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Unique profile of academic learning difficulties in Wiedemann–Steiner syndrome

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Abstract

Background Wiedemann–Steiner syndrome (WSS) is a rare genetic disorder caused by heterozygous variants in *KMT2A*. To date, the cognitive profile associated with WSS remains largely unknown, although emergent case series implicate increased risk of non-verbal reasoning and visual processing deficits. This study examines the academic and learning concerns associated with WSS based on a parent-report screening measure.

Participants and Methods A total of 25 parents of children/adults with a molecularly-confirmed diagnosis of WSS (mean age = 12.85 years, SD = 7.82) completed the Colorado Learning Difficulties Questionnaire (CLDQ), a parent-screening measure of learning and academic difficulties. Parent ratings were compared to those from a normative community sample to determine focal areas in Math, Reading and Spatial skills that may be weaker within this clinical population.

Results On average, parent ratings on the Math (mean Z = -3.08, SD = 0.87) and Spatial scales (mean Z = -2.52, SD = 0.85) were significantly more elevated than that of Reading (mean Z = -1.31, SD = 1.46) (Wilcoxon sign rank test $Z < -3.83$, $P < 0.001$), reflecting relatively more challenges observed in these areas. Distribution of parent ratings in Math items largely reflect a positively skewed distribution with most endorsing over three standard deviations below a community sample. In contrast, distributions of parent ratings in Reading and Spatial domains were more symmetric but flat. Ratings for Reading items yielded much larger variance than the other two domains, reflecting a wider range of performance variability.

Conclusions Parent ratings on the CLDQ suggest more difficulties with Math and Spatial skills among those with WSS within group and relative to a community sample. Study results are consistent with recent case reports on the neuropsychological profile associated with WSS and with Kabuki syndrome, which is caused by variants in the related gene *KMT2D*. Findings lend support for overlapping cognitive patterns across syndromes, implicating potential common disease pathogenesis.

Keywords genetics/genetic disorders, KMT2A, learning disorders, math, spatial processing, Wiedemann–Steiner syndrome

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Introduction

Wiedemann–Steiner syndrome (WSS) is a Mendelian disorder of the epigenetic machinery (MDEM) caused by mutations in *KMT2A*. MDEMs are a highly penetrant group of neurodevelopmental disorders that result from germ-line mutations in genes encoding components of the epigenetic machinery that place, remove and interpret epigenetic or chromatin marks or otherwise remodel chromatin; *KMT2A* places an activating mark on histone H3 lysine 4 (Fahrner & Bjornsson, 2014). MDEMs exhibit shared phenotypic features, most commonly intellectual disability (ID) and growth abnormalities (Fahrner & Bjornsson, 2019). Cardinal features associated with WSS overlap with other MDEMs and include developmental delay and ID (Sheppard *et al.*, 2021), as well as growth retardation (Baer *et al.*, 2018; Jones *et al.*, 2012; Miyake *et al.*, 2016). In addition, hypertrichosis and dysmorphic facial features (Baer *et al.*, 2018; Jones *et al.*, 2012; Miyake *et al.*, 2016) distinguish WSS from most other MDEMs.

To date, the neurocognitive profile associated with WSS remains relatively unknown given lack of literature in this regard. The rarity of the syndrome, which has unknown prevalence or incidence estimates, likely contributes to challenges in prospective data collection and deep phenotyping of the disease. Investigations that included a review of past neurodevelopmental assessments completed by patients with WSS highlight a high rate of intellectual impairment and language/motor developmental delay (Chan *et al.*, 2019; Sheppard *et al.*, 2021) and language deficits with slightly stronger receptive than expressive communication skills (Chan *et al.*, 2019). However, both studies primarily focused on describing the range of intellectual functioning among affected individuals rather than a comprehensive overview of cognitive strengths or weaknesses. Notably, a recent case series suggest that those with WSS are more consistently impaired in non-verbal skills, whereas verbal skills are more variable (Ng *et al.*, 2022), albeit this study included a small sample. More systematic investigations are needed to understand the cognitive and behavioural phenotypes associated with WSS, which can inform targeted clinical and academic interventions.

