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CDK13-related disorder: a deep characterization of speech and language abilities and addition of 33 novel cases.

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Abstract

Speech and language impairments are central features of *CDK13*-related disorder. While pathogenic *CDK13* variants have been associated with childhood apraxia of speech (CAS), a systematic characterisation of communication has not been conducted. Here we examined speech, language, non-verbal communication skills, social behaviour and health and development in 41 individuals with *CDK-13* related disorder from 10 countries (male=22, median-age 7 years 1 month, range 1-25 years; 33 novel). Most participants used augmentative and alternative communication (AAC) in early childhood (24/41). CAS was common (14/22). Performance varied widely across intellectual ability, social behaviour and expressive language skills, with participants ranging from within average through to the severely impaired range. Receptive language was significantly stronger than expressive language ability. Social motivation was a relative strength. In terms of broader phenotype, a quarter had one or more of: renal, urogenital, musculoskeletal, and cardiac malformations, vision impairment, ear infections and/or sleep disturbance. All had gross and fine motor impairments (41/41). Other conditions included mild-moderate intellectual disability (16/22) and autism (7/41). No genotype-phenotype correlations were found. Recognition of CAS, a rare speech disorder, is required to ensure appropriately targeted therapy. The high prevalence of speech and language impairment underscores the importance of tailored speech therapy, particularly early access to AAC supports.

Keywords: CDK13, speech, language, apraxia, intellectual disability, phenotype

Introduction

CDK13 is part of the family of over 30 cyclin-dependent kinases (CDKs) expressed in humans (1). *CDK13* is involved in transcription and posttranscriptional processing (2) and plays a critical role in embryonic development (3). *CDK13* expression is detectable in the heart, brain and craniofacial area (3).

Pathogenic *CDK13* variants cause *CDK13*-related disorder (4). The literature reports over 60 individuals with this condition, with most published *CDK13* variants being missense and occurring *de novo* (4-14). Physical features of *CDK13*-related disorder include recognisable upslanting palpebral fissures, epicanthal folds, a broad nasal bridge, thin upper lip, small mouth, posteriorly rotated ears, peg-shaped teeth, and curly hair (4-8, 14). Other physical phenotypes include congenital cardiac, renal and skeletal abnormalities, hypotonia, feeding difficulties and a high-arched palate (5-8, 13).

The neurodevelopmental profile includes average intellectual ability through to moderate intellectual disability (ID), autism spectrum disorder (hereafter autism), attention-deficit/hyperactivity disorder (ADHD), epilepsy and sleep disturbances (14). Speech and language are reported as among the most commonly impacted areas of neurodevelopment in *CDK13*-related disorder (5, 6, 8, 10, 13, 14). Yet whilst communication difficulties are ubiquitously reported, there has been no specificity to the clinical diagnoses, with very general terms such as 'speech and language delay' being used. Nor have studies used standardised measures/assessment protocols. A variant in *CDK13* was recently associated with a rare and severe speech disorder, childhood apraxia of speech (CAS), in a gene discovery cohort of children ascertained for CAS (13). However, there has been no systematic reverse phenotyping evaluation of speech or language deficits in a cohort of individuals with pathogenic CDK13 variants to date to confirm this association with CAS. Further, the absence of a comprehensive speech and language evaluation in this population

limits prognostic counselling and the provision of targeted intervention. Here, we systematically characterise speech and language abilities, and examine possible genotype-phenotype correlations, in children with *CDK13*-related disorder using standardised outcome measures.

Methods

Participants

Inclusion criteria were a molecularly confirmed pathogenic diagnosis of *CDK13*-related disorder. Exclusion criteria were the existence of other pathogenic variants in other neurodevelopmental genes. Participants were recruited internationally via an online *CDK13* support group or via their treating clinical geneticist from French, Dutch, German, English and Spanish speaking backgrounds. The Royal Children's Hospital Human Research Ethics Committee provided ethical approval (HREC 37353A). Caregivers provided written and informed consent for their children to participate, even in the case of the young adults in the study.

