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Caregiver-reported characteristics of children diagnosed with pathogenic variants in *KDM5C*

Hayden A. M. Hatch[1] | Molly H. O'Neil[2] | Robert W. Marion[3] | Julie Secombe[1,4] | Lisa H. Shulman[2]

[1]Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, Bronx, New York, USA

[2]Rose F. Kennedy Children's Evaluation and Rehabilitation Center, The Children's Hospital at Montefiore, Bronx, New York, USA

[3]Division of Genetic Medicine, The Children's Hospital at Montefiore, Bronx, New York, USA

[4]Department of Genetics, Albert Einstein College of Medicine, Bronx, New York, USA

Correspondence
Lisa H. Shulman, Rose F. Kennedy Children's Evaluation and Rehabilitation Center, The Children's Hospital at Montefiore, 1225 Morris Park Avenue, Bronx, NY 10461.
Email: lshulman@montefiore.org
Julie Secombe, Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, 1410 Pelham Parkway South, Bronx, NY 10461.
Email: julie.secombe@einsteinmed.org

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Abstract

Loss of function variants in the lysine demethylase 5C (*KDM5C*) gene account for approximately 0.7–2.8% of X-linked intellectual disability (ID) cases and pose significant burdens for patients and their caregivers. To date, 45 unique variants in *KDM5C* have been reported in individuals with ID. As a rare disorder, its etiology and natural history remain an area of active investigation, with treatment limited to symptom management. Previous studies have found that males present with moderate to severe ID with significant syndromic comorbidities such as epilepsy, short stature, and craniofacial abnormalities. Although not as well characterized, females have been reported to predominantly display mild to moderate ID with approximately half being asymptomatic. Here, we present caregiver-reported data for 37 unrelated individuals with pathogenic variants in *KDM5C*; the largest cohort reported to-date. We find that up to 70% of affected females were reported to display syndromic features including gastrointestinal dysfunction and hearing impairment. Additionally, more than half of individuals reported a diagnosis of autism spectrum disorder or described features consistent with this spectrum. Our data thus provide further evidence of sexually dimorphic heterogeneity in disease presentation and suggest that pathogenic variants in *KDM5C* may be more common than previously assumed.

KEYWORDS
autism, CJ-XLID, epilepsy, intellectual disability, *KDM5C*

1 | INTRODUCTION

Affecting approximately 2% of the population, intellectual disability (ID) disorders comprise a set of heterogeneous conditions that affect cognitive function and adaptive behavior (Leonard & Wen, 2002; van Bokhoven, 2011). ID presents before the age of 18 and is often accompanied by additional clinical features such as facial dysmorphism, short stature, epilepsy, and autism spectrum disorder (ASD) (Ropers, 2010; Tzschach et al., 2006). Although the causes of some forms of ID, such as fragile X syndrome and Down syndrome, are well-known, others remain elusive (Antonarakis et al., 2020; Ciaccio et al., 2017; Hagerman et al., 2017; Kazemi et al., 2016). Due to recent advances in genetic testing such as whole exome and whole genome sequencing, variants associated with rarer forms of ID are being discovered. However, despite the profound burdens that many of these disorders present, the pathogenesis and natural history of these disorders require further investigation.

Loss of function variants in the transcriptional regulator *KDM5C* (*JARID1C/SMCX*) are associated with a heritable form of X-linked ID (XLID) known as Claes–Jensen-type X-linked ID (CJ-XLID/MRXSCJ; OMIM# 300534) (Claes et al., 2000; Jensen et al., 2005). KDM5C belongs to a family of transcriptional regulators which are best known for altering chromatin by enzymatically removing trimethyl groups from lysine 4 of histone 3 (H3K4me3) (Liefke et al., 2010; Liu et al., 2014; Secombe et al., 2007; van Oevelen et al., 2008). H3K4me3 is a covalent histone modification that is found at high

levels near transcription start sites and is highly correlated with chromatin accessibility and active gene expression (Greer & Shi, 2012). Consistent with this, studies in model organisms such as mice and *Drosophila* have shown that loss of orthologous *KDM5C* genes results in significant changes to gene expression in brain tissue (Belalcazar et al., 2021; Hatch et al., 2021; Scandaglia et al., 2017; Vallianatos et al., 2020; Vallianatos & Iwase, 2015; Zamurrad et al., 2018). In humans, *KDM5C* is predominantly expressed in cortical brain structures and skeletal muscle (Jensen et al., 2005; Xu et al., 2008), suggesting that it plays critical roles in both tissues (Iwase et al., 2016; Mariani et al., 2016; Vallianatos & Iwase, 2015; Vallianatos et al., 2020). Although the exact mechanisms by which pathogenic variants in *KDM5C* contribute to ID remain an area of active investigation, it is likely that KDM5C regulates transcriptional outputs to promote proper neuronal development and cognitive function.