Although also rare, there has been more cognitive research involving Kabuki syndrome (KS)—a MDEM caused by pathogenic variants of *KMT2D*, another related member of the KMT2 methyltransferases involved in methylation of histone 3 lysine 4 (H3K4) (Vallianatos & Iwase, 2015). Case studies and research investigations into KS have documented ID, better characterised by unique deficits in spatial processing, visuoconstruction and non-verbal skills (Harris *et al.*, 2019; Mervis *et al.*, 2005; Sanz *et al.*, 2010; van Dongen *et al.*, 2019). Sanz *et al.* (2010) reported a case study on a paediatric patient with KS using longitudinal objective data, whereby the child presented with relatively intact reading skills but persistent challenges with math achievement. It is possible that the underlying and persistent impairment in visuospatial abilities in affected individuals may contribute to poor math achievement, as seen in neurotypical youth (Lowrie *et al.*, 2017; Sella *et al.*, 2016; Simms *et al.*, 2016). Notably, the research involving humans and animal models with KS has suggested that the associated visuospatial and memory defects are indicative of disrupted neurogenesis of the hippocampus, particularly of the dentate gyrus (Bjornsson *et al.*, 2014; Harris *et al.*, 2019). If indeed anomalies in hippocampal development and ongoing neurogenesis are causative of the cognitive challenges observed in KS, the resulting aberrations in hippocampal–prefrontal circuits—one of the pathways within the complex interconnected network hypothesised to support math achievement (Peters & De Smedt, 2018)—may also contribute to increased challenges with early math acquisition among those with the syndrome (Menon, 2016a). Disruptions in these neural pathways may lead to cascading developmental effects on the early consolidation (Smith & Squire, 2009) and retrieval of math facts (Menon, 2016b). More cognitive research involving WSS and other MDEMS with similar affected epigenetic machineries such as KS are necessary to identifying common causative pathways for these diseases leading to better research and eventual clinical treatment trials, in addition to informing early special education intervention services to support affected individuals.

Accordingly, this study examines learning challenges (Reading, Math and Spatial skills) observed among individuals with WSS (5–33 years of

age) based on parent ratings on a paediatric academic screening inventory—the Colorado Learning Difficulties Questionnaire (CLDQ). In light of emergent evidence suggestive of some overlap in non-verbal and visuoperceptual deficits between WSS and KS (Ng *et al.*, 2022), it is hypothesised that those with WSS will yield relatively elevated ratings in Math and Spatial problems in contrast to Reading. Additionally, we anticipated greater reported difficulties in Math and Spatial domains in contrast to normative means from published community samples (Willcutt *et al.*, 2011).

Methods

Participants

This study involved a combination of (1) chart review of paediatric patients (N = 4) who were evaluated by the Department of Neuropsychology at Kennedy Krieger Institute (KKI) and followed by the Neurogenetics Clinic at KKI and/or the Epigenetics and Chromatin Clinic at Johns Hopkins Medicine and (2) a survey study with participants recruited through international patient advocacy groups for WSS (N = 21). A genetic diagnosis of WSS was confirmed for each participant, based on a review of molecular test results obtained by the authors. A total of 25 mothers of children with WSS were involved in this study (12 females with WSS, mean age of child = 12.85 years, SD = 1.82, range = 5.30–33.93), and all respondents identified as proficient in English. All were residents in the United States with the exception of three—one each from Australia, the Netherlands and Canada. As outlined in Table 1, a majority of patients had undergone whole exome sequencing (N = 20) and a truncating mutation (nonsense, N = 10; frameshift, N = 9). Most of the sample had a variant deemed pathogenic or likely pathogenic (N = 24). One participant had a missense variant that was classified as a variant of uncertain significance based on the reporting laboratory; however, clinical observations suggest the variant is likely pathogenic. Specifically, the patient's clinical features are consistent with a diagnosis of WSS, and the variant, which has not been reported in large population databases like Genome Aggregation database (gnomAD), occurred de novo. Additionally, a different amino acid substitution at the same position was previously reported pathogenic in a person with WSS (Baer

Table 1 Participant characteristics, genetic test results and parent-reported academic difficulties in a sample of individuals with Wiedemann–Steiner syndrome (WSS)

