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ORIGINAL ARTICLE

Exploring the characteristics and most bothersome symptoms in *MECP2* duplication syndrome to pave the path toward developing parent-oriented outcome measures

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Abstract

Background: MECP2 Duplication Syndrome (MDS), resulting from the duplication of Xq28 region, including *MECP2*, is a rare disorder with a nascent understanding in clinical features and severity. Studies using antisense oligonucleotides revealed a broad phenotypic rescue in transgenic mice. With human clinical trials on the horizon, there is a need to develop clinical outcome measures for MDS.

Methods: We surveyed caregivers of MDS individuals to explore the frequency and severity of MDS clinical features, and identify the most meaningful symptoms/domains that need to be included in the outcome measure scales.

Results: A total of 101 responses were eligible for the survey. The top six most meaningful symptoms to caregivers in descending order included epilepsy, gross motor, fine motor, communication, infection, and constipation problems. Epilepsy was present in 58.4% of the subjects and 75% were drug-resistant, Furthermore, ~12% required intensive care unit (ICU) admission. Infections were present in 55% of the subjects, and one-fourth of them required ICU admission. Constipation was present in ~85% of the subjects and one-third required enemas/suppositories.

Conclusion: Our study is one of the largest cohorts conducted on MDS individuals characterizing the frequency and severity of MDS symptoms. Additionally, these study results will contribute to establishing a foundation to develop parent-reported outcomes in MDS.

KEYWORDS

communication, constipation, epilepsy, fine motor, gross motor, infection, meaningfulness survey, MECP2 duplication syndrome

Muharrem Ak and Bernhard Suter contributed equally to this study.

1 | INTRODUCTION

The X-linked gene *MECP2* (methyl CpG-binding protein 2, MIM# 300005)) is associated with two major neurodevelopmental disorders: Rett syndrome and MECP2 Duplication Syndrome (MDS; Sandweiss et al., 2020).

Rett syndrome (MIM# 312750) is characterized by severe developmental delay, hypotonia progressing to spasticity/contractures, growth failure, gastrointestinal problems, including reflux, constipation and bloating, autonomic system dysfunction (e.g., breath-holding/hyperventilation spells, drooling, arrhythmias, and discoloration and cooling of extremities), insomnia, and characteristic midline hand stereotypies (Sandweiss et al., 2020). It is predominantly seen in females with an incidence of 1 in 10,000–15,000 individuals (Hagberg, 1985). RTT is relatively well studied (Amaddeo et al., 2019; Buchanan et al., 2019; Downs et al., 2016; Glaze et al., 2010; Stallworth et al., 2019; Tarquinio et al., 2017) and there are existing severity scales being used for Rett syndrome in clinical trials (Neul et al., 2015).

MDS (MIM# 300260) is caused by genomic duplications (or triplications) of the Xq28 region containing *MECP2* (Meins et al., 2005; Van Esch et al., 2005). The most common clinical features include infantile hypotonia leading to severe developmental delay, motor impairments, absent or little speech, recurrent respiratory infections, and refractory epilepsy. The frequency of MDS is not studied well; one study reports that it is one of the most common genomic rearrangements in males (Lugtenberg et al., 2009), whereas another study reports the prevalence as 1 in 100,000 live male births in Australia (Giudice-Nairn et al., 2019). Given the neurodevelopmental disease nature and origination from the same gene, there is a significant overlap in the symptomatology of Rett syndrome and MDS, including severe impairments in fine/gross motor skills and communication, functional gastrointestinal disorders (e.g., chewing/swallowing problems and constipation), stereotypies, and epilepsy. However, significant qualitative (e.g., stereotypies interfere with hand function in Rett but not MDS) and quantitative differences (e.g., recurrent infections are common in MDS but rarely seen in RTT), as well as different time courses of symptom progression exist. For example, epilepsy starts between 3 and 4 years and can vary in severity in Rett, whereas epilepsy begins between 8 and 9 years and is almost universally refractory, causing regression in MDS (Sandweiss et al., 2020). Thus, scales or outcome measures developed for Rett cannot be used for MDS.

Currently, there is no approved disease-modifying treatment for MDS or Rett syndrome patients, other than symptom management. However, our group applied a promising strategy using the antisense oligonucleotide (ASO)-based technology to modify gene expression levels in a mouse model of MDS, whereby lowering MECP2 levels reversed the MDS phenotypes, even if ASO was given several months after symptom onset (Sztainberg et al., 2015). Furthermore, a follow-up study using humanized Mecp2 duplication mice (mice that bear two human *MECP2* alleles and were designed to test ASOs for human use) showed consistent results of recovery (Shao et al., 2021). Translation from preclinical models to human clinical trials, with any treatment modality, will require specific MDS-focused outcomes measures, thus, there is an urgent need to develop severity scales/outcome measures specific for MDS. Outcome measures, especially for neurological disorders (Morel & Cano, 2017), developed based on patient- or parent-oriented concerns provide valuable insight into the disease progression and burden.

We conducted a meaningfulness survey to characterize the frequency and severity of symptoms in MDS and identify the most bothersome symptoms to families taking care of MDS individuals with a goal of parent-oriented outcome measure development.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

We conducted a cross-sectional study. First, we created an online Health Insurance Portability and Accountability Act (HIPAA)-compliant registry portal to coordinate and implement studies related to patients with MDS. The Institutional Review Board (IRB) at Baylor College of Medicine (BCM) approved to create and maintain this registry and conduct survey studies (Protocol number: H-46176). Participants provided a written consent form for the portal registration, participation in survey studies and publication of the results. All the collected data were stored in password-protected BCM and Texas Children's Hospital-secured computers.

Legal representatives/caregivers of MDS individuals could voluntarily register for the portal to support scientific research. We used the term "caregivers" for the rest of this manuscript to encompass legal representatives, parents and caregivers.

A genetic report confirming the molecular diagnosis of MDS was required to be eligible for this study. Caregivers were invited to participate in the survey through the email they provided in the portal and the survey was advertised via family organizations' social media accounts.