To date, 45 unique pathogenic variants in *KDM5C* have been reported in the literature, representing an estimated 0.7–2.8% of all XLID cases (Carmignac et al., 2020; Gonçalves et al., 2014; Ropers & Hamel, 2005). Genome wide association studies and pedigree analyses reveal that hemizygous males with loss of function variants in *KDM5C* display higher rates of moderate to severe ID compared to females who generally display mild to moderate ID (Carmignac et al., 2020). Additionally, comorbid syndromic features such as short stature, microcephaly, craniofacial dysmorphism, epilepsy, and ASD occur more frequently and with greater severity in males compared to females, with all males reported to-date presenting with syndromic features (Carmignac et al., 2020; Gonçalves et al., 2014). Interestingly, a recent study showed that only 52% of females heterozygous for pathogenic *KDM5C* variants are symptomatic (Carmignac et al., 2020).

Here, we present caregiver-reported data for 37 individuals with *KDM5C* variants; the largest cohort reported to-date. Since not all individuals with *KDM5C* variants have CJ-XLID, we refer to this condition as *KDM5C*-related disorder (*KDM5C*-RD). Data were collected via an IRB-approved survey that was distributed *via* a Facebook support group to caregivers of children previously diagnosed with pathogenic variants in *KDM5C*. Of the 37 individuals with *KDM5C-RD*, 33 (89%) had received genetic testing and a molecular diagnosis confirming a *KDM5C* variant. Notably, 35% of children in our study were affected females, up to 70% of whom were reported to present with syndromic features such as short stature and gastrointestinal and hearing difficulties. Additionally, more than half of individuals reported a diagnosis of ASD or features consistent with this spectrum, suggesting a possible link between *KDM5C* dysfunction and ASD. Although the data presented here are caregiver-reported, they provide additional evidence that this disorder may be more common, with *KDM5C*-RD females presenting with a greater frequency of syndromic features than previously reported. We additionally provide data illustrating the frequent use of specialized educational services among children with *KDM5C*-RD, a parameter which has been underreported in the literature. Together, the results from our survey provide additional insight into the apparently heterogeneous and sexually dimorphic presentation of *KDM5C*-RD and suggest that further research is needed to better understand how pathogenic variants in *KDM5C* contribute to disease etiology.

2 | METHODS

The objective of the study was to examine the clinical phenotype of individuals with *KDM5C*-RD, with an emphasis on identifying caregiver-reported differences in disease presentation between males and females. Participants were recruited through an active Facebook group for caregivers of individuals with previously diagnosed variants in *KDM5C* (https://www.facebook.com/groups/kdm5c). A message was sent to all members of the Facebook group inviting them to participate, with an explanation of the study and a web link to the online questionnaire.

Prior to beginning the survey, participants were asked to complete an electronic informed consent form. To be eligible, the participant had to consent that they were the caregiver of an individual with a previously diagnosed *KDM5C* variant, as confirmed *via* genetic testing. If the respondent was a caregiver to more than one individual with this condition, they were asked to complete the questionnaire for each affected child. The caregiver questionnaire consisted of 33 multiple choice and open-ended response questions. Items collected were caregiver-reported demographic data, as well as genetic, medical, developmental, and behavioral diagnoses. Therapeutic services received by the individual were also collected to determine the extent to which *KDM5C*-RD affected adaptive behaviors. Medical records were not obtained as part of this study, in accordance with IRB guidelines. The study received approval by the Albert Einstein College of Medicine Institutional Review Board on February 14, 2020 (IRB2020-11134).

3 | RESULTS

Thirty-seven caregivers responded to the questionnaire. The median age of mothers at the time of questionnaire completion was 40 (range 27–61 years) and of fathers was 41 (range 25–70 years) (Table 1). Of the 37 individuals reported to have *KDM5C-RD*, 33 (89%) had previously received genetic testing and a molecular diagnosis confirming a *KDM5C* variant. Caregivers for the remaining 11% of individuals did not complete this question, yet had previously consented to being a caregiver of a child with *KDM5C-RD*. Of all individuals, 24 were males (64.9%) and 13 were females (35.1%). The median age of individuals in the study group at the time of survey was 8 years (range 3–27 years) and median age at *KDM5C*-RD diagnosis was 6 (range 3 months–27 years). Four individuals with *KDM5C*-RD had a family member who had also been diagnosed with *KDM5C*-RD or was known to be heterozygous for a *KDM5C* variant.

