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Associations Between Executive Functioning, Behavioral Functioning, and Adaptive Functioning Difficulties in Wiedemann–Steiner Syndrome

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Abstract

Objectives: Wiedemann–Steiner syndrome (WSS) is a neurogenetic disorder caused by heterozygous variants in *KMT2A*. Recent investigations suggest increased anxiety and behavior regulation challenges among those with WSS although the neurobehavioral phenotype remains largely unknown. This study aims to examine the pattern of and associations between executive functioning (EF) and behavior functioning among those with WSS.

Method: This study involved utilizing caregiver-report inventories (Behavior Rating Inventory of Executive Function 2nd Edition, BRIEF-2; Adaptive Behavior Assessment 3rd Edition, ABAS-3; Strengths and Difficulties Questionnaire, SDQ) to assess day-to-day behavior functioning among those with WSS ($N = 24$; mean age = 10.68 years, $SD = 3.19$). Frequency of clinical elevations in daily difficulties in EF, adaptive behaviors, and behavior regulation were reported. Correlations and hierarchical linear regressions were used to determine the relationships between EF with behavior and adaptive functioning.

Results: Out of our sample, 63% met clinical levels of executive functioning difficulties on the BRIEF-2, and 75% with Hyperactivity and 54% with Emotional Problems on the SDQ. In addition, 33% were rated >2 *SD* below the normative mean in overall adaptive functioning on the ABAS-3. Elevated ratings in BRIEF-2 Shift, reflective of challenges with mental flexibility, predicted more Emotional Problems and accounted for 33.5% of its variance. More difficulties in Emotional Control were related to greater adaptive deficits, accounting for 33.3% of its variance.

Conclusions: Those with WSS are at risk for EF deficits, hyperactivity, and emotional dysregulation. EF correlates with adaptive and affective behaviors, highlighting the promise of behavioral interventions to target cognitive flexibility, emotional awareness, and reactivity in this population.

Keywords: Executive control; Behavior regulation; KMT2A; Wiedemann–Steiner syndrome; Emotion regulation; Cognitive flexibility

Introduction

Wiedemann–Steiner syndrome (WSS) is a rare Mendelian disorder of the epigenetic machinery (MDEM), a group of neurodevelopmental disorders caused by variants in genes encoding epigenetic regulators (Fahrner & Bjornsson 2014). MDEMs often have overlapping features, which almost invariably include intellectual disability or developmental delay, although syndrome-specific phenotypes are becoming clear with growing research (Fahrner & Bjornsson, 2019). WSS is specifically caused by variants in *KMT2A*, a gene encoding an epigenetic writer, and is thought to disrupt H3K4 methylation and subsequently

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gene expression (Jones et al., 2012). Individuals with WSS present with short stature, hypertrichosis, and dysmorphic facial features along with variable other structural and functional manifestations (Baer et al., 2018; Jones et al., 2012; Miyake et al., 2016). Recent investigations on the cognitive phenotype have also shown that most individuals with WSS present with mild to moderate intellectual disability (Sheppard et al., 2021) with emergent evidence suggesting marked difficulties with visuospatial, visuoconstruction, and mathematic skills (Ng et al., 2022a, 2023) and executive functioning (EF; i.e., working memory) (Ng et al., 2022a), which are a set of higher order cognitive operations involved in goal-oriented behaviors (Nigg, 2017).