2.2 | Survey development and variables

The survey was developed using expert opinions and current literature knowledge on MDS. Items were written at

an eighth-grade reading level to optimize completion in the study population. The survey was composed of three sections: Section I included 24 questions focusing on demographic information (sex, age, and ethnicity of the MDS individual, along with age, sex, and relationship of the caregiving person); section II involved 19 categories of questions querying the symptoms/systems and the severity of those symptoms; and section III queried the most impactful symptoms in the MDS individuals' life. The survey was hosted at https://mds.nrihub.org and was available to caregiver's between 01 September and 30 November 2020. The approximate duration to complete the survey was 25 min. The primary outcome variables of the study were: (1) the most meaningful symptoms in MDS individuals as perceived by the caregivers and (2) the most important symptom to be treated by a medication. These two outcomes were addressed by the following questions:

1. Caregiver-ranked Bothersome Symptoms in MDS Individuals: Participants were asked to select their top three concerns for their child over the past 6 months from a list of options containing symptoms relevant to MDS: Difficulty in gross motor skills, such as walking, crawling, sitting, rollover, and fine motor skills for hand use; lack of interaction, such as poor eye contact and communication; behavioral problems, such as aggressive behavior and repetitive movements; seizures; gastrointestinal problems, such as feeding issues, constipation/diarrhea, and gas and bloating; sleep difficulties; severe infections; breathing problems; and musculoskeletal findings, including joint contractures/laxity and scoliosis. The calculated weight of each symptom was presented for the first, second, and most bothersome symptoms by multiplying the frequency of the perceived ranks with the pre-coded rank values (most bothersome = 3, 2nd most bothersome = 2, 3rd most bothersome = 1).
2. Most Desired Symptom for Treatment: Caregivers' responses to the question "Which symptom do you think your child would want a treatment to help with most?" were reported in number and percentage. A symptom score was calculated by adding the number of present symptoms (total 24) in each MDS individual.

2.3 | MDS symptoms queried

The survey explored symptoms of neurodevelopmental delay, epilepsy, gastrointestinal problems, infection, sleep issues, visual abnormalities, genitourinary issues, musculoskeletal complaints, scoliosis, atypical body features, and breathing patterns. Symptoms were graded using a five-point Likert scale (never, rarely, sometimes, often, and always). Some categories were merged during the analysis.

2.4 | Developmental quotient

A developmental pediatrician (author H.H.) provided the developmental age equivalent for each MDS individual for gross motor skills, fine motor skills, and expressive and receptive language based on the parent-provided information for the MDS individual's skills. Age equivalents were based on the mean age of acquisition of specific developmental skills (50th percentile), rooted in work done by Arnold L. Gesell, who acquired decades of detailed observations of infants and children and count as the basis of most early assessments of developmental-behavioral functioning. A Developmental Quotient (DQ) can be obtained when developmental age equivalents are established. Gesell first described this method in detail as "a shorthand device for expressing the rate of development" (Accardo & Capute, 2005). The DQ is calculated by dividing the individual's developmental age (DA) by the chronological age (CA) and multiplying by 100 ($DQ = DA/CA \times 100$), giving a DQ ratio. A DQ of <70%–75% indicates delay in the affected area of development (Gesell & Amatruda, 1941).

2.5 | Statistical approach

We used IBM SPSS Statistics for Macintosh, Version 28.0 (Armonk, NY: IBM Corp) for all statistical analyses. Means, standard deviations, and upper and lower scores were calculated with a confidence interval of 95%. One-way ANOVA was used to elicit the differences in the mean symptom scores concerning the groups with different priority choices for treatment. The independent samples *t*-test was used to compare data meeting parametric assumptions between two groups, while the Mann–Whitney *U* test was used for skewed variables. The chi-square test was used to compare categorical variables. The appearance of epilepsy with age was studied using Kaplan–Meier survival analysis, and a *p*-value of $<.05$ was considered statistically significant.

3 | RESULTS

3.1 | Participants

One hundred and twenty-six registrants completed the survey. Twenty-five of them were excluded for several reasons, including the inability to confirm MDS diagnosis molecularly and female sex as those MDS individuals

do not represent the classic MDS features (i.e., MECP2 Duplication is asymptomatic in the majority of female individuals due to X-inactivation, Figure 1). Of note, three female subjects (3.0%) who had translocation to autosomes were included since they had classic MDS features due to skewed X-inactivation. Of the 101 eligible participants, the mean (±SD) age of the MDS individuals was 10.0 ± 8.9 years (median: 7, range: 1–51 years), while the mean age of the caregivers was 40.2 ± 8.6 years (median: 39, range: 24–74 years). Most of the caregivers who completed the survey were mothers (n = 88, 87.1%), followed by fathers (n = 12, 11.9%), and a sister (1.0%). Country of origins were USA (n = 55, 54.5%), Europe (n = 25, 24.8%), Canada (n = 8, 7.9%), Australia (n = 7, 6.9%), and others (n = 6, 5.9%).

MDS symptoms were first recognized at a mean age of 4.4 ± 5.1 months (median: 3, range: 0–24 months). The most common presenting symptoms included developmental delay (n = 37), hypotonia (n = 10), gastrointestinal problems + developmental delay (n = 10), and gastrointestinal problems + respiratory issues (n = 8). See Table S1 for further details with age distribution. MDS was diagnosed at a mean age of 21.8 ± 32.9 months (median: 12.0, range: 0–216 months).

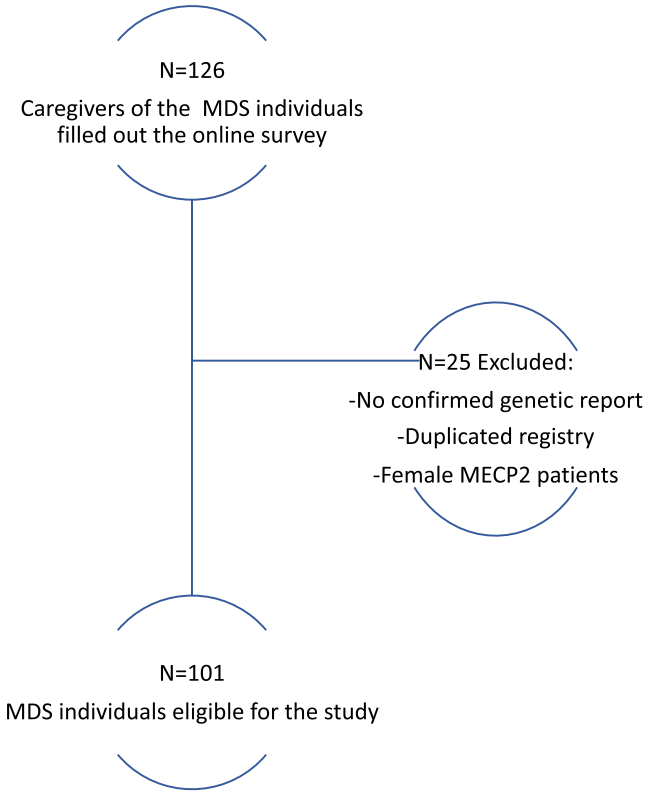

FIGURE 1 Flowchart of the study for inclusion and exclusion. Twenty-five individuals are excluded due to various reasons as written.