	WSS Sample
N	25
Mean age in years	12.85 (1.82)
(SD)[range]	[5.30–33.93]
Sex	12F
Intellectual disability	19
Genetic testing	
Inheritance	
De novo	19
Mosaic	2
Unknown	3
Pathogenicity	
Pathogenic	23
Likely pathogenic	1
Variant of uncertain	1
significance	
Mutation	
Missense	3
Splice Site	3
Nonsense	10
Frameshift	9
Test type	
Whole exome sequencing	20
Single gene panel	3
Cornelia de Lange	1
Research panel	1
CLDQ mean rating	
(SD)[range]	
Reading	3.02 (1.37) [1–5]
Math	4.44 (0.76) [2.4–5]
Spatial	4.09 (0.79) [2.5–5]
CLDQ Mean Z-score	
(SD)[range]	
Reading Z-score[B]	-1.31 (1.46) [−3.41 to 0.84]
Math Z-score[C]	−3.08 (0.87) [−3.71 to −0.76]
Spatial Z-score	−2.52 (0.85) [−3.51 to −0.79]

Z-scores are computed relative to community sample. Wilcoxon sign rank test revealed significantly lower math ($Z = -3.90$, $P < 0.001$) and spatial composites ($Z = -3.83$, $P < 0.001$) relative to reading composite. Difficulties with math were also more prominent than spatial deficits ($Z = -2.17$, $P = 0.03$).
CLDQ, Colorado Learning Difficulties Questionnaire.

et al., 2018). Of note, the pattern of results persisted when we excluded the data from the participant with a variant of uncertain significance; thus, we reported findings from the entire dataset.

Exclusion criteria primarily consisted of additional genetic conditions that could impact neurodevelopmental phenotype—including other chromosomal anomalies—that were previously identified. Data for children under the age of 5 years were not included in the final data analysis in line with prior publications supporting the clinical utility of CLDQ as an academic screening measure (Patrick *et al.*, 2013). This study was approved by the Institutional Review Board at Johns Hopkins University School of Medicine and in accordance with the Helsinki Declaration. Written informed consent and/or assent was obtained by patient's legal guardian and/or the patient prior to inclusion in the study.

Procedure

All caregivers completed a research intake questionnaire regarding their child's developmental history. Subsequently, these caregivers completed the CLDQ (Willcutt *et al.*, 2011), a screening instrument used in identifying risk for learning difficulties. This inventory was selected given prior studies have supported its clinical utility in screening for academic difficulties in multidisciplinary clinics that follows individuals of varying medical backgrounds and ID (Patrick *et al.*, 2013; Wolfe *et al.*, 2022). In rare diseases that are associated with a wide range of intellectual impairment such as WSS, comprehensive neuropsychological testing may be challenging as a function of comprehension skills, behaviour regulation and tolerance for testing. As such, screening measures such as the CLDQ can be useful in providing preliminary clues to refine assessment batteries and study aims across clinical and research settings.

Measures

Research intake form

All parents completed a research intake questionnaire that inquired their child's developmental and medical background. In this form, they reported if their child has a diagnosis of ID. Of the whole sample, 22 parents also provided dichotomous responses (yes/no) to a question regarding the presence of early concerns with their child's reading or math skills and the age in years when concerns emerged.

CLDQ (Willcutt et al., 2011)

The CLDQ includes six items that indexes risk for difficulties in Reading, four items in Spatial skills and five in Mathematics. Respondents are instructed to rate if they have seen the item description by their child based on a 5-point Likert scale (1 = *never/not at all*, 2 = *rarely/a little*, 3 = *sometimes*, 4 = *frequently/quite a bit*, 5 = *always/a great deal*). Previous studies examining CLDQ with objective academic achievement measures have supported its clinical utility in screening for those who may benefit from more comprehensive assessments to rule out learning disorders (Patrick *et al.*, 2013). Specifically, caregiver ratings on CLDQ reading, math and spatial scales were moderately correlated with the child's performance on related achievement (Reading $r = 0.64$, Math $r = 0.44$) and spatial measures (Spatial $r = 0.30$) (Willcutt *et al.*, 2011). The inventory scales have shown strong internal consistency (Cronbach's alpha = 0.80–90) and large effect sizes between clinical samples of individuals with reading/math disability and estimated population mean (Reading d = 1.80; Math d = 1.67) (Willcutt *et al.*, 2011).

Data strategy

Ratings were averaged within scales (Reading, Math and Spatial domains), with elevated ratings representing more observed learning difficulties. These scores were subsequently converted to standardised scores utilising published community psychometric data (Willcutt *et al.*, 2011) to determine the extent participants were rated above or below the normative mean, consistent with past research (Patrick *et al.*, 2013). Descriptive analyses were completed utilising SPSS 26.0 to determine the variance in learning difficulties reported and to examine if the data reflect a normal distribution or a strong trend towards significant challenges in these academic areas. Given the small sample and non-normally distributed data, Wilcoxon sign rank test was used to determine if more difficulties are

observed in select academic areas in the whole sample. Subsequently, the analysis was repeated with subgroups of those with ID or truncating mutations. Given the need to correct for multiple comparisons with smaller subsamples, we were more selective in examining reading and math contrasts.
Mann–Whitney *U* test was applied to determine if parent ratings differed as a function of a prior diagnosis of ID or truncating mutation (missense/splice site vs. nonsense/frameshift).
Benjamini–Hochberg correction with 5% false discovery rate was applied. All significant findings from the above analyses are reported.