Health and development

Families completed caregiver questionnaires concerning individuals' health and developmental history (Supplementary Table 1). Caregiver questionnaires were completed in the participants' language: English, French, Dutch, German, and Spanish. Results were confirmed with a case history via telehealth and provision of additional reports (e.g., cognitive assessments, electroencephalograms, and autism diagnostic reports), a successful method employed previously (15-18). All English-speaking, verbal participants (i.e., used primarily spoken words to communicate) also completed a telehealth assessment with a university-trained speech pathologist.

Adaptive behaviour and motor skills

The Vineland Adaptive Behaviour Scales (VABS II/III) caregiver version, was completed online for English-, Spanish- (third edition) and French-speaking (second edition) participants (19, 20). The VABS II/III provides standardised scores for communication, socialisation, self-care, activities of daily living, motor skills and an overall adaptive behaviour score (that does not include the motor skills subtest).

Language and social communication

The VABS II/III communication domain, with receptive, expressive and written skill subdomains, assessed language in English, French and Spanish speaking individuals English- and Dutch-speaking caregivers of participants younger than 2 years-old completed the Communication and Symbolic Behaviour Scales Developmental Profile (CSBS-DP) standardised questionnaire (21). Children 4-16 years old completed the Children's Communication Checklist – Second Edition (CCC-2) (22). These tools assess speech, receptive and expressive language, non-verbal communication and social communication abilities. Tools were not available in other languages.

The Social Responsiveness Scale-2 (SRS-2) was completed by English- and Dutch-speaking families (23). The SRS-2 caregiver questionnaire is standardised across three versions from pre-school children to adulthood (>2 years). The SRS-2 measures social behaviour based on DSM-V autism diagnostic criteria (23): social awareness, social cognition, social communication, social motivation, restricted interests, and repetitive behaviour (24).

Alternative communication methods and therapy

Minimally verbal children were defined as having less than 50 spoken words (17, 25) and were assessed using the Inventory of Potential Communicative Acts (IPCA) caregiver questionnaire (26). This assessment investigates communication behaviours used by individuals of all ages, such as; facial expression, body movement, gesture, and augmentative and alternative communication (AAC) (e.g., sign language, communication devices) across a range of functions including greeting, protesting, and commenting. Caregiver surveys provided information on current therapy goals and AAC systems.

Speech

Verbal children were assessed using standardised tools which examined performance across speech domains of: articulation, phonology, stuttering, dysarthria and CAS.

Articulation disorder (distorted production of a speech sound, e.g., a lisp), phonological delay (where a child is persisting in the use of speech sound error patterns made by >10% of younger children, e.g., fronting of fricatives or velars; gliding, etc) and phonological disorder (atypical speech sound error patterns, defined as errors made by <10% of children in the general population, e.g., initial consonant deletion, backing of sounds) were diagnosed using the Phonology and Inconsistency subtests of the Diagnostic Evaluation of Articulation and Phonology (DEAP) (27) and confirmed during a five minute conversational speech sample. Stuttering was measured using a Likert scale of 0 (no stuttering) to 9 (severe stuttering) during the 5 minute conversational sample (28). Ratings for CAS were made using the American Speech and Hearing Association CAS Technical Report Protocol consensus features (29). Consensus features for CAS included three criteria: i) inconsistent speech production; ii) disrupted and prolonged co-articulatory transitions; iii) prosodic errors as previously operationally defined and rated using a checklist (15-18, 30, 31). Dysarthria was

rated in the presence of neuromotor tone disruption to one or more of the sub-systems for speech (e.g., phonatory, articulatory) as well as the presence of dysarthric features (e.g., hypernasality) rated using the Mayo Clinic Dysarthria Classification System (32). Dysarthria and CAS ratings were made based on these operationalised criteria using single word responses to the DEAP Phonology and Inconsistency subtests, 5 minute conversational speech sample, and diadochokinetic speech tasks (e.g., 'pataka') (27, 30). Clinician and caregiver reports documented speech diagnoses for non-English speaking individuals, who were not able to be directly assessed.