3.2 | Descriptive findings

Caregivers' selection of the most, second, and third most bothersome symptoms in MDS was explored. The top six most bothersome symptoms for the caregivers were seizures (n = 33, 71.7%), difficulty in gross motor skills (n = 20, 35.7%), lack of interaction/communication with the caregiver (n = 19, 48.7%), frequent and/or severe infections (n = 12, 34.3%), difficulty in fine motor skills (n = 2, 5.7%), and constipation (n = 6, 22.2%). See Table 1 for caregivers' choices regarding the most meaningful symptoms.

Weighted score values of the most meaningful three symptoms are shown in Table 2. The top six domains with the highest impact score in descending order were seizures, difficulty in gross motor skills, lack of interaction with the caregiver, frequent and/or severe infections, difficulty in fine motor skills and constipation.

In addition to exploring the top concerns for the caregivers by asking them to rank the symptoms of MDS, we asked an open-ended question (Which symptom do you think your child would want a treatment to help with most?) to investigate any other problems that we have not captured and to cross-validate their choices. Table 3 compares the mean symptom scores concerning the groups with different priority choices for treatment. Means, standard deviation and, upper and lower scores were calculated with a confidence interval of 95%. Although the top two choices (seizure and difficulty in gross motor skills) were consistently ranked high, there were changes in the order of the remaining symptoms. Moreover, while gastrointestinal problems were the 6th most bothersome symptom in the ranking list, these issues were not considered a top priority concern for a treatment choice for caregivers.

Since seizure was the top concern for families, we investigated whether any particular age group was more concerned about seizures. We divided the individuals into three age groups, including 0–6 years, 7–14 years, and 15 years and older (reasoning for this split is explained in the Discussion). We identified that subjects with epilepsy between 7 and 14 years had the highest concern for epilepsy (Figure S1).

We additionally asked a free-text question to describe any additional symptoms that we did not cover with our questions. Four caregivers reported the lack of potty training as one of the most bothersome symptoms.

3.3 | MDS symptom queries

3.3.1 | Epilepsy

We investigated the burden of seizures by asking the types, frequencies and durations of seizures, and recovery

TABLE 1 Distribution of the most, second, and third most bothersome symptoms in MECP2 duplication syndrome

	n	%
Difficulty in gross motor skills such as walking, crawling, sitting, and rolling over		
Most bothersome	20	35.7
2nd Most bothersome	21	37.5
3rd Most Bothersome	15	26.8
Difficulty in fine motor skills such as reaching, holding and transferring objects, self-feeding		
Most bothersome	2	5.7
2nd most bothersome	14	40.0
3rd most bothersome	19	54.3
Lack of interaction with you, such as poor eye contact and communication		
Most bothersome	19	48.7
2nd most bothersome	11	28.2
3rd most bothersome	9	23.1
Behavioral problems such as aggressive behavior and repetitive movements		
Most bothersome	3	30.0
2nd most bothersome	2	20.0
3rd most bothersome	5	50.0
Seizures		
Most bothersome	33	71.7
2nd most bothersome	10	21.7
3rd most bothersome	3	6.5
Feeding issues		
Most bothersome	0	0.0
2nd most bothersome	5	45.5
3rd most bothersome	6	54.5
Constipation/diarrhea		
Most bothersome	6	22.2
2nd most bothersome	7	25.9
3rd most bothersome	14	51.9
Gas and bloating		
Most bothersome	0	0.0
2nd most bothersome	2	66.7
3rd most bothersome	1	33.3
Sleep difficulties		
Most bothersome	1	14.3
2nd most bothersome	0	0.0
3rd most bothersome	6	85.7
Frequent and/or severe infections		
Most bothersome	12	34.3
2nd most bothersome	13	37.1
3rd most bothersome	10	28.6
The rank of breathing problems		
Most bothersome	2	15.4
2nd most bothersome	8	61.5
3rd most bothersome	3	23.1
The rank of musculoskeletal findings including joint contractures/laxity, scoliosis, and bone fracture		
Most bothersome	0	0.0
2nd most bothersome	2	40.0
3rd most bothersome	3	60.0

outcomes from those seizures (Table 4). Of the participants, 58.4% ($n = 59$) had any type of seizure, including focal, myoclonic, absence, atonic, tonic, and generalized tonic–clonic seizure types. The majority of patients (43/59) had two or more types of seizures. The frequency of spells was as follows: no seizures in the last 6 months (20.6%, $n = 12$), seizures less than monthly (17.2%, $n = 10$), weekly to monthly (12.0%, $n = 7$), between daily to weekly (10.3%, $n = 6$), and daily multiple times (39.6%, $n = 23$). Seizures mostly lasted a few seconds to 1 min (44.1%, 26/59) and between 1 to 5 min (23.7%, 11/59) per the responders. A significant portion of the individuals reported immediate to within hours recovery (83.3%, 49/59). However, 10 out of 59 individuals (16.9%) reported hospitalizations due to seizure activity, including seven intensive care unit admissions with or without intubation. Pearson chi-square test revealed a statistically significant association between the priority choice for treatment and epilepsy ($p = .001$).

3.3.2 | Gastrointestinal symptoms

Gastrointestinal (GI) problems are almost universal in neurodevelopmental disorders. Similarly, nearly all participants (91.0%, $n = 91$) had some GI symptoms in our cohort (Table 5). Twenty-one subjects (21.0%) required gastric tube for feeding/nutrition, including nine fed by G-tube only and 12 G-tube plus pleasure feeding by mouth. Constipation was sometimes present in 20 individuals (21.9%) and often/always present in 62 (68.1%). Thirty out of 84 individuals (35.7%) with constipation required second-tier medications such as suppositories and enemas. However, diarrhea was not an important issue for the majority of MDS individuals (never or rarely reported in 72 individuals (79.1%). Forty-eight of the individuals (52.4%) reported some degree of gastroesophageal reflux (GERD) and 12 of them (25%) required surgery. There was no association between any of the gastrointestinal problems and priority treatment choice ($p = .103$).