Given the rarity of WSS, which currently has an unknown prevalence, prospective research on the neurobehavioral phenotype has been limited. Considering the longstanding literature that has shown an increased risk of EF deficits based on parent-rating inventories (Memisevic & Sinanovic, 2014) and performance-based measures (Spaniol & Danielsson, 2022), behavioral problems such as aggression (Dekker et al., 2002), and internalizing symptoms including anxiety and withdrawn behaviors (Dekker et al., 2002) among individuals with intellectual disability, investigations to illuminate the behavioral presentation of those with WSS are warranted, as affected individuals may be vulnerable to challenges across behavioral and adaptive domains. Until recently, most investigations involving WSS largely rely on natural history data and review of medical records. Accordingly, characterizing the behavioral features associated with the syndrome was challenging given lack of controlled screening measures, heterogeneous clinical samples (e.g., wide age range), and mixed types of providers who provide diagnoses for developmental or mental health disorders. In the past year, prospective investigations have begun to shed light on elevated rate of attention-deficit/hyperactivity disorder (ADHD) symptoms (Durand et al., 2022; Ng et al., 2022b) in addition to anxiety among those with WSS (Durand et al., 2022; Ng et al., 2022c). Specifically, approximately a third of affected individuals in these studies similarly endorsed clinically significant levels of anxiety based on a screening tool, Screen for Child Anxiety Related Disorder. These studies also report nearly 40 to 80% of their sample struggled with clinical levels of hyperactivity and impulsivity (Durand et al., 2022; Ng et al., 2022c). However, given the fact both studies utilized limited proxy-report inventories and recruited individuals with WSS of a wide age range (ages 3–28 years, Durand et al., 2022; ages 4–33 years, Ng et al., 2022c), these trends need to be more closely examined with more controlled sample sets.

Notably, growing evidence from animal models and case studies respectively implicate impairment in EF in mice with Kmt2a deficiency in the prefrontal cortex (Jakovcevski et al., 2015) and among individuals with WSS (Ng et al., 2022a), which may be associated with their behavior and emotion regulation challenges (Ng et al., 2022b). Indeed, everyday difficulties with EF, as measured by caregiver-report inventories, have been linked to greater symptoms of internalizing symptoms among individuals with neurodevelopmental disorders such as autism spectrum disorder (Lawson et al., 2015), neurogenetic conditions such as Williams syndrome (Ng-Cordell et al., 2018), and individuals with PTEN mutation (Mirko et al., 2022). Among individuals with a history of developmental delay or intellectual disability, research suggests day-to-day EF deficits serve as a significant determinant of adaptive and challenging behaviors (Barton & McIntyre, 2022). Accordingly, systematic investigations are necessary to characterize and understand the association between cognitive and behavioral phenotypes associated with WSS, including EF impairment, with behavior functioning. By identifying the relationship between these profiles, clinical investigators can begin to devise and evaluate efficacy of targeted treatment approaches, offering more personalized care to those affected. In addition, these research efforts are critical in determining shared versus distinctive features of WSS as compared to other MDEMs with similar disrupted epigenetic machinery, which may illuminate disease pathogenesis.

Accordingly, this study focused on defining the neurobehavioral phenotype of individuals with WSS by using a combination of caregiver-informant inventories to examine EF, adaptive behaviors, and behavioral functioning (Behavior Rating Inventory of Executive Function 2nd Edition, BRIEF-2; Adaptive Behavior Assessment 3rd Edition, ABAS-3; Strengths and Difficulties Questionnaire, SDQ). Our clinical sample primarily included school-age children and adolescents with WSS to ensure observed results are not due to age-related effects. Given the high rate of developmental delay and intellectual disability (Sheppard et al., 2021), anxiety (Durand et al., 2022; Ng et al., 2022c), hyperactivity, and ADHD symptoms (Durand et al., 2022; Ng et al., 2022b) in the population, we anticipated a large proportion of our sample would meet clinical cut-off in Emotional Problem and Hyperactive scales on the SDQ and fall in the extremely low range in overall adaptive functioning on the ABAS-3. We similarly expected many of our participants to endorse clinical levels of EF difficulties on the BRIEF-2 because a recent case study revealed a high rate of affected individuals with impaired working memory (Ng et al., 2022a). However, no specific prediction was made regarding the association between everyday EF domains with adaptive and behavioral functioning, given the exploratory nature of this investigation and limited extant literature on this topic in intellectual disability.

