Case Report

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Proposed Phenotype for Females with a *SETD5* Gene Variation: A Case Report

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Abstract

Background: SET domain containing 5 (*SETD5*) gene variants have been linked to developmental delays, craniofacial abnormalities, and intellectual disability (ID). Prior research examining the phenotypic presentation of individuals with *SETD5* variations has been based largely on a male-dominated cohort and case studies. Evidence of a possible protective effect in females prompts the need for additional research on the neuropsychological presentation of females with a *SETD5* variation. The current study aims to initiate this effort by discussing the neurocognitive profile of a right-handed 7-year-old Caucasian female with a diagnosed *SETD5* variation.

Methods and findings: The patient was referred for neuropsychological evaluation due to reported reading, writing, and fine motor difficulties. She presented with distinct dysmorphic features: head circumference <1st percentile, syndactyly of toes, clinodactyly of fifth fingers, and a long smooth philtrum with thin upper lip. Interpersonally, the patient was highly social. Cognitive testing revealed low average intelligence, with intact verbal/language functioning and impaired nonverbal/fluid reasoning abilities. Deficits were also observed in fine motor dexterity, visuomotor integration, attention, and broad academic achievement. The patient was ultimately referred for genetic testing, which revealed a de novo *SETD5* frame shift variant resulting in a truncation of the gene copy near the end of the gene.

Conclusion: This case study provides evidence for phenotypic differences between males and females with *SETD5* gene variations. While males exhibit ID, females may present with significant deficits in nonverbal reasoning skills. Females may also display more fully developed social skills and a lack of repetitive stereotyped behaviors. Further research is warranted to clarify the unique presentation among females with *SETD5* variations to better inform diagnosis and treatment planning.

Keywords: *SETD5*; Phenotype; Mutation; Neurocognitive; Genetic; Gender

Introduction

Considerably fewer females have been identified with *SETD5* mutations as compared to males. Consequently, *SETD5* research to date has been limited to male-dominated cohorts, as evidenced by the 2014 and 2015 studies involving 996 individuals in which 93.8% were male and 6.2% were female [1-7]. Additional male-dominated cohort and case studies reported that some females with a *SETD5* gene variant presented with subclinical features, including facial dysmorphism and motor delay [2,5,8-10]. While research thus far has proposed that females can pass along the mutation to their male children, two prior case studies reported families with affected children who inherited *SETD5* alterations from their unaffected mothers [5]. High penetrance has been observed in males and varying phenotypic expression has been observed in females. Since females may present with subclinical features and the mutation is not always inherited from female carriers, findings from the current research suggest a protective factor exists among females with *SETD5* [3,5]. Further exploration is warranted to clarify the neuropsychological intricacies of females with a *SETD5* mutation.

The Current Case Description

Herein we discuss a female patient with a *SETD5* gene mutation. Consistent with the literature, subclinical features were identified that differed from the typical presentation of males with *SETD5*. Clinical features that may be distinct to females were further noted. This case study reinforces the possibility of a protective factor in females with *SETD5* variations while proposing a neurocognitive profile which might be applied to this population. Although the intricate details of genome sequencing and expression are imperative to investigate, we propose that it is equally important to examine the neuropsychological and phenotypical features of the *SETD5* variation. Evaluation of these additional domains may assist providers in more accurate diagnoses, allow for timely referral for genetic testing, and facilitate comprehensive access to support services.

Informed consent was obtained prior to submitting de-identified details of the case for publication. The patient was a 7-year, 5-month-old Caucasian, cisgender, right-handed female who was referred for neuropsychological evaluation due to reported reading, writing, and fine motor difficulties. A thorough review of her developmental and medical history was significant. Prenatal and perinatal development indicates dearly term birth (37-weeks), low birth weight (5-pounds, 0-ounces; 2,268-grams) and jaundice (resolved with phototherapy). Motor delays (crawling at 13-months, first steps at 19-months), sensory differences (seeking proprioceptive input), broad academic difficulties, and social skill concerns (difficulty initiating play with same-aged peers) were further reported. The following domains were assessed: intelligence, academic achievement, attention/emerging executive functioning, language, motor/visual-motor integration, learning/memory, and social-emotional/behavioral/adaptive functioning.