TABLE 2 Calculated impact score for each domain that received a ranking by the parents

	Calculated Impact Score	Most bothersome		2nd most bothersome		3rd Most bothersome	
		n	%	*n*	%	*n*	%
Seizures	122	33	71.7	10	21.7	3	6.5
Difficulty in gross motor skills	117	20	35.7	21	37.5	15	26.8
Lack of interaction with caregiver	88	19	48.7	11	28.2	9	23.1
Frequent and/or severe infections	72	12	34.3	13	37.1	10	28.6
Difficulty in fine motor skills	53	2	5.7	14	40	19	54.3
Constipation	46	6	22.2	7	25.9	14	51.9
Breathing problems	25	2	15.4	8	61.5	3	23.1
Behavioral problems (e.g., aggressive behavior and repetitive movements)	18	3	30	2	20	5	50
Feeding issues	16	0	0	5	45.5	6	54.5
Sleep difficulties	9	1	14.3	0	0	6	85.7
Musculoskeletal findings (i.e., joint contractures/laxity, scoliosis, and bone fracture)	7	0	0	2	40	3	60
Gas and bloating	5	0	0	2	66.7	1	33.3

TABLE 3 Comparison of the mean symptom scores regarding the groups with different priority choice for treatment question

Priority choice for treatment	*n*	Mean	SD	SE	95% CI		Min.	Max.
					Lower	Upper		
Seizures	33	10.4[a]	3.2	0.56	9.3	11.6	4	17
Gross motor	20	9.5[a,b]	3.1	0.70	8.0	10.9	0	17
Infection	12	8.9[a,b]	2.8	0.81	7.1	10.7	4	14
Communication	19	7.7[b]	2.6	0.60	6.5	9.0	3	13
Other	17	6.1[b]	3.9	0.97	4.0	8.1	1	15
Total	101	8.8	3.5	0.35	8.1	9.5	0	17

Note: The same superscript letters denote nonsignificant differences between the means using the independent samples *t*-test ($p \geq .05$).

3.3.3 | Infection

Infections in the form of lung, upper respiratory, urinary tract and middle ear infections and sepsis were queried to assess the presence and severity of infections in MDS. Upper respiratory infections, lung infection, and urinary tract infection were reported by 33 (58.9%), 32 (57.1%), and 17 (30.3%) of MDS individuals, respectively. To investigate the severity of the infections, we asked the level of care typically needed after an infection. Twenty-three of the individuals (41.8%) reported hospitalization and 14 (37.8% of hospitalizations) of the caregivers reported intensive care unit admission due to infections (Table 6). There was no correlation between the infections and priority choice of treatment ($p = .138$).

3.3.4 | Sleep

We investigated the characteristics of sleep disturbances in MDS individuals by asking whether they have problems with sleep initiation, sleep maintenance, or waking up in the morning. Difficulty with maintaining sleep, rated as "often/always" and "sometimes", was a major problem observed in 48% of MDS individuals (Table S2). On the other hand, difficulty with sleep initiation and waking up in the morning were relatively less common, and at least sometimes observed in 35% and 25% of the individuals, respectively.

3.3.5 | Dysautonomia

Dysautonomia is remarkably common and can be bothersome to individuals with Rett syndrome. To investigate the presence and severity of dysautonomia in MDS individuals, we queried the frequency of breathing abnormalities (hyperventilation/breath-holding spells), blood circulation to extremities (color and temperature change in hands and feet) and drooling (Table S3). Hyperventilation was absent or rarely present in 90% ($n = 91$) of individuals. Breath-holding spells were reported in only 35 individuals (35%).

TABLE 4 Epilepsy characteristics in MECP2 duplication syndrome individuals

	n	%
Seizure frequency		
No seizure in the last 6 months	12	20.6
Seizures less than monthly	10	17.2
Weekly to monthly	7	12.0
Daily to weekly	6	10.3
Daily multiple types	23	39.6
Not-responded	1	3.4
Total	59	
Duration of seizure		
Few seconds to 1 min	26	44.0
1–5 min	14	23.7
5–30 min	4	6.7
30 min or longer	4	6.7
Differ in duration	11	18.6
Total	59	
Level of care typically needed following a seizure		
Recovers immediately	30	51.7
Stays at home, recovers within hours	20	34.4
Stays at home, recovers within 1–2 days	3	5.1
Goes to ER and discharges from ER	3	5.1
Hospitalized without ICU	2	3.4
Not-responded	1	1.7
Total	59	
Most severe outcome needed following a seizure		
Recovers immediately	14	23.7
Stays at home, recovers within hours	12	20.3
Stays at home, recovers within 1–2 days	5	8.5
Goes to ER and discharges from ER	11	18.6
Hospitalized overnight	6	10.2
Hospitalized >1 day without ICU	4	6.8
Admitted to intensive care unit and/or requires breathing tube	7	11.9
Total	59	

TABLE 5 Gastrointestinal issues in MECP2 duplication syndrome subjects

	n	%
Feeding issues (How long does it take to complete a meal?)		
Less than 30 min to finish a meal	44	48.3
30–60 min to complete a meal	22	24.1
G-tube plus pleasure feeding by mouth	11	13.1
G-tube only	10	10.9
Over 60 min to finish a meal	4	4.3
Total	91	100
Swallowing difficulty		
No	42	50.6
Yes	41	49.4
Not-responded	8	
Total	91	
Constipation		
Never/Rarely	9	9.8
Sometimes	20	21.9
Often/Always	62	68.1
Total	91	100
Diarrhea		
Never/Rarely	72	79.1
Sometimes/often	19	20.9
Total	91	100
Reflux (GERD)		
No	43	47.2
GERD requiring dietary/positional modifications	16	17.5
GERD requiring medications	20	21.9
GERD requiring surgery	12	13.1
Total	91	100
Management of constipation		
Mainly with diet modifications	16	19.0
First-tier medications such as fibers/softeners/osmotics	38	45.2
Second-tier medications such as suppositories/enemas	30	35.7
Not-responded	4	
Total	88	100

Abnormal blood circulation to extremities was commonly reported, including 24 as sometimes, 26 as often, and 18 as always, totaling 68 (68%) who had this problem. Drooling was reported in two-thirds of individuals (65 out of 98) and only seven individuals were receiving medications for drooling, with one requiring Botox injections.

