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# Clinical severity and quality of life in children and adolescents with Rett syndrome

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## ABSTRACT

**Objective:** The clinical features and genetics of Rett syndrome (RTT) have been well studied, but examination of quality of life (QOL) is limited. This study describes the impact of clinical severity on QOL among female children and adolescents with classic RTT.

**Methods:** Cross-sectional and longitudinal analyses were conducted on data collected from an NIH-sponsored RTT natural history study. More than 200 participants from 5 to 18 years of age with classic RTT finished their 2-year follow-up at the time of analysis. Regression models after adjustment for their *MECP2* mutation type and age at enrollment were used to examine the association between clinical status and QOL.

**Results:** Severe clinical impairment was highly associated with poor physical QOL, but worse motor function and earlier age at onset of RTT stereotypies were associated with better psychosocial QOL; conversely, better motor function was associated with poorer psychosocial QOL.

**Conclusions:** Standard psychosocial QOL assessment for children and adolescents with RTT differs significantly with regard to their motor function severity. As clinical trials in RTT emerge, the Child Health Questionnaire 50 may represent one of the important outcome measures.

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## GLOSSARY

**CHQ-PF50** = Child Health Questionnaire 50; **CSS** = Clinical Severity Scale; **MBA** = Motor Behavior Analysis; **MECP2** = methyl-CpG-binding protein 2; **PhS** = Physical Summary; **PsS** = Psychosocial Summary; **QOL** = quality of life; **RTT** = Rett syndrome.

Rett syndrome (RTT), a neurodevelopmental disorder occurring in 1 of 10,000 female births,<sup>1-5</sup> is characterized by apparently normal psychomotor development during the first 6–18 months of life followed by regression (loss of purposeful hand use and spoken communication skills), social withdrawal, cognitive impairment, gait dysfunction,<sup>6</sup> and stereotypic hand movements, a hallmark of RTT.<sup>7</sup>

Mutations in the methyl-CpG-binding protein 2 gene (*MECP2*), located at Xq28, account for approximately 95% of individuals with RTT.<sup>8,9</sup> Among the more than 250 different pathogenic mutations, the 8 most common point mutations account for about 60% of individuals with RTT. Small deletions in the C-terminal region of MeCP2 represent an additional 7%–9% and large-scale deletions represent 8%–10%.<sup>10</sup>

The spectrum of clinical severity for individuals with RTT correlates with specific mutations. Little is known about the impact of RTT on quality of life (QOL). In anticipation of clinical trials, it is essential to understand the applicability of a general QOL measure, particu-

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larly given the varied clinical status of individuals with RTT. The aim of this study was to examine the relationship between clinical status and general QOL in children and adolescents with RTT. The Child Health Questionnaire 50 (CHQ-PF50) has been used typically in chronic systemic disease in children<sup>11,12</sup> but has also been applied successfully in disorders affecting the central and peripheral nervous systems including cerebral palsy,<sup>13,14</sup> neurofibromatosis,<sup>15</sup> inherited neuropathies,<sup>16</sup> and very preterm birth.<sup>17</sup> As such, the application of this instrument to individuals with RTT was deemed to be appropriate.

**METHODS** **Participants.** Data were derived from the ongoing, multicenter NIH-funded RTT Natural History study initiated in March 2006 at 3 participating sites including Baylor College of Medicine, Greenwood Genetic Center, and the University of Alabama at Birmingham. The RTT Natural History study includes individuals who meet consensus criteria for classic or variant RTT and individuals with *MECP2* mutations who do not meet these criteria. All age, ethnic, and racial groups are eligible. Participants were recruited from those who received care at the study sites or through the assistance of the International Rett Syndrome Foundation. Participants were required to have the ability to travel to one of the study sites for annual evaluations (for those 6 years or older) or biannual evaluation (for those younger than 6 years).

This study included participants from 5 to 18 years of age with classic RTT to remain consistent with the standard CHQ-PF50 protocol. This questionnaire is available in both English and Spanish versions. All participants in this analysis were enrolled in the study for at least 27 months from the baseline to have equal opportunity to provide at least 3 measurements from the baseline, 1-year, and 2-year visits. Demographic and diagnostic information, along with *MECP2* mutation status, was collected at the baseline; clinical severity was assessed at each visit, and the CHQ-PF50 questionnaire was administered annually.

**Standard protocol approvals, registrations, and participant consents.** Approval to conduct the natural history study of RTT was obtained from institutional review boards at each investigative site, and written informed consent was obtained for all participants. In addition, this longitudinal study is registered with clinicaltrials.gov (NCT00299312).

**Clinical status.** Study physicians assessed all participants' clinical severity at each study visit using 2 quantitative scales, Clinical Severity Scale (CSS)<sup>9</sup> and Motor Behavior Analysis (MBA).<sup>18</sup> The CSS was developed as a measure of clinical severity based on key diagnostic and developmental features for RTT including the age at onset of regression and hand stereotypies and the degree of acquired deceleration of head growth. The MBA is more comprehensive in examining motor, behavior, and respiratory dysfunction and, in addition, was intended as a more dynamic measure. Substantial overlap between the CSS and the MBA does exist, but the principal differences are in the more comprehensive nature of the MBA and the developmental features of the CSS.