Results

The patient was evaluated over two office visits. She was appropriately dressed and groomed. Her euthymic affect was consistent with her reported happy mood. Orientation was within normal limits, while hearing and vision appeared adequate for testing purposes. Although speech and nonverbal interactions were age-appropriate, nuances in social interaction were observed; the patient exhibited a number of prosocial traits, such as her gregarious personality, heightened social engagement, and loquacious demeanor. She also presented with distinct dysmorphic features, including: head circumference of 48 cm (<1st percentile for age group), syndactyly of toes, clinodactyly of fifth fingers, and a long smooth philtrum with thin upper lip. With the assistance of scaffolding, structured breaks, and the implementation of a reinforcement program, the patient's impulsive, hyperactive, and inattentive behaviors were sufficiently managed. Appropriate motivation and cooperation were noted throughout the evaluation and results of embedded effort measures as well as parent and teacher report questionnaires indicated no concerns with validity. Therefore, results were considered to be a valid estimate of the patient's neuropsychological functioning, and the evaluation revealed deficits in the following domains: nonverbal/fluid reasoning, motor/visual-motor integration, attention/emerging executive functioning, and academic achievement (**Table 1**) and additional scores available in **Supplemental Materials 1.**

Nonverbal/fluid reasoning

Nonverbal/fluid reasoning abilities (WISC-V FRI, 5th percentile) were very low for her age and highly discrepant from her intact verbal intellect (WISC-V VCI, 50th percentile). A relative difference was also revealed between measures of spatial cognition (WRAVMA Matching, 12th percentile) and language functioning (e.g., WIAT-III Oral Language Index, 34th percentile). These results collectively highlight a lateralized pattern of left hemisphere strengths and right hemisphere weaknesses, which was also noted on learning and memory tasks (ChAMP Lists Immediate, 75th; ChAMP Objects Immediate, 37th percentile). This clinical presentation, characterized by a significant disparity between verbal and nonverbal skills, was consistent with a diagnosis of an Other Specified Neurodevelopmental Disorder, associated with Impairment in Nonverbal Processing [11].

Table 1 List of select neuropsychological test scores.

Measures	Standard Score	Percentile
WISC-V		
Full Scale IQ (FSIQ)	81	10th
Verbal Comprehension Index (VCI)	100	50th
Fluid Reasoning Index (FRI)	76	5th
WRAVMA		
Drawing	79	8th
Matching	82	12th
ChAMP		
Lists Immediate	110	75th
Objects Immediate	95	37th
NEPSY-II		
Auditory Attention	-	-
Combined	60	< 1st
Commission Errors	(raw = 6)	2nd - 5th
Statue Total Correct	75	5th
Visuomotor Precision Combined	70	2nd
KCPT-2		
Detectability	61	< 1st
Perseverations	< 55	< 1st
WIAT-III		
Oral Language Index	94	34th
Total Reading Index	64	1st
Pseudoword Decoding	69	2nd
Mathematics Index	70	2nd
Written Expression Index	67	1st
CTOPP-2		
Phonological Awareness Index	85	16th

Motor/visual-motor integration

Despite a history of participation in several interventions aimed at improving motor functioning (e.g., physical therapy), deficits were evident across measures of visual-motor integration (WRAVMA Drawing, 8th percentile) and fine motor dexterity (NEPSY-II Visuomotor Precision Combined, 2nd percentile). Poor posture and pencil grip were also observed. Neuropsychological findings along with the patient's reported

history of motor delays and continued motor deficits warranted a diagnosis of a Developmental Coordination Disorder (DCD), a neurodevelopmental presentation involving difficulty performing tasks that involve both large and small muscles (e.g., catching balls, fastening buttons, handwriting) [11,12].

Attention/emerging executive functioning

Results revealed deficits in the patient's attention (NEPSY-II Auditory Attention Combined, <1st; KCPT-2 Detectability, <1st percentile), and qualitative observations were significant for on-task distractibility and behavioral dysregulation. Parents and teacher endorsed multiple criteria on rating scales assessing attention deficits, indicating similar behavioral concerns across settings. As commonly observed in children with attention deficits, impairment was also revealed across measures of emerging executive functioning (i.e., higher order processes associated with planning, organization, response inhibition, and cognitive flexibility) [13]. Her response inhibition in particular was significantly below age expectation (NEPSY-II Auditory Attention Commission Errors, 2nd-5th percentile; NEPSY-II Statue Total Score, 5th percentile; KCPT-2 Perseverations, <1st percentile); she had difficulty staying seated, and she was noted to impulsively grab testing stimuli. Taken together, the patient's presentation was consistent with a diagnosis of an Attention-Deficit/Hyperactivity Disorder, Combined Presentation (ADHD-C) [11].

Academic achievement

Broad-based deficits were noted across academic domains, with significant impairment in mathematics (WIAT-III Mathematics Index, 2nd percentile), written expression (WIAT-III Written Expression Index, 1st percentile), and reading (WIAT-III Total Reading Index, 1st percentile). Of note, phonological processing skills were variable (WIAT-III Pseudoword Decoding, 2nd percentile; CTOPP-2 Phonological Awareness, 16th percentile), indicating a potential relative strength within her academic achievement profile, possibly related to her language strengths.