3.3.6 | Behavioral problems

We queried the general mood, affect, alertness, attentiveness, self-mutilation, and teeth grinding behaviors. Details of the behavioral problems are summarized in Table S4. The majority of our subjects were calm and happy/smiling ($n = 85$, 84.1%). Bruxism was a frequently observed feature, at least sometimes in 69 out of 99 respondents (69.9%). Although self-mutilation is not a preeminent feature of MDS, it is observed rarely in 14.8% ($n = 15$), sometimes in 8.9% ($n = 9$), and often in 3.9% ($n = 4$) of the MDS individuals.

TABLE 6 Types of infections and their outcomes in MECP2 duplication syndrome individuals

	n	%
Frequent infections		
Yes	56	55.4
No	45	44.6
Total	101	100.0
Level of care typically needed for an infection		
Hospitalization	23	41.8
Doctor's office visit management	15	27.2
Intensive care unit admission	14	25.4
Supportive care at home	3	5.4
Not-responded	1	1.8
Total	56	100
Most common infections		
Upper respiratory infection	33	58.9
Lung infection	32	57.1
Urinary tract infection	17	30.3
Middle ear infection	14	25.0
Sepsis	2	3.5

3.3.7 | Other features

Eye problems were relatively common and were reported in 67 of the individuals. The most common eye problems included hypermetropia ($n = 23$, 37.0%), amblyopia ($n = 11$, 17.7%), myopia ($n = 9$, 14.5%), and strabismus ($n = 8$, 12.9%). Dry eyes, infection, ptosis, and hemangioma were reported in single subjects (Table S5).

Functional and anatomical genitourinary abnormalities were identified in 48 individuals, including 19 with cryptorchidism (39.5%), 15 with urinary retention (31.2%), 12 with a small penis (25.0%), and only two with kidney anomalies (Table S5).

Various musculoskeletal anomalies were reported in 69 individuals with the most common ones being scoliosis ($n = 26$, 37.6%), joint laxity/dislocation ($n = 20$, 28.9%), bone fracture ($n = 13$, 18.8%), and contracture ($n = 6$, 8.6%). Additionally, webbed toe, coxa valga, hip dysplasia, and osteochondroma were reported in single subjects (Table S5).

Atypical facial/body features (i.e., dysmorphism) were reported by 54 out of 56 (96.4%) of the respondents (Table S5).

Lastly, we asked an open-ended question to freely describe other health issues that we did not query. Eczema was the most common clinical feature ($n = 27$, 51.9%) and allergy was the second most reported health issue. ($n = 21$, 40.3%). Further details for additional problems are provided in Table S6.

4 | DISCUSSION

We conducted a survey study to identify symptom domains that are most meaningful to caregivers of MDS individuals using an impact scoring system and investigated the extent and degree of symptoms in MDS individuals. We identified epilepsy, gross motor challenges, lack of interaction/communication, infection, difficulty in fine motor skills, and constipation as the most bothersome features in MDS. Our study further provided a comprehensive clinical characterization and severity of those clinical features by applying the survey on one of the largest MDS cohorts.

Epilepsy ranked as the most bothersome symptom in both the ranking list and in the priority choice for treatment question. The frequency of epilepsy ranged from 43% to 63% of MDS individuals with an average age of onset between 6 and 9 years between different large MDS cohorts (Lim et al., 2017; Marafi et al., 2019; Miguet et al., 2018; Pascual-Alonso et al., 2020; Peters et al., 2019). The Kaplan–Meier survival curve showed that in MDS individuals epilepsy becomes universal as age progresses (Figure S2), consistent with literature findings (Lim et al., 2017). Based on the average age of seizure onset described in the literature, we stratified the age into three groups; 0–6 years (before the seizure onset), 7–14 years (mid-age group when seizures start and become refractory), and 15 years and above (advanced age group, when seizures are stable but refractory). The middle age group (7 to 14 years) had the highest bothersome score and likely the onset of seizures in this age group had a significant impact on the caregiver choice (Figure S1). It may be confusing to observe seizures as the top concern in 60% of caregivers in the 0–6 years age group despite their child probably never experiencing seizures. One potential explanation for this discrepancy is that MDS families are in close communication through social media and learn from each other about the symptoms. It is well-known among families that the regression in MDS occurs when the seizures become refractory. This concern/anxiety is probably the reason for those families to pick seizure as their top concern. It is ranked relatively lower in the advanced age group (15 years and above), with one probable explanation that caregivers have gained more experience and are thus comfortable with seizure management. Notably, ~80% of these seizures were reported to be resistant to medical/surgical treatment (Lim et al., 2017; Marafi et al., 2019; Miguet et al., 2018). In our cohort, we identified the presence of epilepsy in 58.4% of MDS individuals and ~73% of them had multiple types of seizures, supporting their refractory status. Several studies have shown that epilepsy is the main contributor to regression in MDS individuals (Marafi et al., 2019; Ramocki et al., 2010; Takeguchi et al., 2021), likely leading to significant demand/burden

in caregivers. Our study revealed that almost one-third of subjects who had epilepsy required hospitalization and even ~12% of epilepsy positive individuals had to be admitted to intensive care unit with/without intubation, likely adding financial and psychosocial burden on these families. The high rank of epilepsy in the meaningfulness ranking is apprehensible given its devastating consequences on MDS individuals and families.

MDS is a severe neurodevelopmental disorder, characterized by significant delay in gross motor, fine motor, and communication skills. Difficulties in gross motor skills were the second most bothersome symptom both in the ranking list and the priority choice for treatment question. In individuals with MDS a wide range of ambulatory statuses has been reported (39–79%) between different world populations (Giudice-Nairn et al., 2019; Lim et al., 2017; Miguet et al., 2018; Pascual-Alonso et al., 2020; Peters et al., 2019). Additionally, individuals with MDS are not prone to growth restriction. Thus, they mostly have normal age-equivalent weight and height. We have subjects with MDS up to 51-year-old; therefore, one could expect that delayed gross motor skills and lack of age-appropriate mobility cause a significant burden on their caregivers. Ambulation is one of the key domains that consistently correlates with higher severity scores in Rett syndrome (Cuddapah et al., 2014; Wang et al., 2022). Moreover, ambulation prevents the development of a series of additional physical problems, such as contractures of small and large joints, scoliosis muscle wasting, cardiorespiratory health (e.g., preventing airway clearance), gastrointestinal problems, and personal independence (Layne et al., 2018; Young et al., 2020). Thus, given the impact of ambulation on the overall health of MDS individuals, it is expected that gross motor skills/ambulation would be one of the critical domains included in the severity scale assessments specific to MDS individuals.

