166 never been assessed for ID. A diagnosis of developmental delay (DD) by a paediatrician was
167 taken as a comparable measure of ID and was present in 78/81 (96.3%) of individuals. There

168 was high incidence of eye anomalies and vision disturbances (48/81, 59.3%), most
169 commonly strabismus and hyperopia; structural brain anomalies in those with brain imaging
170 results (33/62, 53.2%), most commonly changes to or agenesis of the corpus callosum;
171 dental problems (36/72, 50.0%) including too few teeth and complex orthodontics; sleep
172 disturbances (33/81, 40.7%) often frequent and early waking; musculo-skeletal problems
173 (32/81, 39.5%) including scoliosis and joint laxity; cardiac defects (32/81, 39.5%) commonly
174 atrial septal defects; and epilepsy and seizures (29/81, 35.8%). To a lesser extent but still
175 highly prevalent were skin conditions (26/81, 32.1%) i.e., eczema; renal/urogenital
176 complications (25/81, 30.9%), including hydronephrosis and vesicoureteral reflux;
177 gastrointestinal concerns (24/81, 29.6%), often constipation; and mental health problems
178 (23/81, 28.4%) often anxiety. 21/46 (45.7%) males had cryptorchidism. 29.6% (24/81) had
179 hearing loss (HL), most often moderate (i.e., 40-69dB HL) and conductive in nature. A
180 complete and detailed list of individual patient comorbidities can be found in Supplemental
181 Table 1.

182 *Language, literacy, and adaptive behaviour*

183 Adaptive functioning was impaired across all participants (mean=71.6, SD=10.2) on the
184 Vineland-3, compared to a population mean=100, SD=15, and no participant performed
185 within the average range across all subdomains. Four participants (ID23, ID29, ID26, ID51)
186 scored within the average range on the ABC; however, even these individuals scored below
187 average on at least one subdomain. Daily Living Skills were most severely affected
188 (mean=67.4, SD=12.4), followed by Communication (mean=70.2, SD=15.2) (Table 3).
189 Socialisation was a relative strength (mean=79.1, SD=14.3) across the group. Motor skills
190 were also impaired (mean=72.8, SD=11.0). A Kruskal-Wallis test found a significant
191 difference across Communication, Daily Living Skills and Socialisation Scores ($p<0.005$). A

192 Wilcoxon Signed-Rank tests revealed that Socialisation scores were better than Daily Living
193 Skills ($p<0.005$) and Communication ($p<0.005$). Communication and Daily Living Skills did not
194 differ from one another ($p=0.16$).

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

203 In regard to subdomain differences, Wilcoxon Signed-Rank tests revealed that in the
204 Communication domain, 'Written' language scores were poorer than 'Receptive' ($p<0.005$)
205 and 'Expressive' ($p<0.005$) language scores; in the Daily Living Skills domain 'Domestic' skills
206 were better than 'Community' skills ($p<0.005$) and 'Personal' skills ($p=0.008$); and in the
207 Socialisation domain 'Interpersonal Relationships' scores were better than 'Play and Leisure'
208 scores ($p=0.024$). 'Gross Motor' scores were higher than 'Fine Motor' scores ($p<0.003$)

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

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

225 *Speech disorder profile*

226 *CAS and dysarthria*

227 19/81 individuals (23.5%) were classified as non-verbal or minimally-verbal at the time of
228 assessment, however n=2 of these were younger than 2 years of age. The remainder of the
229 non-verbal or minimally-verbal individuals were aged 2 years 1 month to 6 years 9 months.
230 All individuals classified as minimally-verbal utilised alternative and augmentative
231 communication (AAC) options or multimodal strategies to communicate, including non-
232 verbal gestures and sign language, low tech options such as picture communication systems,
233 or high tech options such as iPads with dedicated communication applications and speech
234 generating devices. Verbal speech was assessed, for the remainder of the participants
235 (62/81, 76.5%). Differential diagnoses revealed CAS and dysarthria profiles were most
236 prominent. 39/62 (62.9%) had CAS, many alongside mild articulation errors (e.g., interdental
237 lisp) (20/39; 51.3%) and phonological impairment (10/39; 25.6%). 27/62 (43.5%) had clinical
238 features of dysarthria. 68/80 (85.0%) had delayed communication milestones, and 63/80
239 (78.8%) reported the use of multimodal/AAC options prior to their child’s verbal speech