Discussion

The multifaceted and intricate nuances of the *SETD5* gene mutation have been widely studied in males, yet the phenotypical presentation in females is largely unknown due to its lack of representation in the literature [2,3,5,8-10]. Although a possible protective effect has been identified in females with a *SETD5* mutation (i.e., subclinical features), no studies to date have initiated a female-based cohort or case study extending this hypothesis. Results of our evaluation suggested a possible genetic underpinning to the patient's neuropsychological profile, which prompted timely referral to a medical geneticist. While chromosome microarray was reportedly normal, genetic exome sequencing was read as demonstrating a de novo *SETD5* frameshift variant resulting in a truncation of the gene copy near the end of the gene (p.S1286LfsX37; c.3855dupC). Therefore, findings from the current case report provide initial support for a generalized phenotypical profile of females with a *SETD5* gene variant. Results also offer additional evidence for an underlying protective factor based on gender. An array of both clinical and subclinical characteristics were identified; some domains present as less severe or comparable to males with *SETD5*, and some domains are distinctive to females with *SETD5*.

Although *SETD5* mutations frequently express ID [3], results from the patient's neuropsychological evaluation are consistent with the current literature, suggesting a possible protective effect [2] in which females may present with nonverbal/fluid reasoning impairment rather than global ID. Muotri et al. (2018) reported a 69.0% incidence of predominantly male individuals with *SETD5* mutations presenting with speech impairment/delay [3]. Conversely, speech/language acquisition was identified as the patient's protected developmental factor, and current language functioning was within the average range for her age. Nonverbal processing weaknesses can impact other domains (e.g., attention, fine motor skills, executive functioning, math achievement, and social acumen), all of which were identified as areas of concern in the patient's reported history or test results [14,15]. Primary deficits in visual and tactile perception can further disrupt problem solving, hypothesis testing, and concept formation [14]. Therefore, females with *SETD5* mutations should be screened for discrepancies within their intellectual profiles (i.e., verbal vs. nonverbal) to mitigate potential functional impacts associated with nonverbal/fluid reasoning deficits (e.g., learning and applying visual concepts, identifying and understanding general themes or inferences in text and in conversations) [14,15].

Findings from the current study parallel existing literature, which approximates 71.4% of individuals with *SETD5* mutations present with motor impairment/delay [3]. Deficits in visual-motor integration as well as fine motor skills were noted, which aligned with the patient's delayed motor development and persistent functional difficulties involving motor coordination (e.g., eating, riding a bicycle, handwriting). In general, forming letters when writing, throwing or catching balls, and buttoning buttons can be difficult for individuals with broad motor deficits, placing them at risk for academic, social, and/or adaptive weaknesses [12]. Results of the current case study strengthen findings from prior literature, indicating that females and males with *SETD5* mutations likely share a common phenotype within the domain of motor functioning and should be monitored for secondary impacts of this weakness.

While children with developmental motor difficulties more often present with attention concerns (comorbidity rate as high as 50%) [16], researchers have yet to explore the association between *SETD5* and attention deficits. However, results from the current case report revealed broad attentional and emerging executive functioning impairments across multiple domains, including sustained attention, impulse control, and hyperactivity. As these building blocks support higher level cognition (e.g., cognitive flexibility, critical thinking, novel problem solving, abstract reasoning,

organization and planning), deficits may result in functional impairments on learning and academic achievement, which were observed in this patient [13]. Taken together, evidence from this study suggests that females with *SETD5* may be at risk for exhibiting behaviors consistent with ADHD. Moreover, given the high comorbidity of ADHD with other impairments identified in *SETD5* literature [3] (e.g., ID [17], ASD [18]), it is possible that males may present with attention difficulties as well, which should be considered as diagnostically independent of their primary diagnoses.

Academic achievement has not been addressed in prior *SETD5* research; yet, the core risk factors of both males and females with *SETD5* mutations suggest this population has an increased chance of developing co-occurring academic difficulties [11,15,19-21]. Accordingly, the patient's phenotypical, developmental, and complex neuropsychological risk factors likely contributed to reading, writing, and mathematics deficits, which were all below age level. Although the academic achievement of males with *SETD5* has not been examined, both males and females would likely benefit from school-based evaluations to rule out comorbid specific learning disorders and identify targeted support services.

Approximately 23.8% of individuals with *SETD5* mutations present with autistic-like features, which was defined in a previous study as impaired social interaction, communication deficits, stereotyped behaviors, and difficulty with eye contact [3]. Notwithstanding the patient's social differences (i.e., difficulty initiating play), hyper-sociability was observed interpersonally; the patient maintained conversation and interest during a variety of non-preferred activities, rapport was quickly established with the examiner, and heightened preference toward social engagement was demonstrated. Although females with ASD tend to present with more covert internalizing behaviors and fewer overt externalizing behaviors than males with ASD [22], the patient's social presentation was more fully developed compared to high functioning females with ASD. Thus, results from the current study indicate that females with *SETD5* mutations may exhibit more intact social skills along with a lack of repetitive stereotyped behaviors compared to males with *SETD5* mutations.