The most commonly reported diagnoses and characteristics related to muscles, nerves, or coordination ($N = 27$, 87.1%), as well as vision ($N = 23$, 74.2%), and short stature/impaired growth ($N = 22$, 70.9%). Additional characteristics included hypertonia, trouble walking/moving, tremors, difficulty balancing, and carpal tunnel syndrome. Seizures, which are commonly cited in the *KDM5C* literature, were reported in nine of the children (29.0%). Fifteen children (48.4%) were reported to have phenotypes related to the gastrointestinal tract,

TABLE 1 Frequency of clinical features in males and females based on caregiver report. Fisher's exact test; *$p = 0.050$; **$p = 0.045$. All other data comparing male and females are nonsignificant

	Total		Male		Female	
	Count	Percentage	Count	Percentage	Count	Percentage
Child's sex	$N = 37$		$N = 24$		$N = 13$	
Male	24	65%	24	100%	0	0%
Female	13	35%	0	0%	13	100%
Age						
Age of mother (mean ± *SD*)	41 ± 8		42 ± 8		40 ± 7	
Age of father (mean ± *SD*)	43 ± 8		43 ± 7		43 ± 10	
Child's current age (mean ± *SD*)	9 ± 6		10 ± 6		8 ± 5	
Child's age at diagnosis (mean ± *SD*)	8 ± 6		8 ± 6		8 ± 5	
Medical diagnoses	$N = 31$		$N = 21$		$N = 10$	
Short stature/growth problems	22	71%	15	71%	7	70%
Seizures	9	29%	7	33%	2	20%
Physical	27	87%	20	95%	7	70%
Hearing	4	13%	1	5%	3	30%
Vision	23	74%	17	81%	6	60%
Heart	3	10%	1	5%	2	20%
Lungs	0	0%	0	0%	0	0%
Gastrointestinal	15	48%	9	43%	6	60%
Kidney-related	1	3%	0	0%	1	10%
Allergies	9	29%	6	29%	3	30%
Skin	8	26%	4	19%	4	40%
Teeth	12	38.71%	9	43%	3	30%
Other	9	29%	6	29%	3	30%
Developmental conditions	$N = 31$		$N = 21$		$N = 10$	
Developmental delay	30	97%	20	95%	10	100%
Intellectual disability	23	74%	17	81%	6	60%
Autism or autism spectrum disorder	9	29%	8	38%	1	10%
Language impairment	30	97%	20	95%	10	100%
Learning disability	21	68%	14	67%	7	70%
Fine motor delays	27	87%	19	90%	8	80%
Gross motor delays	25	81%	18	86%	7	70%
Cerebral Palsy	3	10%	3	14%	0	0%
Hearing impairment	4	13%	1	5%	3	30%
Visual impairment	14	45%	10	48%	4	40%
Other	7	23%	3	14%	4	40%
Type of developmental delay	$N = 30$		$N = 20$		$N = 10$	
Mild	6	20%	2	10%	4	40%
Moderate	9	30%	5	25%	4	40%
Severe*	15	50%	13	65%	2	20%
Borderline	0	0%	0	0%	0	0%
Type of intellectual disability	$N = 23$		$N = 16$		$N = 7$	
Mild**	6	26%	2	12%	4	57%
Moderate	8	35%	6	38%	2	29%
Severe	9	39%	8	50%	1	14%
Borderline	0	0%	0	0%	0	0%

(Continues)

TABLE 1 (Continued)