Results

CLDQ Reading and Math composites across the whole sample

Throughout the following results, it should be noted that *elevated ratings* on the CLDQ and *lower standard scores* when compared to a community sample reflect greater learning problems. Based on parent report of diagnostic history, 19 participants (76%) out of our sample have a diagnosis of ID. Of the 22 caregivers who completed questions pertaining their child's history of academic concerns in our research intake questionnaire, approximately 54.5% reported

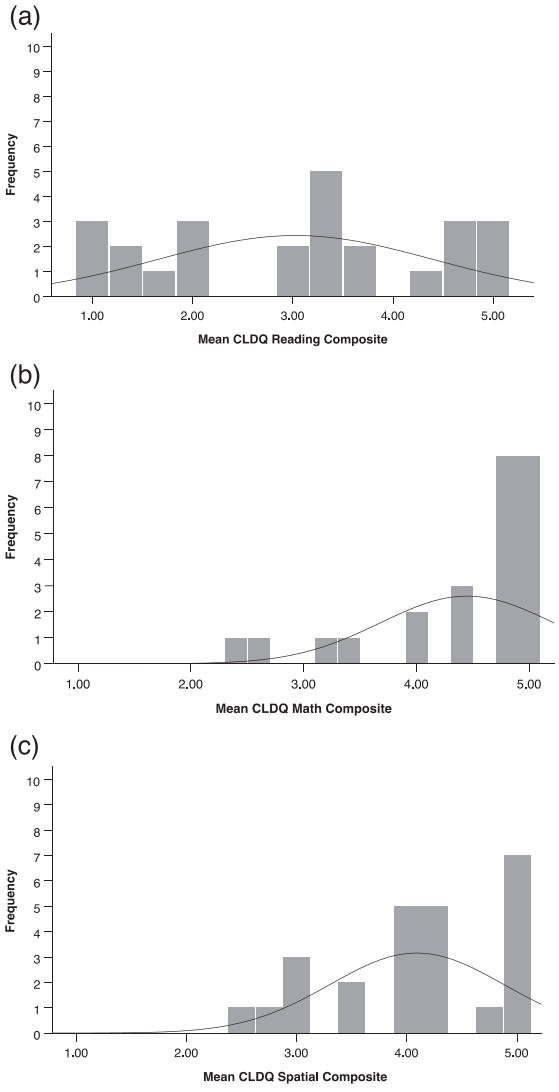

Figure 1. (a–c) Frequency distribution of average CLDQ Reading, Math and Spatial composites. Lower average composites reflect less challenges in the domain.

concerns with early reading skills, while 81.8% reported observing early math difficulties. McNemar's test revealed a marginal difference in the proportion of participants with observed math difficulties compared to reading challenges ($P = 0.07$). However, the average age of onset when caregivers start developing concerns with reading and math were comparable ($M_{Reading} = 4.63$ years; $M_{Math} = 5.00$ years).

Table 1 outlines mean Reading, Math and Spatial composites and standardised scores when compared to a large community sample (Willcutt *et al.*, 2011). Relative to Reading, average Math and Spatial composites were more elevated reflecting greater concerns in these areas (Wilcoxon rank test, Math $Z = 3.90$, $P < 0.001$, Spatial $Z = 3.83$, $p < 0.001$). Compared to the community sample, Reading composite was approximately 1.3 standard deviation below the normative mean, whereas Spatial and Math composites were about 2.5 and 3 standard deviations below the mean, respectively.