Methods

Participants

Study participants were recruited through international patient advocacy groups for WSS ($N = 24$). All participants had a molecularly confirmed diagnosis of WSS, as genetic test records were reviewed by the authors. Respondents comprised of

mothers of children with WSS (10 females, mean age of child = 10.68 years, *SD* = 3.19, range = 6–16), who reported proficiency in English. All but three participants reside in the United States (one from the Netherlands and two from Canada). Racial and ethnic composition of our sample was non-Hispanic, White. A majority of patients had received their diagnosis through whole exome sequencing (exome sequencing, $N = 21$; research panel, $N = 1$; targeted panels, $N = 2$), the greatest proportion had truncating variants (missense, $N = 2$; splice site, $N = 2$; nonsense, $N = 11$; frameshift, $N = 9$), and nearly all variants were de novo ($N = 21$). One patient inherited the variant from a parent with 10% mosaicism and two had never had parental testing. It should be noted that of those with de novo occurrence, two are siblings and germline mosaicism in a parent is suspected. All but one participant had a variant classified as pathogenic or likely pathogenic. A subset of our sample (70%) completed the SDQ with other sleep measures in separate published study (Ng et al., 2022b).

Exclusion criteria included additional genetic anomalies that were previously identified through genetic testing. This study was approved by the Institutional Review Board at Johns Hopkins Medicine. Written informed consent and/or assent were obtained by the patient's legal guardian and/or the patient prior to inclusion in the study.

Procedure and Materials

All caregivers completed a set of caregiver-informant questionnaires commonly used to assess day-to-day behavior and adaptive functioning, in addition to a research intake questionnaire regarding their child's developmental history and sociodemographic background.

Behavior Rating Inventory of Executive Function 2nd Edition. On the BRIEF-2, caregivers rate their child's behaviors on a 3-point Likert scale (Never, Sometimes, or Often a Problem) (Gioia et al., 2015). This measure provides nine clinical scale areas that comprise three indices—Behavior Regulation (Inhibit, Self-Monitor), Emotion Regulation (Shift, Emotional Control), and Cognitive Regulation (Initiate, Working Memory, Plan/Organize, Task-Monitor, Organization of Materials). These scales yield the Global Executive Composite that represent the extent of day-to-day difficulty with EF. On the BRIEF-2, *T*-scores of ≥70 indicate clinically significant problems in the area, and 60 to 69 represent elevated difficulties or potentially clinically significant challenges.

Adaptive Behavior Assessment 3rd Edition. Caregivers were instructed to rate their child's performance of a behavior on a 4-point scale (0 = Is Not Able, 1 = Never When Needed, 2 = Sometimes When Needed, 3 = Always When Needed). The ABAS-3 (Harrison & Oakland, 2015) captures adaptive behaviors across three broad domains (Conceptual, Social, Practical), which are composed of multiple adaptive skill areas. The Conceptual domain indexes Functional Communication, Functional Academics, and Self-Direction. The Social domain comprises Social and Leisure scales. The Practical domain includes Community Use, Home Living, Health and Safety, and Self-Care. Collectively, the domain composites yield a General Adaptive Composite. Composite scores are standard scores ($M = 100$, $SD = 15$) whereas the adaptive skill areas are scaled scores ($M = 10$, $SD = 3$). In accordance to the inventory manual, descriptors for adaptive skills are based on the following scaled scores or standard score bands: scaled scores of 1–3 or standard scores of <70 are extremely low; scaled scores of 4–5 or standard scores of 70–79 are low; scaled scores of 6–7 or standard scores of 80–89 are below average; scaled scores of 8–12 or standard scores of 90–109 are average; and all other scaled or standard scores above these bands are above age level. Consequently, higher scores on the ABAS-3 reflect stronger adaptive skills.

Strengths and Difficulties Questionnaire. The SDQ (Goodman, 1997) requires the respondent to rate their child's behavior on a 3-point Likert scale (0 = Not true, 1 = Somewhat true, 2 = Certainly true). This study focuses on the three scales regarding behavior regulation—Emotional Problems, Conduct Problems, and Hyperactivity. Elevations in these scales reflect more problematic behaviors. The original three-band categorization (Within normal limits, Borderline, Clinically Significant) was applied to determine clinical significance of the resulting scale score. Notably, the clinical use of this tool among children with intellectual disability has been previously reported (Kaptein et al., 2008). Prior research supports the validity of the borderline cut-off of the SDQ (Rice et al., 2018). The SDQ was included in our study given its brevity as a screening tool and its applicability for a wide age range (age 2 to adulthood).