	Total		Male		Female	
	Count	Percentage	Count	Percentage	Count	Percentage
Type of learning disability	$N = 20$		$N = 13$		$N = 7$	
Language	2	10%	1	8%	1	14%
Math	0	0%	0	0%	0	0%
Mixed	18	90%	12	92%	6	86%
Emotional behavioral conditions	$N = 27$		$N = 18$		$N = 9$	
Attention deficit hyperactivity disorder	15	56%	12	66%	3	33%
Oppositional defiant disorder	6	22%	4	22%	2	22%
Anxiety disorder	9	33%	5	27%	4	44%
Mood disorder or depression	8	30%	5	27%	3	33%
Obsessive compulsive disorder	3	11%	2	11%	1	11%
Schizophrenia	0	0%	0	0%	0	0%
Aggressive behavior	11	41%	6	33%	5	56%
Self-injurious behavior	8	30%	7	39%	1	11%
Severe tantrums	7	26%	3	17%	4	44%
Elopement	4	15%	3	17%	1	11%
Other	5	19%	2	11%	3	33%
Child treated with meds for emotional/psychiatric issues?	$N = 30$		$N = 20$		$N = 10$	
Yes	16	73%	12	60%	4	40%
No	14	27%	8	40%	6	60%
Receive early intervention?	$N = 31$		$N = 21$		$N = 10$	
Yes	29	94%	19	90%	10	100%
No	2	6%	2	10%	0	0%
Which EI services?	$N = 30$		$N = 20$		$N = 10$	
Speech therapy	28	93%	18	90%	10	100%
Occupational therapy	21	70%	13	65%	8	80%
Physical therapy	24	80%	17	85%	7	70%
Feeding therapy	6	20%	3	15%	3	30%
Special instruction	7	23%	5	25%	2	20%
Applied behavioral analysis	5	17%	5	25%	0	0%
Other	11	37%	8	40%	3	30%
Child currently receiving special education services?	$N = 30$		$N = 20$		$N = 10$	
Yes	26	87%	17	85%	9	90%
No	4	13%	3	15%	1	10%
Child have an IEP?	$N = 29$		$N = 19$		$N = 10$	
Yes	25	86%	18	95%	7	70%
No	4	14%	1	5%	3	30%
Type of class	$N = 27$		$N = 18$		$N = 9$	
Mainstream	6	22%	3	17%	3	33%
Integrated co-teaching	9	33%	5	28%	4	45%
Self-contained	12	45%	10	56%	2	22%
Services received in school	$N = 26$		$N = 17$		$N = 9$	
Does not receive services in school	0	0%	0	0%	0	0%
Speech therapy	24	92%	15	88%	9	100%
Occupational therapy	19	73%	15	88%	4	44%
Physical therapy	14	54%	11	65%	3	33%

TABLE 1 (Continued)

	Total		Male		Female	
	Count	Percentage	Count	Percentage	Count	Percentage
Counseling	2	8%	2	12%	0	0%
SETSS/resource room	5	19%	3	18%	2	22%
504 accommodations	2	8%	1	6%	1	11%
1:1 paraprofessional	8	31%	8	47%	0	0%
Other	5	19%	3	18%	2	22%

Abbreviation: IEP, individualized education plan.

which included constipation and Crohn's disease. Nine of the children (24%) required tonsillectomy and/or adenoidectomy and five (14%) had myringotomy with tube placement.

Nonsignificant trends suggested that males were more likely than females to have physical challenges (95.2 vs. 70.0%), vision impairment (80.9 vs. 60.0%), short stature (71.4 vs. 70.0%), and seizures (33.3 vs. 20%). These trends also suggested that females were more likely to have hearing impairments (30.0 vs. 4.8%) and gastrointestinal impairments (60.0 vs. 42.9%).

In terms of achieving developmental milestones, caregivers reported that 96.8% ($N = 30$) of children with *KDM5C*-RD had a diagnosis of developmental delay and language impairment. Four caregivers reported that their children were nonverbal and four others specified that their children had a diagnosis of apraxia. Respondents also indicated high rates of ID ($N = 23$, 74.2%), fine motor delay ($N = 27$, 87.1%), gross motor delay ($N = 25$, 80.7%), and learning disability ($N = 21$, 67.7%) among their children. Although developmental delay was reported to be quite common in both males ($N = 20$, 95.2%) and females ($N = 10$, 100%), the extent of delay was significantly more severe in males than females (65 vs. 20%, $p = .05$). Caregivers reported that males were more likely to have a formal diagnosis of ID (80.9%) than females (60%), and that ID was significantly more likely to be severe (57 vs. 12%, $p = 0.05$). Language impairment was common in both males ($N = 20$, 95.2%) and females ($N = 10$, 100%), as was fine motor delay (90.5 vs. 80.0%), gross motor delay (85.7 vs. 70.0%), and learning disability (66.7 vs. 70.0%).