Lack of interaction/communication ranked third in the ranking list and fourth in the priority choice for treatment question. Lack of a meaningful word or presence of just a few words was observed in 98%–100% of MDS individuals (Giudice-Nairn et al., 2019; Lim et al., 2017; Miguet et al., 2018; Peters et al., 2019; Takeguchi et al., 2021). Wang et al. showed a correlation between the severity of Rett syndrome and their socio-communicative, adaptive behavioral, and daily functional skills (Wang et al., 2022). An MDS individual's inability to interact or communicate results in a significant challenge for the caregivers, who are left to decipher what their child wants or needs, likely leading them to rank lack of interaction/communication among the top concerns for which they are seeking improvement with treatment.

Recurrent infections ranked fourth in the ranking list and third in the priority choice for treatment question. Recurrent infections are one of the defining features of MDS in the Online Mendelian Inheritance in Man (OMIM) database. Bauer et al. showed that subjects with MDS are susceptible to infections due to IgA/IgG2 deficiency, low antibody titers against pneumococci, and elevated acute-phase responses (Bauer et al., 2015). A follow-up study showed the efficacy of antibiotic prophylaxis and immunoglobulin substitution in preventing infections in MDS (Bauer et al., 2018). In our cohort, 56 individuals (55.4%) had frequent infections, the most common being upper respiratory infections and lung infections. The infections were severe and led to hospitalization in two-thirds of the MDS individuals (67.2%) and more importantly, approximately 40% of those hospitalizations required intensive care unit admissions, indicating the burden of infections on MDS families. Studies are needed to assess the efficacy of antibiotic prophylaxis and immunoglobulin replacement in MDS individuals.

Difficulty in fine motor skills (i.e., hand skills) ranked high in the ranking list and in the priority choice for treatment list. Fine motor skills are required for many tasks of daily living, and independence, such as eating, drinking, dressing, and toileting. Although there is limited literature on hand/fine motor functions in the MDS population, our internal dataset of 81 individuals demonstrates that most of these individuals do not attain fine motor skills beyond partial use of a spoon. Thus, MDS individuals mostly rely on their caregivers for fine motor skills, which causes an extra burden to caregivers of MDS individuals.

Constipation was one of the most meaningful domains in our ranking list and it was reported frequently (85%) in our survey, which parallels what is commonly reported (50–80% of subjects) in various MDS cohorts (Giudice-Nairn et al., 2019; Lim et al., 2017; Miguet et al., 2018; Pascual-Alonso et al., 2020; Peters et al., 2019; Takeguchi et al., 2021). Gastrointestinal problems are prevalent in Rett syndrome patients (Baikie et al., 2014; Lotan & Zysman, 2006). Strati et al. showed the altered gut microbiota in Rett syndrome individuals is likely secondary to impairment in MECP2 functioning (Strati et al., 2016). Wong et al. studied the parental distress in children with Prader Willi syndrome (another neurodevelopmental disorder) and they found that somatic symptoms were the only factor related to high parenting stress (Wong et al., 2021). More than one-third of subjects in our cohort required second-tier medications to manage constipation (i.e., not responding to dietary modifications or first-tier medications). Our survey reflects this impact of constipation on caregivers as it was ranked high on the meaningfulness scale. Therefore, constipation should be considered as one of the items to be included in a severity scale, or the development of an outcome measure specific to constipation should be considered.

Lastly, we investigated the impact of different age groups on the caregivers' choice. We observed a gradual

increase in the top concerns for infection and constipation, and a gradual decrease in gross motor, fine motor, and communication skills as the MDS individuals get older (Figure S1). According to our clinical experience, as MDS individuals get older and their seizures become more refractory, they suffer more frequent and severe infections (mostly aspiration pneumonia) due to poorly controlled seizures. Additionally, both infection and constipation require medical treatment and potential admission to hospital which brings extra hurdles to families. The decrease in top concern in developmental skills (gross motor, fine motor, and communication) is likely due to caregivers' adaptation to their children's abilities, which decreases the expectations for them and does not cause an urgent medical intervention similar to seizure and constipation.

Peters et al. reported the top concerns on 69 MDS individuals from Natural History Study of Rett Syndrome and Related Disorders (Peters et al., 2021). The authors identified the top six concerns in descending order as lack of effective communication, abnormal walking/balance problems, constipation, seizures, lack of effective chewing/swallowing, and frequent infections. Although there were differences in the design and content of the questions, there is considerable overlap between the top choices in their study and the results reported here, with some differences in order (e.g., epilepsy was ranked top in our list, but it was ranked fourth in their list). One domain differed in both studies; fine motor challenges were one of the top concerns in our study, whereas lack of effective chewing/swallowing ranked high in their study. Together, these studies provide valuable information for the foundation of a severity scale development.

There are several limitations to our study. First, we relied on the caregivers' report for the developmental skills (gross/fine/language/communication) without a direct assessment of skill level by a medical professional; thus, their developmental skills may not be accurate/precise. Second, the study was conducted as a cross-sectional study. Hence, families' meaningfulness choices are probably impacted by MDS individuals' most recent bothersome symptoms (e.g., epilepsy may have a significant impact on a family, but if the seizure burden is less over the last year or two, the caregiver may not rank it high). Third, most of the participants in the survey were from North America and Europe, which may cause bias in the selection of their choices due to cultural and socioeconomic differences. Lastly, the study was conducted during the COVID pandemic. According to our communication with families, several MDS individuals had fewer infections during COVID due to self-quarantining, which may have caused the infection to be ranked lower by caregivers.

In summary, we conducted a meaningfulness survey on the caregivers of MDS individuals. We further investigated the frequency and the severity of symptoms by targeting the clinical features specific to MDS and explored whether the severity of symptoms had influenced caregivers' choices. Our study paves the path toward developing a severity scale specific to MDS for use in future clinical trials by identifying the symptom domains. One of the strengths of this study is that identified domains were selected through parent-reported data based on one of the largest MDS cohorts in the literature. Additionally, data from this study may help clinicians manage individuals with MDS and guide the governmental agencies dedicated to improving the lives of individuals with MDS.