The Intelligibility in Context Scale (ICS) (33) was completed by caregivers to assess how well a participant is understood (intelligibility) based on their speech in the past month, with different communication partners (e.g., friends, family members) on a scale of 1 (never understood) to 5 (always understood) (Supplementary Figure 1).

Feeding and nonspeech oral motor skills

English-speaking children aged 6 months to 7 years completed the Child Oral and Motor Proficiency Scale (ChOMPS) (34). The assessment separates eating and drinking skills into: complex movement patterns (e.g., licking food from lips), basic movements (e.g., sitting), oral motor coordination (e.g., moving jaw to chew), and fundamental oral skills (e.g., closing lips). Caregivers of children who drooled completed the Drooling Impact Scale (35), whereby the frequency and impact of drooling was rated 1 (none) through 10 (all the time). The structure and function of the oral articulators was assessed (36) to support interpretation of the speech and feeding results.

Statistical analyses

Non-parametric statistical analyses were conducted due to the data not being normatively distributed. A Wilcoxon Signed Rank tests compared individual differences between VABS II/III receptive and expressive language scores, CCC-2 domains, and SRS-2 domains. To explore genotype-phenotype associations, a Mann Whitney test compared VABS II/III adaptive behaviour and communication scores between groups with different variants. A Kruskal-Wallis test compared VABS II/III domains. Ages, VABS II/III, CCC-2, CSBS-DP, SRS-2, and ICS data were reported using descriptive statistics detailing central tendency (mean, median) and variability (SD).

Results

Participants

Forty-one participants were recruited, ranging from 1 year 6 months to 18 years 9 months (Median=7 years; Male=22) (Table 1). Participants were from the United States (19), France (5), Australia (4), United Kingdom (3), Canada (3), the Netherlands (2), Belgium (1), Spain (1), Switzerland (1) and Qatar (1). Thirty-three participants were novel and eight were previously published [IDs 18, 23 (4), ID 31 (5), ID 7 (5), IDs 5, 9, 33 (14), ID 27 (13, 14)]. Most participants had missense variants (n=37) (Figure 1). Seventeen had the same missense variant (n=17, c.2525A>G, p.Asn842Ser). Six other participants shared a further missense variant (c.2149G>A, p.Gly717Arg) and a further fifteen participants had other missense variants. Of the four participants who did not have missense variants, three had truncating variants (IDs 39, 40, 41) and one had a splice site variant (ID 38). Thirty-nine were confirmed *de novo* and two were of unknown inheritance (IDs 14, 18). The average age at genetic diagnosis was 6 years and 4 months.

Health and development

Medical conditions

Cardiac malformations (15/41) and heart surgeries were common (9/14) (Table 1). The most frequent cardiac malformation was atrial septal defect (9/14). Renal and urogenital abnormalities were present in almost half the cohort (19/41) (Supplementary Table 2).

Most participants (34/41) had undergone brain magnetic resonance imaging (MRI) or computerised tomography (CT) scans and almost half had findings (15/34) (Table 1) including hypoplasia of the corpus callosum (6/14) and Chiari malformation (2/14). Three participants had epilepsy (IDs 6, 19, 31) with all taking anticonvulsant medication for seizure management. Insomnia symptoms were evident (23/41), including frequent waking (12/23), early waking (8/23), difficulty falling asleep (9/23) and little sleep (2/23) or a combination of these issues.

Musculoskeletal problems were apparent (15/31), although findings were heterogenous. Hypotonia was common in infancy (11/41). Small stature and difficulties gaining weight were frequent (11/40).