KDM5C-RD individuals were also reported to have emotional/behavioral diagnoses, with attention deficit hyperactivity disorder (ADHD) being the most commonly reported comorbid psychiatric condition ($N = 15$, 55.6%). This was twice as common in males than females (66.7 vs. 33.3%). Caregivers also reported aggressive behavior ($N = 11$, 40.7%), anxiety disorder ($N = 9$, 33.3%), depression/mood disorders ($N = 8$, 29.6%), and self-injurious behavior ($N = 8$, 29.6%). For males, 38.1% ($N = 8$) had a reported diagnosis of ASD compared to that of a single female (10%). Almost three quarters (73.3%) of the children were treated with medications for these conditions.

Caregivers described a variety of dysmorphic features/physical differences in their children with *KDM5C*-RD. Many mentioned a broad nasal bridge/forehead, abnormal head shape/size (e.g., macrocephaly and microcephaly), almond-shaped eyes, orodental abnormalities such as high palate and wide-spaced teeth), and thick hair. There were also two males with urologic abnormalities (one with hypospadias and another with undescended testes), five with foot abnormalities (e.g., hammer toe, leg length discrepancies, toe-walking gait) being reported in both sexes. One child was reported to have a diagnosis of atrial septal defect.

Most caregivers reported that their children received early intervention (EI) services ($N = 29$, 93.6%), including speech and language therapy ($N = 28$, 93.3%), physical therapy ($N = 24$, 80.0%), and occupational therapy ($N = 21$, 70.0%). Twenty-six children (86.7%) received special education services and 25 (86.2%) had an individualized education plan (IEP) in school. There was a nonsignificant trend suggesting that males were more likely to be in self-contained classrooms ($N = 10$, 55.6%) than females ($N = 2$, 22.2%), with females tending to be in mainstream classrooms (33.3 vs. 16.7%). Speech therapy was the most common service received in school ($N = 24$, 92.3%).

4 | DISCUSSION

We describe caregiver-reported medical diagnoses and characteristics of 37 children with *KDM5C*-RD, the largest cohort reported to-date. Although individual pathogenic *KDM5C* variants have been reported in a number of studies, few have described the behavioral, physical, cognitive, and psychological consequences of *KDM5C*-RD in a group of unrelated individuals (Abidi et al., 2008; Carmignac et al., 2020; Jensen et al., 2005; Rujirabanjerd et al., 2010; Santos-Rebouças et al., 2011; Tzschach et al., 2006; Vallianatos et al., 2018). Because this study solicited information through a Facebook support group, it is likely that our sample was biased, in terms of ethnic make-up, socio-economic status and disease severity. Of the 37 individuals with *KDM5C-RD*, 33 (89%) had received genetic testing confirming a *KDM5C* variant, although it should be noted that we do not know the molecular nature of these genetic changes. However, we rely on caregiver-reported genotypic and phenotypic data making it possible that our data may differ from that contained within patient medical records. Despite these potential caveats, given the low prevalence of *KDM5C*-RD and the variable expressivity of disease-causing *KDM5C* variants, our study provides much needed additional characterization of disease presentation. Understanding the diverse clinical manifestations of *KDM5C*-RD could provide valuable insight into disease etiology and progression.

As an X-linked disorder, *KDM5C*-RD has been shown in the literature to affect males at a greater rate and severity than females, with 90% (62/69) of males displaying ID and/or developmental delay compared to 51% (34/67) of females (Carmignac et al., 2020). Significantly, all reported males with pathogenic *KDM5C* variants have been shown to be symptomatic with features such as craniofacial abnormalities, epilepsy, and short stature. In contrast, only 52% of females have been shown to be symptomatic with similar, yet less severe, clinical characteristics (Carmignac et al., 2020). The difference in phenotypic penetrance and expressivity between males and females is thought to be attributed to the ability of *KDM5C* to partially escape X chromosome inactivation (XCI) (Horvath et al., 2013; Li & Carrel, 2008). XCI is a process that occurs in female mammals by which one of two X chromosomes is randomly inactivated and transcriptionally silenced during embryonic development. Indeed, previous in vitro studies have demonstrated that *KDM5C* lies within a nonpseudoautosomal region and is able to partially escape XCI at an expression level of approximately 40% compared to that on the active X (Li & Carrel, 2008). This partial escape has been shown to be attributed to sequence-specific properties that are intrinsic to the *KDM5C* locus (Horvath et al., 2013; Li & Carrel, 2008). It is through this unique mechanism, coupled with XCI skewing, that loss of function variants in *KDM5C* are thought to contribute to the usually milder and more variable phenotypic traits observed in females.