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CONFLICT OF INTEREST

BS and DP receive funding support by the Ionis Pharmaceuticals. KB and LM are employees of Ionis Pharmaceuticals and own Ionis stocks. Other authors declare no conflict of interest related to this work.

AUTHOR CONTRIBUTIONS

BS, KB, LM, DGG and DP designed the study. BS, SP, and DP conducted the study. MA, BS, ZA, HH, KB, LM, DD and DP analyzed the data and wrote the manuscript. ZA and MA conducted statistical analysis.

ETHICAL APPROVAL

This material is the authors' own original work, which has not been previously published elsewhere and the study is conducted according to HIPAA law.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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REFERENCES

Accardo, P. J., & Capute, A. J. (2005). *The Capute scales: Cognitive adaptive test/clinical linguistic & auditory milestone scale (CAT/CLAMS)*. Brookes Publishing.

Amaddeo, A., De Sanctis, L., Arroyo, J. O., Khirani, S., Bahi-Buisson, N., & Fauroux, B. (2019). Polysomnographic findings in Rett syndrome. *European Journal of Paediatric Neurology*, *23*, 214–221.

Baikie, G., Ravikumara, M., Downs, J., Naseem, N., Wong, K., Percy, A., Lane, J., Weiss, B., Ellaway, C., Bathgate, K., & Leonard, H. (2014). Gastrointestinal dysmotility in Rett syndrome. *Journal of Pediatric Gastroenterology and Nutrition*, *58*, 237–244.

Bauer, M., Kolsch, U., Kruger, R., Unterwalder, N., Hameister, K., Kaiser, F. M., Vignoli, A., Rossi, R., Botella, M. P., Budisteanu, M., & Rosello, M. (2015). Infectious and immunologic phenotype of MECP2 duplication syndrome. *Journal of Clinical Immunology*, *35*, 168–181.

Bauer, M., Kruger, R., Kolsch, U., Unterwalder, N., Meisel, C., Wahn, V., & von Bernuth, H. (2018). Antibiotic prophylaxis, immunoglobulin substitution and supportive measures prevent infections in MECP2 duplication syndrome. *The Pediatric Infectious Disease Journal*, *37*, 466–468.

Buchanan, C. B., Stallworth, J. L., Scott, A. E., Glaze, D. G., Lane, J. B., Skinner, S. A., Tierney, A. E., Percy, A. K., Neul, J. L., & Kaufmann, W. E. (2019). Behavioral profiles in Rett syndrome: Data from the natural history study. *Brain and Development*, *41*, 123–134.

Cuddapah, V. A., Pillai, R. B., Shekar, K. V., Lane, J. B., Motil, K. J., Skinner, S. A., Tarquinio, D. C., Glaze, D. G., McGwin, G., Kaufmann, W. E., Percy, A. K., Neul, J. L., & Olsen, M. L. (2014). Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome. *Journal of Medical Genetics*, *51*, 152–158.

Downs, J., Torode, I., Wong, K., Ellaway, C., Elliott, E. J., Christodoulou, J., Jacoby, P., Thomson, M. R., Izatt, M. T., Askin, G. N., McPhee, B. I., Bridge, C., Cundy, P., & Leonard, H. (2016). The natural history of scoliosis in females with Rett syndrome. *Spine (Phila Pa 1976)*, *41*, 856–863.

Gesell, A., & Amatruda, C. S. (1941). *Developmental diagnosis; normal and abnormal child development*. Hoeber.

Giudice-Nairn, P., Downs, J., Wong, K., Wilson, D., Ta, D., Gattas, M., Amor, D., Thompson, E., Kirrali-Borri, C., Ellaway, C., & Leonard, H. (2019). The incidence, prevalence and clinical features of MECP2 duplication syndrome in Australian children. *Journal of Paediatrics and Child Health*, *55*, 1315–1322.

Glaze, D. G., Percy, A. K., Skinner, S., Motil, K. J., Neul, J. L., Barrish, J. O., Lane, J. B., Geerts, S. P., Annese, F., Graham, J., McNair, L., & Lee, H. S. (2010). Epilepsy and the natural history of Rett syndrome. *Neurology*, *74*, 909–912.

Hagberg, B. (1985). Rett's syndrome: prevalence and impact on progressive severe mental retardation in girls. *Acta Paediatrica Scandinavica*, *74*, 405–408.

Layne, C. S., Lee, B. C., Young, D. R., Glaze, D. G., Schwabe, A., & Suter, B. (2018). Temporal gait measures associated with overground and treadmill walking in Rett syndrome. *Journal of Child Neurology*, *33*, 667–674.

Lim, Z., Downs, J., Wong, K., Ellaway, C., & Leonard, H. (2017). Expanding the clinical picture of the MECP2 duplication syndrome. *Clinical Genetics*, *91*, 557–563.

Lotan, M., & Zysman, L. (2006). The digestive system and nutritional considerations for individuals with Rett syndrome. *Scientific World Journal*, *6*, 1737–1749.

Lugtenberg, D., Kleefstra, T., Oudakker, A. R., Nillesen, W. M., Yntema, H. G., Tzschach, A., Raynaud, M., Rating, D., Journel, H., Chelly, J., Goizet, C., Lacombe, D., Pedespan, J. M., Echenne, B., Tariverdian, G., O'Rourke, D., King, M. D., Green, A., van Kogelenberg, M., ... de Brouwer, A. P. M. (2009). Structural variation in Xq28: MECP2 duplications in 1% of patients with unexplained XLMR and in 2% of male patients with severe encephalopathy. *European Journal of Human Genetics*, *17*, 444–453.

Marafi, D., Suter, B., Schultz, R., Glaze, D., Pavlik, V. N., & Goldman, A. M. (2019). Spectrum and time course of epilepsy and the associated cognitive decline in MECP2 duplication syndrome. *Neurology*, *92*, e108–e114.

Meins, M., Lehmann, J., Gerresheim, F., Herchenbach, J., Hagedorn, M., Hameister, K., & Epplen, J. T. (2005). Submicroscopic duplication in Xq28 causes increased expression of the MECP2 gene in a boy with severe mental retardation and features of Rett syndrome. *Journal of Medical Genetics*, *42*, e12.