Infant feeding difficulties (34/41) were treated with nasogastric (10/34) and gastrostomy tubes (5/34) (Supplementary Table 2). Participants 29 and 33 had tracheomalacia and participant 31 also had a tracheostomy tube in situ at the time of assessment. Complex dentition was observed (24/41) (Supplementary Table 2).

Ear infections (16/41) were common. One participant had mild, conductive hearing loss (ID 34, 25-39dBHL). A subset of participants had procedures for tympanostomy tubes (7/40), tonsillectomies (7/41), and adenoidectomies (8/41). More than half the group had vision impairment (24/41), with myopia (12/24) and strabismus (11/24) being the predominant diagnosis. Shared facial features were also evident (Supplementary Table 2).

Development

Most participants learned to sit and walk after the expected milestones of 7 (35/41) and 15 months (33/41), respectively (Tables 2, 3 for milestones). Twenty-six participants had delayed acquisition of first words (>15 months) and four had not yet said their first words (aged between 2- to 12-years). Similarly, only eight participants made short sentences at the expected age (2-3 years), and 19 participants (aged up to 15 years old) were not yet combining words. The remaining 15 participants began combining words between 5 to 7 years old.

Neurodevelopmental conditions

Co-occurring neurodevelopmental conditions were common (Table 2) (25/41). Of the 22 participants with psychometric cognitive assessment data available, most had a moderate ID (12/22, 35-55 FSIQ) and some had a mild ID (4/22, 55-70 FSIQ). Six participants scored in the very low (4/22, 70-85 FSIQ) and average ranges (2/22, >85 FSIQ). Of the remaining 19 participants without psychometric based cognitive assessments, 16 had paediatrician reported developmental delays. Intellectual abilities are often not assessed until a child begins school and half of the participants without cognitive assessment had not yet started school (9/19). DSM-V (24) diagnoses reported by caregivers and confirmed by health professional reports included developmental coordination disorder, (8/25), autism (7/25), ADHD (5/25). One individual had neurobehavioural disorder associated with prenatal alcohol exposure. Other formal diagnoses included sensory processing disorder (13/25), and auditory processing disorder (ID 25). Seventeen percent (7/41) of participants had an anxiety disorder, and participant 3 was also diagnosed with depression.

Education

Twenty-three participants were school aged or older. Two children were home-schooled, 13 attended special schools and eight attended mainstream settings.

Most participants had accessed speech therapy (39/41). Many accessed physiotherapy (36/41) and occupational therapy (36/41) for gross and fine motor impairments.

Adaptive behaviour and motor skills

A range of profiles was noted in the range of adaptive behaviour composite scores (mean=61.86). No single domain of daily living socialisation or communication was significantly different to any other (p=0.26).

VABS II/III scores from participants with the same variant (c. 2525A>G, p.Asn842Ser, n=15), were compared to the rest of the cohort (n=22) (Figure 2). There was no statistically significant difference between participants with this variant and the rest of the cohort on the adaptive behaviour composite score ($p=0.39$, $p>0.05$) or their communication score ($p=0.36$, $p>0.05$). However, when descriptively assessed via a boxplot (Figure 2), the participants with the same variant tended to be more similar to one another on their adaptive behaviour composite score (SD=15.97) than the rest of the group (SD=23.39).

Language and social communication

At a group level, average receptive language skills (mean=10.20) were significantly stronger than average expressive language ability (mean=8.71) ($p=0.03$, $p<0.05$) on the VABS II/III. Overall communication scores (test standard score mean=100, SD=15) indicated generally low communication skills (mean=63.76), however scores ranged from within average limits to severely impaired (Figure 2, Table 3).

Six female participants had expressive and/or receptive language skills within the normal range of performance (IDs 5, 26, 27, 36, 38, 40). There were five participants with

average social behaviour and moderate to severe language impairment however (IDs 7, 13, 14, 22, 29).

CSBS-DP emotion and eye gaze (mean=9.75), words (mean=8) and understanding (mean=7.75) were in the average range (Table 4). High variability in the group was also observed in CSBS-DP subdomains.