Figure 1 illustrates the non-normal distribution of mean Reading, Math and Spatial composites. Table 2 outlines the distribution of ratings (*never* to *rarely*, *sometimes*, *frequently* to *always*) across individual scale items. Shapiro–Wilk test revealed ratings across Reading items yielded non-normal distributions (Ws: 0.79–89, ps: <0.001–0.012). Inspection of the individual item data generally reflect a symmetric but flat distribution (difficulty with spelling, phonics and reading fluency; reading below grade level) (Reading skewness values: −0.39–0.21, kurtosis values: −1.18 to −1.60) with the exception of moderately negatively skewed responses for one item (need for extra instruction in school for reading) (Skewness value: −0.60; kurtosis value = −1.16) and another positively skewed distribution (difficulty learning letter names) (Skewness value: 0.42; kurtosis value = −1.31).

Parent responses across Spatial and Math items similarly did not show a normal distribution (Spatial: Ws: 0.59–0.86, ps: <0.001–0.003; Math: Ws: 0.57–0.76, ps < 0.001); however, these distributions were negatively skewed, reflecting more consistent elevated ratings of concerns across Spatial items (disorganised handwriting, disorganised/messy paperwork, difficulty lining numbers, immature

Table 2 Distribution of parent-ratings across Reading, Math and Spatial items on the Colorado Learning Difficulties Questionnaire

Composite Scales	Never to Rarely	Sometimes	Frequently to Always
Reading			
Difficulty with spelling	11/25 (44.0%)	5/25 (20.0%)	9/25 (36.0%)
Difficulty learning letter names	14/25 (56.0%)	3/25 (12.0%)	8/25 (32.0%)
Difficulty learning phonics	12/25 (48.0%)	4/25 (16.0%)	9/25 (36.0%)
Reads slowly	10/25 (40.0%)	5/25 (20.0%)	10/25 (40.0%)
Reads below grade or expectancy level	9/25 (36.0%)	2/25 (8.0%)	14/25 (56.0%)
Required extra help in school because of problems in reading and spelling	7/25 (28.0%)	3/25 (12.0%)	15/25 (60.0%)
Math			
Worse at math than at reading and spelling	1/25 (4.0%)	4/25 (16.0%)	20/25 (80.0%)
Makes careless errors in math, such as adding when the sign indicates subtraction	2/25 (8.0%)	3/25 (12.0%)	20/25 (80.0%)
Trouble learning new math concepts such as carrying or borrowing	1/25 (4.0%)	3/25 (12.0%)	21/25 (84.0%)
Difficulty learning early math facts	0/25 (0%)	3/25 (12.0%)	22/25 (88.0%)
Difficulty with math word problems	1/25 (4.0%)	2/25 (8.0%)	22/25 (88.0%)
Spatial			
Handwriting spatially disorganised	4/25 (16.0%)	4/25 (16.0%)	17/25 (68.0%)
Papers look disorganised or messy	2/25 (8.0%)	7/25 (28.0%)	16/25 (64.0%)
On arithmetic problems, has difficulty keeping numbers lined up in column	0/25 (0%)	6/25 (24.0%)	19/25 (76.0%)
Drawings look immature for his/her age	1/25 (4.0%)	3/25 (12.0%)	21/25 (84.0%)

drawing) (Spatial skewness values: −0.30 to −2.21, kurtosis values: −0.06 to 5.51) and Math items (worse at math than reading, makes careless errors in math, difficulty learning new math concepts, difficulty learning math facts, difficulty with math word problems) (Math skewness values: −1.04 to −1.85, kurtosis values: −0.15 to 2.34).

CLDQ Reading and Math composites among those with ID

CLDQ Reading and Math composites did not significantly differ as a function of prior diagnosis of ID (Intellectual Disability: $M_{Reading}$ = 3.19, $Z_{Reading}$ = −1.49; M_{Math} = 4.68, Z_{Math} = −3.35; No Intellectual Disability: $M_{Reading}$ = 2.50, $Z_{Reading}$ = −0.75; M_{Math} = 3.70, Z_{Math} = −2.23). Consistent with the trend observed in the whole sample, Math and Spatial composites were generally more elevated than Reading across ID (Intellectual Disability: Math Z = 3.46, $P < 0.001$, Spatial Z = 3.22, $P = 0.001$; No Intellectual Disability: Math Z = 1.75, $P = 0.080$, Spatial Z = 2.20, $P = 0.043$). All the contrasts survived Benjamini–Hochberg correction with the exception of the mild discrepancy in Reading and Math composites for those without ID, which may be due the very limited subsample size ($N = 6$).