Data Strategy

Descriptive and frequency analyses were completed to determine the variance in adaptive, behavior and behavior functioning difficulties across inventories, and the proportion of our sample with impaired adaptive skills (ABAS-3) or clinical levels of

concern in EF (BRIEF-2). Of note, standard scores and scaled scores have means of 100 and 10 and standard deviation of 15 and 3, respectively. *T*-Scores have a mean of 50 with a *SD* of 10. Elevated composite scores on the ABAS-3 reflect stronger skills but more difficulty on the BRIEF-2 and SDQ. Average ratings that are >2 *SD* from the mean were considered impaired or meeting clinical cut-off on the ABAS-3 or BRIEF-3. One-sample *t*-test was utilized to determine behavioral and adaptive functioning, based on caregivers' ratings, of our sample relative to the normative mean. Friedman test was subsequently applied to assess behavioral trends within our sample.

To examine the association between EF (BRIEF-2 Behavior Regulation, Emotion Regulation, Cognitive Regulation Indexes) with adaptive functioning (ABAS-3 General Adaptive Composite) and behavioral functioning (SDQ Hyperactivity, Emotional Problems, Conduct Problems), bivariate correlations were used. Subsequently, Benjamini–Hochberg correction with 10% false discovery rate was applied. Results from the correlational analyses were used to determine the BRIEF-2 subscales (Shifting, Emotional Control) to include in hierarchical linear regression models with SDQ Emotional Problems and ABA General Adaptive Functioning as the outcome variables.

Results

Behavioral Functioning Among Children With WSS

Behavior Rating Inventory of Executive Function 2nd Edition

Caregivers' ratings revealed significant difficulties with EF, across all scales, compared to normative mean ($ps < .001$). Compared to the third of the sample with adaptive functioning challenges, over half our participants present with EF deficits (62.75%). Emotion Regulation (70.33%) was rated as the area with greatest concern, followed by Behavior Regulation (66.66%) and Cognitive Regulation (50.00%). Non-parametric tests and subsequent Bonferroni pairwise comparisons showed Emotion Regulation yielded more elevated ratings than Cognitive Regulation ($Z = 6.13$, $p = .04$). Over half our sample met clinical cut-off in problems with Shifting (e.g., ability to tolerate changes in transitions, routines) (66.66%) and Inhibit (e.g., ability to resist impulses) (58.33%). Even in those EF domains that had the lowest rate of impairment in our sample—Task monitoring, Organization of materials, and Task initiation subscales—still about one third of the sample met clinical cut-off for impairment (29.16–33.33%), highlighting the extent EF deficits permeate among those with WSS.

Adaptive Behavior Assessment 3rd Edition. Like EF results mentioned previously, adaptive functioning in our sample was rated more elevated, reflecting more difficulties, as compared to normative mean, an effect that was seen across scales ($ps < .001$). As outlined in Table 1, approximately a third of participants demonstrate deficits in Conceptual (29.16%) and Practical domains (33.33%). In contrast, fewer participants show difficulty in the Social domain (12.50%). Non-parametric tests showed this trend of relative strength in Social domain, as compared to the other areas, reached marginal significance ($\chi^2(2) = 4.61$, $p = .09$). Across adaptive skills, Self-Care (25%), Health and Safety (29.16%), and Functional Academics (33.33%) were rated lowest, reflecting areas of most difficulty. Social skills (8.33%) followed by Communication and Community Use (12.50%) had the least number of participants in the "extremely low" range.

Strengths and Difficulties Questionnaire. As outlined in Table 2, consistent with prior findings (Ng et al., 2022b), the majority of our sample (75%) met the clinical cut-off for Hyperactivity on the SDQ. About half our sample (55%) were rated in the clinical range for Emotional Problems and a third in Conduct Problems (30%).