Language skills on the CCC-2 (n=22) and CSBS-DP (n=4) were low across most subdomains (mean=10, SD=3) (Table 4). CCC-2 subdomains ranged between -1 to -2 SD of the mean, except speech (mean=2.05), syntax (mean=2.91) and semantic scores (mean=3.68) which were >-2 SD (Supplementary Figure 2). Speech was the lowest subdomain and was significantly different to all subdomains except syntax ($p<0.05$, Table 4). High variability amongst the group was observed in all subdomains.

SRS-2 T-scores demonstrated a range of social communication abilities, from within normal limits (10/28) to severely impaired (10/28) (normative mean=60, SD=10) (Figure 3, Table 3). Moderate to severe scores indicate a high likelihood of autism (16/28), however only five had confirmed diagnoses of autism and four more had sensory processing disorder. Restricted and repetitive behaviours were slightly impaired (mean=70.53, -1 SD), and were significantly different from social motivation ($p=0.0003$, $p<0.01$). All other domain means were within normal limits

Alternative communication methods and therapy

Caregivers identified speech production (32/41), receptive language skills (23/41), social language skills (20/41), low-technology AAC (e.g., communication boards, 19/41), high-technology AAC (e.g., speech generating device, such as an electronic tablet, 19/41), and Key Word Sign/Makaton (KWS, i.e., using single signs to communicate, 12/41) as

beneficial focuses of speech therapy sessions. One participant was receiving specific speech therapy targeting CAS.

More than half of the cohort used AAC (24/41) (Table 3). KWS was commonly the sole AAC system (11/24) and was used by younger children (<3 years old, 4/11) or those with verbal communication who on occasion used single signs while speaking (6/11). All other AAC users had graphic AAC systems (Table 3). Four minimally verbal participants older than 3 years old, when children typically learn to combine words, did not have an AAC system.

Eleven minimally verbal participants completed the IPCA (Supplementary Table 3). In terms of symbolic communication, almost half the group used speech to greet and farewell others and seek attention (5/11) and used sign to request 'more' (6/11). Graphic AAC was mostly used for requesting objects (4/11). Participants also used symbolic gesture (e.g., hugging, pointing) to request objects and seek comfort and answer yes or no. Challenging behaviours were exhibited when participants felt angry (6/11).

Speech

Twenty-two verbal, English-speaking, participants had a standardised speech assessment (Table 3). CAS and phonological delay were the most frequently occurring speech disorders (14/22), with co-occurring diagnoses being common (11/14). Dysarthria (8/22), phonological (9/22) and articulation disorders (8/22, interdental lisp 6/8, lateral lisp 2/8) were also present. The fourteen participants with CAS had features across all three diagnostic criteria (Figure 4) (29, 30). The most prevalent CAS features distinct from dysarthric features were inconsistent production of the same phoneme (consonant or vowel) across different words (92.86%), difficulty sequencing sounds and syllables (85.71%), and increased errors with increased word length and complexity (71.43%). Participant 3 had a history of CAS that had largely

resolved. One participant (ID 36) had a mild stutter (28). Four of the eight participants with dysarthria also had CAS. Dysarthric features were seen across all speech dimensions (Figure 4). Only five participants had a speech disorder diagnosis in isolation (CAS 1/5, dysarthria 2/5, articulation disorder 1/5, phonological delay 1/5). Two participants did not have a speech disorder.

For non-English speaking participants who were not able to be assessed over telehealth (n=19), 10 caregivers reported clinical diagnosed speech disorders and nine individuals were minimally verbal. Of the 10 with clinically diagnosed speech disorders, articulation disorder was most common (9/10), followed by CAS (6/10), phonological delay/disorder (5/10) and dysarthria (4/10).