240 development, and as a facilitator to this development. Most utilised multiple AAC forms and
241 systems to support communication, with 39/80 (48.8%) using sign language, 32/80 (40.0%)
242 using low technology visual communication systems like communication boards, and 24/80
243 (30.0%) using high technology visual communication systems (e.g., Proloquo2Go on an
244 iPad).

245 *Stuttering*

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

249 Stuttering was observed in 36/47 (76.6%). Individuals had an average stuttering
250 rating of 4.36 across the 10-point severity rating scale (Figure 3a). Stuttering behaviours
251 were varied, with the most common being sound repetitions (n=17, 47.2%), whole word
252 repetitions (n=17, 47.2%), syllable repetitions (n=16, 44.4%), and phrase repetitions (n=16,
253 44.4%) (Figure 3b).

254 16/36 did not display accompanying physical behaviours alongside their stutter
255 (44.4%), although for those who did, the most common physical behaviours were facial
256 grimaces (including groping) (n=18, 50.0%), head movements (n=8, 22.2%), and trunk or
257 limb movements (n=7, 19.4%) (Figure 3d).

258 Stuttering onset occurred most often during the ages of 5-6 years (n=13, 36.1%) and
259 <4 years (n=11, 30.6%), however stuttering onset was also reported into the adolescent
260 years for others (participants 69, 63, 71, 77) (Figure 3c). For most individuals (n=22, 61.1%)
261 stuttering had not resolved at the time of assessment and remained a current and
262 significant challenge. For others (n=10, 27.8%), parents reported their child's stuttering
263 "comes and goes" significantly over time, often characterised by blocks of time (i.e.,

264 months) with consistent stuttering followed by blocks of time without any stuttering at all,
265 with ongoing cycles of this pattern. Individuals who experienced this fluctuating presence of
266 stuttering were aged between 4 years 6 months and 24 years 3 months (mean = 12y 7mo;
267 SD = 6y 11mo). At the point of assessment, only n=4 (11.1%) reported that the stuttering
268 had resolved; this occurring at the ages of 5 years, 7 years, 12 years, and 14 years
269 respectively (Figure 3e).

270 9/36 (25.0%) reported that their stuttering is brought on by specific situations (under
271 pressure, nervous, or tired), however the majority (27/36, 75.0%) did not report any such
272 triggers. Most parents reported their children were aware of their stutter (28/36, 77.8%)
273 and in turn, the majority reported some degree of anxiety due to their stuttering (25/36,
274 69.4%) (Figure 3f). Of these, parents report that “specific situations” caused the most
275 anxiety (13/27, 48.1.3%) (Figure 3g).

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

286 *Analysis of factors potentially associated with stuttering development*

287 Several phenotypic and genotypic factors were analysed to identify any associations with
288 the presence of stuttering. Statistically and qualitatively, we saw no association between
289 stuttering and the following factors: history of seizures or epilepsy, medication taken for a
290 neurological condition (i.e., ADHD, epilepsy), or in those with 17q deletions (as opposed to
291 smaller *KANSL1* variants).

292 *Co-occurrence of diagnoses*

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

299 **Discussion**

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

305 A consistent observation [i.e., 7-8] that has not been comprehensively quantified
306 within a cohort, are the strong social skills of those with KdVS. Only one study has examined
307 this systematically in n=3 [8]. Our data confirmed that social skills are a relative strength for
308 individuals with KdVS. Although standard scores for social skills do sit below the population
309 average, those with KdVS show relative strengths in their development of play skills and
310 ability to form interpersonal relationships with others, in comparison to their overall

311 communication skills and daily living skills. In addition, their higher scores in the 'Coping'
312 subdomain, confirm previous reports of resilience and high frustration tolerance [8]. Such
313 relative strength in coping is perhaps a positive predictive factor for why individuals with
314 KdVS persist with therapies (speech and physical) so successfully; a key in their continued
315 functional gains over many years.