CLDQ Reading and math composites in truncating mutations

As illustrated in Fig. 2, CLDQ Reading and Math composites did not significantly differ between truncating mutations (nonsense, frameshift) vs. non-truncating types (missense, splice site). Like the pattern observed in the whole sample, parent ratings reflect more challenges in Math and Spatial composites than in Reading regardless of truncating mutation (Non-truncating mutation: Math Z = 2.02, $P = 0.04$, Spatial Z = 2.03, $P = 0.04$; Truncating mutation: Math Z = 3.42, $P < 0.001$, Spatial Z = 3.24, $P = 0.001$). These results persisted multiple contrast corrections.

Discussion

To our knowledge, this is the first study to examine academic learning difficulties among a relatively large sample of individuals with molecularly confirmed diagnosis of WSS. Findings generally suggest increased math and spatial difficulties among those with WSS, whereas problems with reading may be more variable among those affected, regardless of ID status and truncating mutation. Interestingly, this pattern was observed both within sample and relative to a large community sample (Willcutt *et al.*, 2011). In brief, those with WSS may benefit from early comprehensive testing of academic and spatial skills, with particularly greater attention on early acquisition of math knowledge.

In line with a recent case series on neuropsychological profile of 10 paediatric patients with WSS (Ng *et al.*, 2022), whereby sight word reading was more intact and math computation and nonverbal skills were impaired, our study with a larger sample similarly showed consistent math and spatial difficulties as reported by parents, whereas reading skills were heterogeneous. As shown in Ng *et al.* (2022), the large variance in verbal and language skills in addition to increased risk for attention and executive functioning deficits may contribute to poor reading achievement. Specifically, poor language skills have been postulated to impact oral reading and phonological processing (phonological core deficit

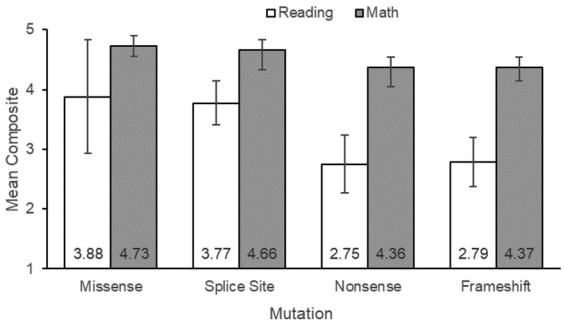

Figure 2. Average CLDQ Math and Reading composites across mutations. Mean ratings are labelled in the corresponding bars. Higher ratings reflect greater difficulties in the domain.

model; Stanovich & Siegel, 1994) (speech processing deficit model; Poeppel *et al.*, 2008), while impairment in attention and executive functions are hypothesised to affect reading fluency (Shaywitz & Shaywitz, 2008) and reading comprehension, respectively (Sesma *et al.*, 2009). Importantly, reading skills are supported by a complex neural network that involves left-sided frontal, occipitotemporal and temporoparietal regions (e.g. inferior frontal gyrus, supramarginal gyrus, middle temporal gyrus, superior temporal gyrus and ventral occipitotemporal cortex; for a review, see Ashkenazi *et al.*, 2013). Research on mouse models has shown neurogenesis of the prefrontal region may rely on the regulated methylation of H3K4, as ablation of *KMT2A* in this neural region was associated with deficits in working memory, anxiety and social cognition (Jakovcevski *et al.*, 2015). Thus, it is possible that the mutation in *KMT2A* that causes WSS triggers a downstream effect on the prefrontal development that may subsequently impact reading development. Given the high variability in reading skills among our participant sample, which include aspects of fluency, phonics and orthographic mapping, it remains challenging to determine which of these circuits or structures may be implicated in WSS. Consequently, prospective longitudinal research integrating repeated cognitive and academic evaluations, combined with imaging studies, is needed to better identify the specific neural pathways that are disrupted with the epigenetic imbalance secondary to loss of function of *KMT2A*.

Among our participant sample, Reading composite was on average 1.3 standard deviations below the normative mean of a community sample, which continues to suggest risk for learning challenges in this area albeit relatively reduced difficulties compared to math or spatial processing. These findings highlight importance of early neuropsychological testing for diagnostic clarification, and assistance in academic programming for children with WSS, as early introduction of personalised instruction tailored to the unique learning profile of those with ID are more likely to facilitate academic progress and improve quality of life.