Intelligibility ranged from 1 (never understood) to 5 (always understood) across a variety of communication partners (n=41) (Supplementary Figure 1). Participants were most intelligible to their caregivers (mean=3.98, sometimes to usually understood), and least intelligible to strangers (mean=2.65, rarely to sometimes understood).

Feeding and nonspeech oral motor skills

The ChOMPS (n=17) indicated that feeding difficulties were almost universal (16/17) in young children (Supplementary Figure 3). Most participants (15/17) had highly concerning feeding skills (<5th percentile). Only one participant had feeding skills within normal limits. Complex movement patterns (e.g., licking food off the top lip) were descriptively most challenging, while basic movement patterns were a strength (e.g., bringing a bottle to mouth). Drooling prevalence ranged from never drooling to frequent drooling, with drooling generally delayed and resolving only by the late primary school years.

Oral motor skills were impaired in all participants able to complete testing (21/21, Table 3). Greatest difficulty was seen in moving the tongue vertically and horizontally (14/21 and 13/21, respectively), as well as in rounding the lips (10/21), and coordinating two or more non-speech movements (13/21, e.g., bite then lick lips).

Discussion

Here we provide the most comprehensive characterisation of speech and language in *CDK13*-related disorder. With the addition of 33 novel cases to the existing 60 cases in the literature, we also provide a description of over a third of all published cases of *CDK13*-related disorder to date.

Speech production was substantially more impaired when compared to other communication domains, such as social communication. Speech disorder was the most prevalent phenotypic feature, where CAS was dominant (63.6%) and considerably more prevalent than general population diagnostic frequencies (0.1%) (37, 38). CAS frequently co-occurred with other speech =disorders. Despite this frequency of CAS, only one participant was receiving a CAS specific intervention. This lack of recognition of CAS may be hindering opportunities for more targeted therapy with negative implications for longer-term outcomes. Expressive syntax (the arrangement of words to form sentences), can also be impacted by severe speech disorder (39). Development of speech was generally protracted, e.g., not combining words until after 15 months of age, with most participants using AAC to support their communication needs while speech developed. Some participants remained minimally verbal or had severely impaired speech intelligibility, requiring AAC aides into adolescence. Comprehensive AAC supports are required so that individuals can meet all their communication needs where speech cannot.

Historically, the terms speech/language and delay/disorder have been used to describe the features observed in *CDK13*-related disorder. Our systematic characterisation of speech and language is critical for the provision of tailored interventions. Our findings suggest access to AAC in the early years, with ongoing support for AAC into adolescence if needed, is of paramount importance to optimise communication outcomes. Typically developing children are immersed in their language system from birth and say their first words around 12 months of age. A child with *CDK13*-related disorder should be exposed to both verbal language and AAC before their first birthday to allow for optimal learning opportunities with a trained speech pathologist (40). AAC is not used as a replacement for verbal development, but rather it is known to support verbal development (41) and particularly support growth of expressive vocabulary and grammar (42). AAC should continue to be implemented if the child cannot be understood by different individuals across communication settings (e.g., school, home, with friends), so as to meet all of their communication needs. Consequently, AAC systems that can execute a range of communication functions should be considered. Further, a combination of AAC systems can be used, such as KWS and a high-tech graphic AAC (43).

The most common speech disorder in this group, CAS, disrupts motor planning and programming for speech. In line with this speech motor involvement, fine and gross motor impairment were also widespread. The frequency of co-occurring fine, gross and speech motor disorders implicates an underlying mechanism of disordered movement planning abilities in *CDK13*-related disorder. Evidence for the motor involvement in *CDK13*-related disorder is consistent with neurobiological evidence showing high *CDK13* expression in the cerebellum; which is responsible for precision of speech sounds, physical movement, executive functioning and language ability (44-46). Further, almost half of those with MRI findings in our cohort had hypoplasia of the corpus callosum. Callosal aberrations have also

been implicated in speech disorder (47). Further evidence is required to better understand the neurobiological bases of CDK-13 and their association to speech disorder.