Associations Between Executive Functioning With Adaptive and Psychosocial Skills

Given the exploratory nature of this study, bivariate correlations were utilized to first examine associations observed between EF domains (BRIEF-2 Behavior Regulation, Emotion Regulation, Cognitive Regulation Indexes) with overall adaptive functioning (ABAS-3 General Adaptive Composite) and behavioral functioning (SDQ Emotional Problems, Conduct Problems, Hyperactivity). Emotion Regulation Index was associated with greater Emotional Problems ($r = .59$, $p = .002$) and lower General Adaptive Composite ($r = -.51$, $p = .01$). Elevated ratings in Behavior Regulation Index were also correlated with greater Hyperactivity ($r = .52$, $p = .009$). Cognitive Regulation Index was linked to more Hyperactivity ($r = .44$, $p = .031$) and lower General Adaptive Composite ($r = -.42$, $p = .041$). All of these findings survived Benjamini–Hochberg correction with the exception of the association between Cognitive Regulation Index and General Adaptive Composite.

Table 1. Mean ratings on the Adaptive Behavior Assessment Scale 3rd Edition (ABAS-3) and Behavior Rating Inventory of Executive Function 2nd Edition (BRIEF-2)

	Total sample ($N = 24$)		
	Mean (*SD*)	Range	Percentage of sample significantly deviant (≥2 *SD*) from normative mean
ABAS-3			
Composites, standard score (SS)			
General Adaptive Composite	73.21 (10.46)	49–92	33.33%
Conceptual	74.88 (12.40)	49–99	29.16%
Social	79.58 (9.42)	54–91	12.50%
Practical	72.88 (11.64)	52–94	33.33%
Subscales, scaled score			
Communication	6.25 (2.67)	1–13	12.50%
Community Use	5.92 (2.37)	1–9	12.50%
Functional Academics	5.54 (2.85)	1–10	33.33%
Home Living	5.88 (2.55)	1–11	16.66%
Healthy and Safety	5.08 (2.56)	1–10	29.16%
Leisure	5.71 (2.27)	1–9	20.83%
Self-Care	5.12 (2.72)	1–9	25.00%
Self-Direction	5.17 (2.25)	1–10	20.83%
Social	6.50 (1.86)	1–9	8.33%
BRIEF-2			
Composites, *T*-score			
Global Executive Composite	73.58 (8.71)	57–88	62.75%
Behavior Regulation Index	71.33 (8.37)	54–87	66.66%
Emotion Regulation Index	73.79 (10.37)	53–90	70.33%
Cognitive Regulation Index	68.63 (8.24)	52–83	50.00%
Subscales, *T*-score			
Inhibit	70.54 (9.08)	51–84	58.33%
Self-Monitor	68.08 (7.42)	58–79	37.50%
Shift	74.71 (11.78)	44–90	66.66%
Emotional Control	69.42 (9.46)	46–84	45.33%
Initiate	65.33 (7.57)	52–84	33.33%
Working Memory	69.71 (9.53)	50–85	45.33%
Planning/Organization	66.75 (8.27)	50–79	37.50%
Task Monitoring	66.25 (7.01)	54–77	29.16%
Organization of Materials	61.75 (9.71)	45–77	29.16%

Note. Standard score has a mean of 100 with a *SD* of 15. Scaled score has a mean of 10 with a *SD* of 3. *T*-Score has a mean of 50 and a standard score of 10. Higher scores on the ABAS-3 reflect stronger adaptive skills whereas elevated ratings on the BRIEF-2 reflect greater difficulties in the specified area. On the BRIEF-2, *T*-scores of 60–69 reflect elevated or at-risk concerns with the executive function, whereas *T*-scores ≥70 indicate clinically significant concern. The proportion of our sample with impairment in adaptive and executive skills refers to the participants with standard score of <70 or scaled score <4 on the ABAS-3, or *T*-score >70 on the BRIEF-2.

Table 2. Mean ratings on the Strength and Difficulties Questionnaire (SDQ)

	Total sample ($N = 24$)		
	Mean (*SD*)	Range	Percentage of sample in the clinically significant range
SDQ			
Emotional Problems	4.41 (2.82)	0–9	54.33%
Conduct Problems	2.95 (1.65)	0–8	29.16%
Hyperactivity	7.75 (1.87)	0–10	75.00%

Note. SDQ items are rated on a 3-point Likert scale with 0 = not true to 2 = certainly true. Elevations in SDQ subscales reflect greater difficulties in the specified area. Based on the original 3-band categorization, total score of 5–10 reflects clinically significant difficulty in Emotional Problems, 4–10 in Conduct Problems, and 7–10 in Hyperactivity.