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

329 Previous research suggested receptive language skills were more intact in
330 comparison to expressive language [5], yet these were commensurate with one another
331 across our group. Reading and writing subdomains were, however, more severely impacted
332 in comparison to receptive language. Considering strikingly delayed early speech milestones
333 in KdVS, and the known impact of such delays on later literacy, this is unsurprising but
334 warrants emphasis, as literacy skills should remain a therapy focus. It is important to note

335 that the literacy subdomain used within our measures includes reading and writing as one
336 score, however it was noted, descriptively, that poor fine motor skills were a significant
337 factor in lowering the literacy scores overall. This is important, as individuals should be
338 provided with other means of developing written communication skills that do not rely so
339 heavily on precise fine motor control (e.g., using a keyboard rather than pen and paper).

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

351 Previous reports indicate around 17% of individuals with KdVS present with
352 stuttering [5], however the prevalence appears to be higher than originally reported, such
353 that it is one of the key and distinctive speech features of KdVS; not only in comparison to
354 the typical population but also relative to other neurodevelopmental disorders. Half of the
355 sample from Morgan et al. [7] were under 5 years of age, and so it is not surprising that the
356 true prevalence has not been previously captured, as here we saw many individuals develop
357 persistent dysfluency beyond 5 years of age. Past research indicates that stuttering
358 prevalence in individuals with ID and in typically developing individuals is 5% and 1%

359 respectively [21-22], and so a prevalence of 76.6% in our sample is striking. Across the
360 general population, previous research consistently reports onset of stuttering between 2-4
361 years of age, with very few reporting onset of stuttering beyond 9 years [22-25]. Yet
362 stuttering in KdVS appears to emerge later; most often between 5-8 years, but sometimes
363 even in adolescence. Stuttering onset is thought to coincide with preschool linguistic
364 development, i.e., when children begin combining words and producing longer sentences.
365 Considering the delayed communication milestones in KdVS, it is unsurprising that
366 stuttering onset would also be delayed; however, this does not explain such high
367 prevalence. Stuttering in KdVS is distinct, not only in onset but in presentation. Typically,
368 stuttering severity is negatively correlated with age, and is characterised by blocking as the
369 most common behaviour [23]. In KdVS, we found stuttering severity to be higher on average
370 in adults and most often characterised by sound and word repetitions. Interestingly, those
371 with KdVS described lower levels of anxiety associated with their stutter (i.e., “a little
372 anxious”/“never anxious”) compared to those who typically experience stuttering, who
373 more often report being “fairly”/“very anxious” [23].

374 For most individuals in the wider population who have a persistent stutter (i.e.,
375 longer than 6 months), variability in severity across time and situations is common. In other
376 words, individuals may have times where certain words, sounds, or situations prove more
377 challenging for speech fluency, and other times when they experience a different
378 combination of triggers, a different level of severity, or a different frequency in stuttering
379 moments [26]. Our preliminary data suggest that individuals with KdVS have a unique
380 presentation, in that for a significant proportion of the group, stuttering is completely
381 present or completely absent for extended periods of time (e.g., three months with
382 absolutely no stuttering, followed by three months with daily stuttering moments, followed

383 by no stuttering again, etc). Whilst we provide a sizable sample size in the context of a rare
384 population, we did not follow individuals longitudinally over time and our data did not
385 reveal any trends as to why stuttering presents this way in KdVS. Further longitudinal
386 research is needed in this area.