Six female participants had average expressive and/or receptive language skills. These participants demonstrate that speech and language disorders may dissociate, given that all of this group had speech disorders in the presence of intact language abilities. Participants with moderate to severe social behavioural impairment all had similarly impaired language skills. Yet there were also participants with average social behaviour and impaired language ability. Hence, impaired social behaviour was always associated with impaired language skills, but not vice versa. It is important to acknowledge that speech and language impairment can be present in the absence of ID, with linguistic behaviours having their own biologically driven neurological pathways (48).

Receptive language was a relative strength when compared to expressive language ability. In genetic conditions with a high prevalence of CAS systematically characterised to date, stronger receptive language skills compared to expressive language skills have not been seen across cohorts (15-18). This suggests that receptive language may be a strength for individuals with *CDK13*-related disorder, at least relative to other genetic conditions involving CAS that are understood at this time (15-18). A limitation of our study was that assessment tools and access to trained clinicians for examining speech and language in individuals from non-English speaking backgrounds were more limited than those available for English-speaking individuals.

Moderate ID generally corresponded with moderate to severely impaired language skills. However, three participants with very low to average FSIQ had moderate to severely impaired language skills. Consequently, intellectual and language ability are typically congruent, but can be distinct from one another in some individuals.

The incidence of ID was less in this cohort than previously reported (14), with around one quarter of assessed participants having borderline to average FSIQ. However, this cohort may be biased, as caregivers may only self-refer to a speech and language study for children with stronger language and intellectual ability. Additionally, previous literature largely characterises individuals drawn from cohorts of children ascertained for ID, so here we broaden the phenotype of *CDK13*-related disorder with the inclusion of individuals without ID.

The occurrence of other neurodevelopmental conditions such as autism and ADHD was consistent with previously published cases (14). However, most participants with moderate to severe social behaviour impairment did not have a clinical diagnosis of autism. This indicates that rates of autism may be higher still in individuals with pathogenic *CDK13* variants. For the first time, sensory processing disorder was identified as a commonly occurring feature of *CDK13*-related disorder, with over one-quarter of the cohort affected. However, sensory processing disorder and autism are difficult to differentially diagnose, especially on a background of intellectual and language impairment, and sensory processing disorder is not considered a DSM-V diagnosis (24, 49). The range of co-occurring neurodevelopmental conditions highlights the importance of systematic neuropsychological assessment, to provide optimal, individualised support.

With regards to genotype-phenotype correlations, there was little evidence to indicate that genetic variants were closely associated with specific phenotypes. Of the 17 participants who shared the same variant, considerable heterogeneity emerged in intellectual, language, speech, and medical presentations.

The health and medical profile in *CDK13*-related disorder was expanded here with our addition of 33 novel cases to the literature. Feeding problems had a significant impact in infancy and early childhood. Similarly, renal, urogenital, and musculoskeletal malformations,

and vision impairment were more common than cardiac malformations in our cohort who, as noted earlier, may have been a more biased group. Cryptorchidism was present in our cohort (38% of males), having been recently described in individuals with pathogenic *CDK13* variants (14).

We are the first to characterise sleep disturbances in *CDK13*-related disorder, highlighting prevalent insomnia features. Sleep quality and duration can negatively impact receptive and expressive language skills (50).

Rouxel & colleagues (14) linked anxiety with *CDK13*-related disorder in 50% of their cohort (all >7 years). Anxiety disorder was also present in our cohort, although less prevalent (17.5%, all >8 years bar one 5-year-old). The median age of Rouxel et al.'s cohort was markedly older (median age=12 years) than our cohort (median age=7 years). Hence, without additional in-depth and longitudinal research, it is difficult to implicate *CDK13* as causative for anxiety.