Hierarchical linear regression showed that Behavior Regulation and Cognitive Regulation subscales were not strong predictors for Hyperactivity (Variance Inflation Factor: 1.41–2.88, Tolerance: 0.38–0.70). Given our small sample size, low statistical power likely contributes to poor detection of predictors. In addition, regression models showed significant associations

Table 3. Multiple linear regression models (standardized betas) showing the independent association between BRIEF-2 Emotion Regulation Index (Shifting, Emotional Control) with SDQ Emotional Problems and ABAS-3 Adaptive Functioning

	Emotional Problems		General Adaptive Composite
	Standardized betas (*T* value)		Standardized betas (*T* value)
Shifting	0.43 (2.04)*	Shifting	−0.04 (0.18)
Emotional Control	0.25 (1.22)	Emotional Control	−0.55 (2.54)*
R^2	0.38*	R^2	0.33*
F	6.43**	*F*	5.26*

*$p \leq .05$. **$p < .01$.

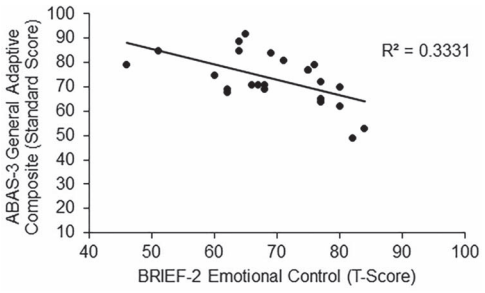

Fig. 1. The association between BRIEF-2 Emotional Control with adaptive functioning (ABAS-3 General Adaptive Composite).

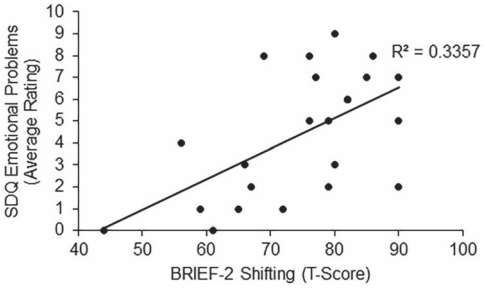

Fig. 2. The association between BRIEF-2 Shifting with affective behaviors (SDQ Emotional Problems).

between Emotion Regulation Index subscales and behavioral/adaptive functioning difficulties with low multicollinearity (Variance Inflation Factor: 1.00–1.52, Tolerance: 0.66) (see Table 3). Specifically, Emotion Regulation Index subscales (Shifting, Emotional Control) contribute to 38% and 33% of the variance in Emotional Problems and General Adaptive Functioning, respectively. Deficits in Shifting, representing poorer mental flexibility, was the only predictor of Emotional Problems ($\beta = 0.43$, $t = 2.04$, $p = .05$), whereas poor Emotional Control was related to more impaired General Adaptive Functioning ($\beta = -0.55$, $t = 2.54$, $p = .02$), each individually contributing to 33% of the variance (Figs. 1 and 2). It should be noted that regression models yielded the same resulting determinants when age was accounted for.

Discussion

Key findings from this study implicate profound EF challenges, particularly mental flexibility, in daily life among children with WSS. Day-to-day EF deficits were associated with emotional problems and poorer adaptive behaviors. These patterns of results are in part consistent with past research linking deletion of Kmt2a in mice with working memory defects and anxiety in addition to disrupted synaptic plasticity of prefrontal and striatal neurons (Jakovcevski et al., 2015). Notably, investigations link day-to-day EF to the structural development of the frontal lobe in children undergoing typical development (Mahone et al., 2009) and among youth with ADHD (Hai et al., 2022). In another longitudinal study, poor day-to-day executive functioning in preschool age, reflected by high scores on the BRIEF, was associated with greater structural connectivity of the nucleus accumbens and orbitofrontal cortex; however, this association was uniquely observed among a cohort of typically developing children who demonstrated low executive function performance in later childhood (Chan et al., 2022). This trend observed in this subset of youth was posited to reflect reduced functional flexibility in the reward network (which includes the nucleus accumbens

and orbitofrontal cortex), namely, less restrictive recruitment of these neural substrates based on the situational or task demands. Taken together, it is possible that loss of function variants in *KMT2A* may have a downstream effect on the maturation of frontal-limbic and frontal-subcortical circuits, which undergirds the processing and regulation of emotions and reward-related stimuli (Paulesu et al., 2010; Bierman & Torres, 2016), and subsequently results in increased risk for psychopathology and disruptive behaviors (Ng et al., 2022b, 2022c).