Finally, our study findings—which showed homogeneity in reported math and spatial difficulties—combined with reported observations of non-verbal, visuospatial processing and executive functioning deficits in Ng *et al.* (2022) collectively suggest prefrontal and temporal, namely, hippocampal dysfunction among those with WSS. As reviewed by Menon (2016a), while the network dedicated to math achievement is complex, developmental investigations have pointed to the vital role of prefrontal–hippocampal circuit in early consolidation of math knowledge, which precedes the functional transition to hippocampal–neocortex pathways that support retrieval of math facts or strategies. In effect, our study findings combined with Ng *et al.* (2022) suggest deficiencies in H3K4 methyltransferase may result in a cascade of abnormal development in hippocampal and prefrontal regions, which in turn drives early onset and chronicity of math learning difficulties, as the typical functional neural reorganisation that underpins math achievement may not ensue. Additionally, a large body of evidence has shown strong associations between spatial and math skills, implicating the role of the parietal lobe, and more specifically, intraparietal sulcus (Cui & Guo, 2022; Hawes *et al.*, 2019). It has been postulated that the number line may be represented spatially (e.g. spatial visualisation of digits) and both spatial processing and arithmetic require visual working memory (e.g. mental manipulation of numbers or visual–spatial information) (Hawes & Ansari, 2020). Future investigations involving those with WSS should consider more comprehensive imaging and behavioural approaches to determine whether the mutation may result in aberrant functioning in this neural substrate and whether interventions directed at spatial training can indirectly enhance math learning as seen in typically developing children (Cheng & Mix, 2014).

Despite the novelty of our findings, several study limitations should be considered. Although WSS is a rare disease, larger samples are needed to ensure these findings are representative of the broader general population. Given our survey was conducted remotely, our sample may be biased towards families with more financial resources (e.g. access to electronic devices and reliable Internet). Inclusion of control samples, including those without medical or neurodevelopmental conditions or mental-age matched participants, will be critical for subsequent investigations dedicated towards characterising the cognitive phenotype of WSS. Comparison groups—including those with KS, other MDEMs with

similarly affected epigenetic machinery and specific learning disability in math without the genetic condition—will be necessary to identify common disease pathogenic and developmental factors. A developmental approach should be applied in examining academic learning trajectories. Specifically, our cohort composed of individuals ranging from preschool age to adulthood. While no association between participants' age and caregiver ratings was observed in our sample, the youngest and oldest participants in our study may have limited engagement in the academic curricula, resulting in biased responses. For example, caregivers of adults with WSS may have experienced difficulties rating their child's academic skills given they may not be engaged in school curriculum currently. Likewise, caregivers of young participants with significant academic and cognitive delays may struggle to respond to the inventory, as their children may not have mastered foundational pre-academic concepts that precede arithmetic skills. It should be noted that none of the caregivers indicated any problems with the survey completion to the authors. Regardless, applying a developmental and longitudinal framework (e.g. monitoring the academic progress of individuals with WSS of a similar age range) will be essential to understand the effect the mutation in *KMT2A* has on the maturation processes of related neural networks. Moreover, our sample may have been exposed to different academic instruction than the original community sample in Willcutt *et al.* (2011). Technology and computerised academic programmes may have been more heavily incorporated in school curriculum for our cohort as compared to the original community sample. Gathering a detailed history of and response to academic intervention services should be incorporated in research and clinical care for those with WSS.

Finally, it should be highlighted that our study primarily included a broad academic screening measure that is based on a parent report. To improve diagnostic sensitivity, clinicians who work with individuals with WSS across medical and research settings should integrate multi-informant inventories (e.g. parents vs. teachers), clinical observations, review of educational records and performance-based cognitive and academic testing to identify focal academic areas that require more extensive intervention services. By applying mixed methodological approaches in phenotyping efforts, we may begin to uncover the distinctive cognitive functions and dedicated neural regions that contribute to the unique academic profile in WSS.

In brief, results from this study show a unique pattern of spatial and math difficulties that was uniformly found across a relatively large sample of individuals with WSS. Longitudinal research that integrates interdisciplinary phenotyping approaches, control groups and cross-MDEM comparison groups such as KS is needed to ascertain whether common cognitive and academic difficulties are attributed to shared deficiency in epigenetic regulators.

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Conflict of interest

Dr. Bjornsson is a consultant for Mahzi Therapeutics. Dr. Harris receives research funding from Oryzon Genomics.

Ethics statement

This study was approved by the Institutional Review Board at Johns Hopkins University School of Medicine, and in accordance with the Helsinki Declaration. Written informed consent and/or assent was obtained by patient's legal guardian and/or the patient prior to inclusion in the study.

Data availability statement

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

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