Miguet, M., Faivre, L., Amiel, J., Nizon, M., Touraine, R., Prieur, F., Pasquier, L., Lefebvre, M., Thevenon, J., Dubourg, C., Julia, S., Sarret, C., Remerand, G., Francannet, C., Laffargue, F., Boespflug-Tanguy, O., David, A., Isidor, B., Vigneron, J., ... el Chehadeh, S. (2018). Further delineation of the MECP2 duplication syndrome phenotype in 59 French male patients, with a particular focus on morphological and neurological features. *Journal of Medical Genetics*, *55*, 359–371.

Morel, T., & Cano, S. J. (2017). Measuring what matters to rare disease patients—Reflections on the work by the IRDiRC taskforce on patient-centered outcome measures. *Orphanet Journal of Rare Diseases*, *12*, 171.

Neul, J. L., Glaze, D. G., Percy, A. K., Feyma, T., Beisang, A., Dinh, T., Suter, B., Anagnostou, E., Snape, M., Horrigan, J., & Jones, N. E. (2015). Improving treatment trial outcomes for Rett syndrome: The development of Rett-specific anchors for the clinical global impression scale. *Journal of Child Neurology*, *30*, 1743–1748.

Pascual-Alonso, A., Blasco, L., Vidal, S., Gean, E., Rubio, P., O'Callaghan, M., Martinez-Monseny, A. F., Castells, A. A., Xiol, C., Catala, V., & Brandi, N. (2020). Molecular characterization of Spanish patients with MECP2 duplication syndrome. *Clinical Genetics*, *97*, 610–620.

Peters, S. U., Fu, C., Marsh, E. D., Benke, T. A., Suter, B., Skinner, S. A., Lieberman, D. N., Standridge, S., Jones, M., Beisang, A., Feyma, T., Heydeman, P., Ryther, R., Glaze, D. G., Percy, A. K., & Neul, J. L. (2021). Phenotypic features in MECP2 duplication syndrome: Effects of age. *American Journal of Medical Genetics. Part A*, *185*, 362–369.

Peters, S. U., Fu, C., Suter, B., Marsh, E., Benke, T. A., Skinner, S. A., Lieberman, D. N., Standridge, S., Jones, M., Beisang, A., Feyma, T., Heydeman, P., Ryther, R., Kaufmann, W. E., Glaze, D. G., Neul, J. L., & Percy, A. K. (2019). Characterizing the phenotypic effect of Xq28 duplication size in MECP2 duplication syndrome. *Clinical Genetics*, *95*, 575–581.

Ramocki, M. B., Tavyev, Y. J., & Peters, S. U. (2010). The MECP2 duplication syndrome. *American Journal of Medical Genetics. Part A*, *152A*, 1079–1088.

Sandweiss, A. J., Brandt, V. L., & Zoghbi, H. Y. (2020). Advances in understanding of Rett syndrome and MECP2 duplication syndrome: Prospects for future therapies. *The Lancet Neurology*, *19*, 689–698.

Shao, Y., Sztainberg, Y., Wang, Q., Bajikar, S. S., Trostle, A. J., Wan, Y. W., Jafar-Nejad, P., Rigo, F., Liu, Z., Tang, J., & Zoghbi, H. Y. (2021). Antisense oligonucleotide therapy in a humanized mouse model of MECP2 duplication syndrome. *Science Translational Medicine*, *13*, eaaz7785.

Stallworth, J. L., Dy, M. E., Buchanan, C. B., Chen, C. F., Scott, A. E., Glaze, D. G., Lane, J. B., Lieberman, D. N., Oberman, L. M., Skinner, S. A., Tierney, A. E., Cutter, G. R., Percy, A. K., Neul, J. L., & Kaufmann, W. E. (2019). Hand stereotypies: Lessons from the Rett syndrome natural history study. *Neurology*, *92*, e2594–e2603.

Strati, F., Cavalieri, D., Albanese, D., De Felice, C., Donati, C., Hayek, J., Jousson, O., Leoncini, S., Pindo, M., Renzi, D., & Rizzetto, L. (2016). Altered gut microbiota in Rett syndrome. *Microbiome*, *4*, 41.

Sztainberg, Y., Chen, H. M., Swann, J. W., Hao, S., Tang, B., Wu, Z., Tang, J., Wan, Y. W., Liu, Z., Rigo, F., & Zoghbi, H. Y. (2015). Reversal of phenotypes in MECP2 duplication mice using genetic rescue or antisense oligonucleotides. *Nature*, *528*, 123–126.

Takeguchi, R., Takahashi, S., Akaba, Y., Tanaka, R., Nabatame, S., Kurosawa, K., Matsuishi, T., & Itoh, M. (2021). Early diagnosis of MECP2 duplication syndrome: Insights from a nationwide survey in Japan. *Journal of the Neurological Sciences*, *422*, 117321.

Tarquinio, D. C., Hou, W., Berg, A., Kaufmann, W. E., Lane, J. B., Skinner, S. A., Motil, K. J., Neul, J. L., Percy, A. K., & Glaze, D. G. (2017). Longitudinal course of epilepsy in Rett syndrome and related disorders. *Brain*, *140*, 306–318.

Van Esch, H., Bauters, M., Ignatius, J., Jansen, M., Raynaud, M., Hollanders, K., Lugtenberg, D., Bienvenu, T., Jensen, L. R., Gecz, J., & Moraine, C. (2005). Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. *American Journal of Human Genetics*, *77*, 442–453.

Wang, S. Y., Lee, W. T., Shieh, J. Y., Huang, Y. H., Wong, L. C., Tsao, C. H., Chiu, Y. L., & Wu, Y. T. (2022). Multidimensional development and adaptive behavioral functioning in younger and older children with Rett syndrome. *Physical Therapy & Rehabilitation Journal*, *102*, pzab297.

Wong, S. B., Wang, T. S., Tsai, W. H., Tzeng, I. S., & Tsai, L. P. (2021). Parenting stress in families of children with Prader-Willi syndrome. *American Journal of Medical Genetics. Part A*, *185*, 83–89.

Young, D. R., Suter, B., Levine, J. T., Glaze, D. G., & Layne, C. S. (2022). Characteristic behaviors associated with gait of individuals with Rett syndrome. *Disability and Rehabilitation*, *44*, 1508–1515.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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