Neuropsychological assessments are recommended to assess cognitive abilities, given the incidence of ID and other neurodevelopmental conditions. Likewise, occupational and physiotherapy are warranted as fine and gross motor impairment was ubiquitous. Lastly, speech pathology services should be sought to implement AAC in early childhood, and then provide targeted speech and language therapy (e.g., evidence-based CAS therapy) when verbal speech develops.

In conclusion, we characterise speech and language in *CDK13*-related disorder and identify CAS as a common feature. Until this study, CAS had only been described in one individual (ID 27) in the literature (13, 14). Specific speech and language diagnoses reflect the neurobiological underpinnings and associated linguistic implications of a disorder. The profile of speech, language and ID, on the background of significant health disorders,

emphasises the importance of comprehensive, multidisciplinary assessment and intervention for individuals with *CDK13*-related disorder.

Data availability statement: The datasets generated and analysed during this study are not publicly available because participants have not given permission for data to be made public but may be requested from the corresponding author (ATM) who could go back to the participants to request data sharing. Genotypic data were submitted to Decipher (https://decipher.sanger.ac.uk/).

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Author contributorship statement

LDM: generated data, analysed data, interpreted data, wrote manuscript

OV: generated data, analysed data, interpreted data, revised manuscript

EF: analysed data, interpreted data, revised manuscript

FR: generated data, analysed data, revised manuscript

LF: generated data, analysed data, revised manuscript

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ATM: designed and conceptualised study, directed project, generated data, analysed data, interpreted data, wrote manuscript.

Ethical approval

Ethics approval was obtained from the Royal Children's Hospital, Melbourne, Human Research Ethics Committee (HREC 37353A). Adult participants and caregivers of child participants provided informed consent to participate in the study and for results of this study to be published.

Competing Interests

The authors declare no conflicting interests.

Figure legends

Figure 1. Lollipop chart of *CDK13* missense variants in this cohort.

16 different missense variants present in the 37 participants with missense variants in *CDK13*. (NM_003718)

Figure 2. The Vineland Adaptive Behaviour Scales domain scores of participants (n=36) with c.2525A>G, p.Asn842Ser missense variants (n=15) and other pathogenic variants (n=21).

The Vineland Adaptive Behaviour Scales Second and Third Edition (mean=100, SD=15) scores <70 are low/severe, 71-85 moderately low/moderate, >85 average/within normal limits (minimum score = 20, maximum score = 140). Domain scores for c.2525A>G, p.Asn842Ser

missense variants (indicated by the first box plot in each domain): communication (COM, mean=63.53), daily living (DLS, mean=55.93), socialisation (SOC, mean=61.20), motor skills (MOT, mean=67.20). Domain scores for all other variants (indicated by the second box plot in each domain): communication (mean=64.05), daily living (mean=58.38), socialisation (mean=68.33), motor skills (mean=57.95). There were no significant differences between the two groups for the four Vineland domains. Outliers = •, median = centre line, mean = x.

Figure 3. Social behaviour domains on the Social Responsiveness Scale Second Edition (T scores) (n=28).

Higher T scores indicate higher autistic traits (mean=60, SD=10, range 34-90). ≤59 social behaviour within normal limits, 60-65 mild difficulty, 66-75 moderate, ≥ severe. Social awareness (mean=65.5), social cognition (mean=64.3), social communication (mean=65.03), social motivation (mean=62.4), restricted interests and repetitive behaviour (mean=70.5). Individual data points = •, median = centre line, mean = x.

Figure 4. Motor speech disorders in assessed participants (n=22).

Figure 4a. Specific speech features in 8 individuals with dysarthria across speech dimensions (prosody, articulation, resonance, pitch, volume, quality) rated by the Mayo Clinic Dysarthria Classification System (Duffy, 2005).

Figure 4b. Specific speech features in 13 individuals with childhood apraxia of speech (CAS) rated by the ASHA CAS Technical Report protocol's diagnostic criteria (2007), operationalised by Mei et al (2008). DDK = diadochokinetic speech task (e.g., say 'pataka').