Similar to existing literature, caregiver data reported here suggest that pathogenic variants in *KDM5C* are strongly associated with developmental delay (reported in 96.8% of children) and ID (reported in 74.2%), with hemizygous males more severely affected intellectually than females. Features such as short stature, epilepsy, and craniofacial differences which have also been reported in the literature were similarly described among caregivers of both males and females in this sample. Additionally, the high number of children reported to have required tonsillectomy and adenoidectomy, as well as those needing myringotomy and tube placement, suggests that more research is needed to determine the impact of pathogenic *KDM5C* variants on otorhinolaryngologic health. It is also noteworthy that there was a nonsignificant trend toward females reporting to have more hearing impairments compared to males ($p = 0.08$). To our knowledge, this has not previously been documented in the literature and warrants additional exploration.

Psychological features associated with *KDM5C*-RD were also quite notable with comorbid ADHD, ASD, anxiety, mood, and self-injurious behaviors reported to occur with such regularity that nearly three-quarters of children had been treated with psychotropic medications. Of particular note, a diagnosis of ASD was reported in nearly one-third of children ($N = 9$, 29%). Clinical experts reviewing the results of the questionnaire observed that for some children not previously diagnosed with ASD, the caregiver description of behavioral symptoms suggested that such a diagnosis might be warranted.

As with most ID disorders, the clinical features of *KDM5C*-RD are recognized during early childhood and are lifelong, leading to significant challenges for patients and their caregivers. Surveys utilizing caregiver-reported data are thus invaluable in evaluating the unique burdens that result from *KDM5C*-RD, many of which are underreported in the literature. We thus investigated the need for EI services, IEPs, special education, and other educational accommodations among children with *KDM5C*-RD. Strikingly, nearly all children were reported to utilize EI services (93.55%), IEPs (86.21%), special education (86.67%), or other services offered through their schools (100%). These results demonstrate the importance of these services while highlighting the financial strain that some families may experience while caring for a child with *KDM5C*-RD.

KDM5C has been shown to be broadly expressed in multiple mammalian tissues, suggesting that it my function through distinct mechanisms depending on developmental context (Xu et al., 2008). Indeed, we show here that children with independent pathogenic variants in *KDM5C* display a diverse spectrum of clinical manifestations affecting multiple organ systems. *KDM5C*, along with its paralogs *KDM5A*, *KDM5B*, and *KDM5D*, are well-known in the context of gene expression and histone modification. While studies in mice, rats, and flies have largely focused on the role of *KDM5C* in regulating the expression of genes necessary for neuronal development and cognitive function, less is known about its role in other tissues (Drelon et al., 2018, 2019; Iwase et al., 2007; Iwase et al., 2016; Scandaglia et al., 2017; Vallianatos et al., 2020; Zamurrad et al., 2018). The heterogeneity of reported characteristics in our study suggests that *KDM5C* may function pleiotropically to regulate genetic programs critical for diverse adaptive behaviors.

As genetic testing is more routinely recommended and available in the context of etiologic evaluation of developmental delays and autism, and as the ability of genetic testing to pick up smaller abnormalities has become a reality, we can likely expect that *KDM5C*-RD may become a more common diagnosis. Additional research filling in the details of the clinical, medical, developmental, behavioral, and educational needs of this population are warranted. In particular, more research is needed to elucidate the full clinical phenotype in heterozygous females. Future work by us and others will thus include validation of individual *KDM5C* variants through whole exome/genome sequencing and methylation microarray analysis (Schenkel et al., 2018). Investigation into the type of inheritance (sporadic or inherited) would also prove useful and could be done via parental specimen collection. The data presented here are thus critical in directing future research regarding affected organ systems and represent a substantial addition to the number of affected individuals reported in the literature.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Hayden A. M. Hatch, **Molly H. O'Neil**, **Robert W. Marion**, **Julie Secombe**, and **Lisa H. Shulman**: Conceived of and designed the study. **Hayden A. M. Hatch**, **Molly H. O'Neil**, and **Lisa H. Shulman**: Acquired, analyzed, and interpreted the data. **Hayden A. M. Hatch**, **Molly H. O'Neil**, **Robert W. Marion**, **Julie Secombe**, and **Lisa H. Shulman**: Wrote the manuscript.

DATA AVAILABILITY STATEMENT

The authors confirm that all relevant data are included in the article.

ORCID

Hayden A. M. Hatch https://orcid.org/0000-0001-5922-7291
Julie Secombe https://orcid.org/0000-0002-5826-7547
Lisa H. Shulman https://orcid.org/0000-0001-9832-1897

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