The purpose of this case report was to present phenotypical and neurocognitive features of a female with a *SETD5* mutation in an effort to propose a profile that might inform diagnosis, treatment planning, and recommendations. Consistent with prior findings, this study reinforces support for an underlying protective factor in females with *SETD5* variations. Within this population, we propose females may present with intact verbal comprehension, which is a departure from males who often present with broad impairment across intellectual domains [2]. In contrast, motor delays and persistent motor difficulties may be consistent across genders [3]. Given the high comorbidity with other risk factors, attention difficulties are a likely sequelae of *SETD5* in both females and males. Low academic achievement is another probable ramification of *SETD5* across genders for differing reasons. Certainly, the implications of both male (i.e., ID, ASD) and proposed female (i.e., nonverbal/fluid reasoning weakness) factors as well as potentially shared traits (i.e., motor deficits) can impact academic achievement. However, the broad level of the patient's impairments implies underlying developmental differences beyond what would be expected by the identified neuropsychological disorders alone. Finally, social presentations appear to vastly differ between males and females, with males adopting more ASD-like features and females presenting with relatively more developed social skills and prosocial behaviors. The identification of the *SETD5* gene mutation in females and the intentional exploration of a potential neuropsychological profile provides patients and clinicians with an etiological foundation for the constellation of neuropsychological challenges faced within this unique population.

Limitations

Results from the current case report include limitations that should be taken into account. Findings from a single patient cannot be generalized to an entire gender. While prevalence of *SETD5* within the generalized population is rare, and even less frequently observed among females, further research among a predominantly female cohort with *SETD5* mutations is needed to clarify the nuances of their collective phenotypical and neuropsychological presentation compared to males with *SETD5*. Moreover, elucidation of the male neuropsychological presentation is needed, as prior studies did not include neuropsychological diagnoses as part of their design. Rather, participants met inclusion criteria for studies based on pre-existing genetic conditions, and neuropsychological conditions were noted based on past medical records.

High comorbidity among neuropsychological sequelae exists within the clinical population (e.g., ADHD and ID). As such, it is difficult to differentiate whether characteristics of this patient's neurocognitive profile (i.e., nonverbal/fluid reasoning weakness, motor impairment, attention deficit, low academic achievement) are unique to this case or can be generalized to the female *SETD5* population. Therefore, future studies with a cohort of *SETD5* patients should control for the aforementioned comorbidities as well as gender to determine the effect size of each independent diagnostic consideration.

Future Directions

Results of the current case report have important implications for practitioners and researchers. Because females with *SETD5* may present with subclinical features, an underlying genetic condition is inherently more difficult to detect at face value. For example, school-age children with the patient's developmental risk factors (i.e., early term, low birth weight) are more likely to present with motor impairments, attention deficits, and reduced academic performance [23]. As applied to our study, while the patient exhibited similar neuropsychological impairments, certain characteristics of her presentation (i.e., language strengths/fluid reasoning deficits, dysmorphic features, social presentation) are not typically expected in children with the aforementioned risk factors alone, prompting the need for genetic testing. The proposed

female *SETD5* phenotype outlined in our case report offers clinicians a better understanding of the shared and variable traits based on gender within this population. It will be important for clinicians to act on reasonable suspicion of a genetic etiology in an effort to provide families with a fuller diagnostic picture as well as identify risk factors for associated family members.

As noted by Szczałuba et al. [10], while early studies of *SETD5* mutations were uniformly reported as de novo in origin, evidence of familial transmission has also been observed. Little is known regarding the inheritance patterns of *SETD5*, yet it is generally understood that there is higher penetrance in males. While risk factors among males with a *SETD5* variation are fairly understood, no consensus exists regarding the severity to which females are impacted by *SETD5*. Therefore, once the mutation is discovered within a family's gene pool, we propose that all children should be screened for the genetic variant regardless of gender. Similar to carriers of other heritable conditions (e.g., cystic fibrosis), this knowledge will allow families increased preparedness for gene expression in future biological children, which will ultimately inform family planning. Earlier identification of *SETD5* may better prepare families for associated risk factors of the mutation, which will promote advocacy for affected children and timely implementation of support services.

Conclusion

SETD5 mutations were discovered within the last decade and little is known regarding their genetic expression, heritability, and neuropsychological presentation. This case report provides evidence for nuances in phenotypical expression based on gender and, consistent with the current literature, supports a protective effect in females. While males tend to exhibit more global intellectual and social difficulties, females may present with nonverbal/fluid reasoning deficits; however, motor delays and risk factors for attention deficits and low academic achievement appear to be consistent across genders. Although further research is required to clarify the implications of the *SETD5* phenotype, clinicians should consider referral to a medical geneticist for more accurate and timely diagnoses to better inform family planning and treatment considerations.

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