Interestingly, a larger proportion of our sample were rated to show significant difficulties with executive functioning difficulties as compared to adaptive functioning (i.e., >2 *SD* from the normative mean). Within BRIEF-2 scales, Behavior Regulation and Emotion Regulation Indexes were areas rated particularly more elevated and thus representing areas more likely to cause daily challenges than the Cognitive Regulation Index. Given recent investigations highlight a tendency for those with WSS to focus on routines and repetitive behaviors (Ng et al., 2023), it is possible that this discrepancy in parent ratings may represent their responsivity to learning adaptive behaviors through repetition and organized schedules (e.g., a daily routine with embedded activities of daily living such as grooming or bathing). In addition, caregivers may be biased and focus more on dysregulated mood and behaviors when completing the BRIEF-2, as these are often less predictable and challenging to prepare for in advance, particularly when combined with their significant problems with hyperactivity/impulsivity (Ng et al., 2022b). It is also possible that parents provide low ratings for items comprising the Cognitive Regulation subscales (i.e., "Never" demonstrate a problematic behavior), when their child has not been given opportunities to show this skill. For example, those with WSS and more severe cognitive impairment may not receive homework assignments regularly as part of their modified curriculum, and as such do not have the opportunity to show problems with task organization. More research is needed to support the clinical utility of BRIEF among those with a range of cognitive and adaptive functioning levels (Shishido et al., 2020).

Importantly, the identified associations between EF with affective symptoms (low mood, anxiety) and adaptive behaviors highlight potential areas for behavioral intervention to support quality of life in those with WSS. Interventions directed at specific EF skills—such as mental flexibility and emotion reactivity—may improve everyday ability to manage stress or negative affect and execute functional life skills. Indeed, extant literature among typically developing children underscore the promise of EF interventions and prevention programs on daily functioning, including the development of academic skills and behavior regulation in the school context (Bierman & Torres, 2016). Facilitation of EF development can also be promoted through school curricula (e.g., Tools of the Mind) (Riggs et al., 2006), supporting caregiver–child interactions that promote child's autonomy (Meuwissen & Carlson, 2019), mindfulness exercises (Zelazo, 2020), and physical activities (Diamond & Lee, 2011). Developmental research has also shown scaffolded practice across a variety of settings can optimize generalization of EF skills (Zelazo, 2020). In turn, improved EF may indirectly bolster engagement in adaptive behaviors and emotion regulation strategies, and functional independence more broadly. The vast majority of intervention/prevention research involving EF are focused in typically developing children. A growing body of literature has begun to show that modifications in the environment (Mazzoli et al., 2021) and integration of regular physical activity (Hartman et al., 2017) may lead to benefits in executive functions such as improved working memory among individuals with cognitive impairment or intellectual disability; however, research on the efficacy of in-person and/or remote cognitive training on attention and EF among individuals with intellectual disability has yielded mixed results with some reporting some improvement across cognitive functions and behavior regulation (Torra Moreno et al., 2021) and others reporting poor treatment effects (Kirk et al., 2017). Recent reviews of literature pertaining to cognitive training with individuals with intellectual disability and/or genetic conditions highlight discrepant findings on intervention efficacy may stem from heterogeneous clinical samples, medical history, study methodology, and the cognitive load required for treatment engagement (Corti et al., 2022; Kirk et al., 2015). Although emerging literature shows that EF similarly contributes to functional challenges among those with neurodevelopmental disorders regardless of intellectual deficits (Schmitt et al., 2019), more intervention research involving those with developmental disabilities is necessary to determine if these behavioral approaches are equally effective.