387 Only a handful of children had received an evidence-based stuttering intervention,
388 and amongst these, none saw a complete resolution of their stutter. Yet considering many
389 individuals had co-occurring speech and language diagnoses, speech pathologists may be
390 conflicted in choosing therapy targets. That is, most children also present with CAS where
391 speech development is hard-won in the early years, with individuals needing to acquire
392 individuals sounds, sound combinations, and early words with repetitive therapy. Hence
393 stuttering may be seen to be of secondary importance. For some individuals there may also
394 be difficulty clearly delineating CAS from stuttering, as these diagnoses can share
395 characteristics (e.g., revisions/repetitions/perseverations of sounds or syllables) [27]. Into
396 the future, quantitative brain imaging studies may help pinpoint underlying neurobiological
397 mechanisms of the condition, and provide further insights into the speech phenotypes,
398 leading to better targeted therapies.

399 **Conclusion**

400 In summary, those with KdVS present with a relatively homogenous profile of speech
401 development with slowed communication milestones, childhood apraxia of speech, and
402 dysarthria, impacting heavily on intelligibility in the early years. Early multimodal
403 communication options are key during early development, yet we emphasise that the vast
404 majority begin to rely more on verbal speech by early childhood (6-7 years). In addition to,
405 stuttering is a core feature in KdVS, following a unique onset pattern compared to idiopathic
406 stuttering in the general population. Evidence for stuttering management in complex

407 genetic disorders is lacking (let alone in KdVS specifically). Speech therapists should utilise
408 the best evidenced-based stuttering therapies applicable in the typical population (i.e.,
409 Lidcombe program, Demands and Capacities Model) and modify these according to age and
410 cognitive ability [20, 22, 28-30]. Well-developed social skills, behaviour, and emotional
411 control across situations are a relative strength in KdVS, as shown here with standardised
412 measures, and such social competence and resilience should be utilised in therapy plans.
413 Literacy (reading, spelling) and writing are challenging for those with KdVS, however written
414 communication is often complicated by poor fine motor development. Alternative options
415 should be used to develop such skills. Individuals with KdVS should continue to access
416 speech therapy throughout development, as the therapeutic focus shifts from motor speech
417 control and language understanding, to successful literacy acquisition, and to the
418 development of more complex communication skills required for life beyond school and
419 into the community.

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423 **Conflict of Interest Statement**

424 The authors declare no conflict of interest.

425 **Data Availability Statement**

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

428 **Ethical Approval**

429 Ethical approval was obtained through the Royal Children's Hospital, Melbourne, Human
430 Research Ethics Committee (HREC #37353). Written informed consent was obtained from

431 the participant or their parents/legal guardian in the case of minors or adults with
432 intellectual disability.

433 **Author Contribution Statement**

434 MSJ: collected data, analysed data, interpreted data, wrote/edited manuscript. OVR:
435 collected data, analysed data, edited manuscript. DAK: collected data, edited manuscript.
436 BBADV: collected data, edited manuscript. DJA: designed and conceptualised study,
437 interpreted data, directed project, wrote/edited manuscript. ATM: designed and
438 conceptualised study, directed project, interpreted data, wrote/edited manuscript.
439

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- 523

524 **Figure Legends**

525 Figure 1. Core medical and neurodevelopmental comorbidities

526

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

534

535 Figure 3a. Number of participants with each level of stuttering severity

536 Figure 3b. Number of participants presenting with various stuttering behaviours. Reps,
537 repetitions

538 Figure 3c. Onset of stuttering according to age bandings

539 Figure 3d. Number of participants presenting with accompanying physical behaviours

540 Figure 3e. Current presence of stuttering

541 Figure 3f. Number of participants with anxiety associated with stuttering and the level of
542 anxiety

543 Figure 3g. Number of participants reporting individual stuttering-related anxiety triggers

544

545 Figure 4. Heatmap showing the co-occurrence of intellectual disability, expressive
546 language impairment, receptive language impairment, motor speech diagnoses and
547 functional speech diagnoses. At each intersection, the percentage indicates the

548 proportion of individuals who had both diagnoses (of those with results for both). Closer
549 to magenta indicates a higher percentage; closer to teal indicates a lower percentage.
550 Based on n=54 with ID results; n=68 with language results; n=60 with speech results
551 (n=47 with stuttering results).