Although our study focused on daily EF based on caregiver-rating inventories, more research utilizing performance-based EF measures and multiple informants is necessary to identify focal EF domains that are at greater risk in WSS. Prior studies have shown that behavior rating inventories of EF do not correlate well with performance on EF measures (Soto et al., 2020). Whereas EF rating scales generally show strong relationships with behavior functioning, academic behaviors have been found to be more consistently associated with test measures of EF (Soto et al., 2020), highlighting that different EF metrics are variably linked to outcome factors. Consequently, investigations focused on EF and frontal lobe functioning should integrate both assessment methods, as each offers unique and complementary information.

Cross-syndrome investigations involving other MDEMs with shared pathogenic variants in the *KMT2* family members such as Kabuki syndrome and Kleefstra syndrome 2 are necessary to shed light on the role of epigenetic regulatory processes involved in neurogenesis of the frontal cortical networks. Interestingly, an emerging body of literature suggests common cognitive and behavioral features between those with WS and Kabuki syndromes, including visuospatial and visuoconstruction deficits paired with elevated anxiety (Kalinousky et al., 2022; Ng et al., 2022a, 2022c). Further research directly comparing neuropsychological

profiles between these two MDEMs is warranted, as identifying overlapping features may offer clues on shared disease origins and on viable outcome markers for the development of clinical trials. In addition, subsequent investigations should consider inclusion of control samples, such as unaffected siblings without the genetic condition or cognitive impairment, to account for shared gene variance and social environment to some degree. In effect, multiple comparison groups are needed to delineate whether observed behavioral trends are unique to WSS, or MDEMs with similar affected epigenetic apparatus.

Prospective investigations should consider our study limitations in their research design. First, as noted previously, research and clinical assessments of EF should incorporate multiple proxy respondent inventories and performance-based measures. Multiple informants should be considered in the assessment of EF to determine whether deficits are observed across settings or in select environments—information that can be utilized to individualize behavioral intervention approaches. Recent studies highlight differences in reported severity of EF difficulties in self-ratings of individuals with autism spectrum disorder as compared to caregiver's ratings, implicating self-report add key cognitive information beyond the parents' observation (Kenworthy et al., 2022). Altogether, multiple informants are needed to determine if EF difficulties result from the effect of select social settings or experiences on the child's cognitive development, or through an interaction of both organic dysfunction and select environments. In addition, to examine the relationships between EF (based on behavior) with structural and/or functional alterations of the frontal lobe networks, imaging methods such as functional MRI or MRI are warranted. Notably, our sample lacked diversity in racial and ethnic composition. Socioeconomic data, including family income and caregiver education, were not collected. Future research should consider expanding collaborations with family-led organizations such as the Wiedemann-Steiner Syndrome Foundation to optimize recruitment efforts and work toward ensuring equitable access to clinical research participation, which may yield more representative clinical samples. Finally, subsequent studies should incorporate assessments of intelligence and expand recruitment to include other comparison groups (e.g., youth with intellectual disabilities without genetic anomalies, siblings of participants with WSS, age-matched typically developing children). Given intellectual functioning estimates were not obtained, it is unclear if the associations observed between EF and behavioral/adaptive measures differ as a function of cognitive impairment, which in turn suggests that efficacy of EF interventions may vary. Follow-up research in this area may want to consider examining our observed relationships across those with WSS and different severity of intellectual disability, in addition to control samples with varying cognitive levels and without the genetic condition.

In brief, our study results add to the limited behavioral research on WSS by offering preliminary evidence of marked EF difficulties associated with the disease, which are related to problems with internalizing and adaptive behaviors. Behavioral interventions targeting EF skills such as mental flexibility may indirectly support functional independence and reduce risk for psychopathology. More systematic research with multiple comparison groups, mixed research methods, and diverse informant inventories are necessary to determine whether the observed trends are unique to this Mendelian disorder or common among those with similar affected epigenetic machinery.

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Conflict of Interest

H.T.B. is a consultant for Mahzi Therapeutics. J.H. receives research funding from Oryzon Genomics.

Authors' contributions

Rowena Ng (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing—original draft, Writing—review & editing), Hans Bjornsson (Writing—review & editing), Jill Fahrner (Writing—review & editing), and Jacqueline Harris (Methodology, Writing—review & editing)

Data availability

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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