The CSS is based on 13 individual, ordinal categories measuring clinical features common in RTT.<sup>9</sup> The CSS form evaluates age at onset of regression (range 1–5), somatic and head growth status (range 0–8), motor (range 0–19), communication (range 0–9), and RTT behaviors/other neurologic symptoms (range 0–17). Scores for all items were summed to create a total score (range 1–58). The MBA incorporates measures of behavior/social assessment (range 0–64), orofacial/respiratory assessment (range 0–28), and motor assessment/physical signs (range 0–56).<sup>18</sup> Scores for all items were summed to obtain an overall score (range 0–148). In both measures, higher scores indicated more severe clinical status.

**QOL.** The CHQ-PF50 is a generic QOL instrument designed and normed for children from 5 to 18 years of age. This instrument is a well-validated general QOL measure in pediatric populations with chronic illness. It measures QOL of the child and the family by parent or child report. In this study, the same parent or guardian was asked to complete the questionnaire for each visit to maintain the same reporter. The CHQ-PF50 includes broad-spectrum areas, which can be divided into 12 domains: Physical Functioning, Role/Social Limitations–Emotional/Behavioral, Role/Social Limitations–Physical, Behavior, Mental Health, Self-Esteem, General Health, Bodily Pain, Family Activities, Parent Impact–Time, Parent Impact–Emotional, and Family Cohesion. Each score ranges from 0 to 100; a higher score indicates better QOL. Based on the Physical Functioning, Role/Social Limitations–Physical, General Health, Bodily Pain, Parent Impact–Time, and Parent Impact–Emotional domains, the standardized Physical Summary (PhS) scores were generated, and the standardized Psychosocial Summary (PsS) scores were generated based on the Role/Social Limitations–Emotional/Behavioral, Self-Esteem, Mental Health, Behavior, Parent Impact–Time, and Parent Impact–Emotional.<sup>19</sup>

**Statistical analysis.** To assess any impact of clinical status on QOL for children and adolescents, we examined both cross-sectional and longitudinal relationships between clinical status scores and the CHQ-PF50 PhS and PsS scores. Because the relationship may differ by *MECP2* mutation,<sup>9</sup> we first examined the effect of *MECP2* status on each clinical severity measure and CHQ-PF50 summary scores. We controlled for age to minimize age-related differences associated with the temporal profile of RTT. We used general linear models for cross-sectional analysis and a linear mixed-effect model for longitudinal analysis. For the linear mixed-effect model, we considered random intercept and random slope, as well as unstructured correlation for 3 measures from the same subject. To fit the model, the PROC MIXED procedure with a Kenward-Roger correction was implemented because the correction is known to perform better with missing data in terms of keeping the type I error close to the nominal significance level. To consider different scales between 2 scores, the Spearman rank correlation coefficient was assessed between the CSS and MBA scores and between the 2 QOL summary scores. Statistical significance was compared with the level of 0.05. All analyses were conducted using SAS, version 9.1.3 (SAS Institute, Inc., Cary, NC).

**RESULTS** **Participants.** At the time of the analysis, 260 participants with classic RTT were included. Mean age was 10 years, and 90% were white with 2.7% Asian/Pacific Islander, 4.6% black/African American, and 3% other). Table 1 describes the distribution of *MECP2* mutations. T158M, R255X,

**Table 1** MECP2 mutation distribution

MECP2 mutation	No. (%)
C316TR106W	7 (2.7)
C397TR133C	15 (5.8)
C473TT158M	31 (11.9)
C502TR168X	25 (9.6)
C763TR255X	27 (10.4)
C808TR270X	16 (6.2)
C880TR294X	18 (6.9)
C916TR306C	19 (7.3)
Large-scale deletion	19 (7.3)
C-terminal	21 (8.0)
Other mutation types	47 (18.1)
No mutation	15 (5.8)

and R168X were common mutations, representing about 10% for each; 18% of participants carried uncommon *MECP2* mutations, and no mutation was found in 6%.

About 20% of participants did not have completed CHQ-PF50 questionnaires at the baseline and 1-year visit, and close to 30% did not have completed questionnaires at the 2-year visit. However, no difference was found in age, mutation type, and clinical severity scores between participants who completed the CHQ-PF50 questionnaires and those who did not.

**Clinical status and QOL.** Cronbach  $\alpha$  was examined to assess the reliability of using the CHQ-PF50 summary scores in this population. At each visit, Cron-

bach  $\alpha$  values for PhS were 0.73, 0.72, and 0.67 and those for PsS were 0.78, 0.75, and 0.75, indicating that scores are within an acceptable range. Each CHQ-PF50 domain score was compared with the standard US girl score reported in the QOL manual. All scores other than those for Behavior and Family Cohesion were significantly lower than those from standard US girls. The Behavior and Family Cohesion scores were higher than those for the standard US girls, without statistical significance (results not shown).

The summary statistics and Spearman rank correlations for clinical severity and QOL are shown by study visit in table 2. The mean of CSS scores was 24.1 (SD 7.2) and that of MBA scores was 53.0 (SD 13.6) at the baseline. The means of the CHQ-PF50 PhS and PsS scores were 16.9 (SD 16.2) and 45.4 (SD 11.2) at the baseline, respectively. Annual visits for 2 years did not show any significant change in either clinical status or QOL, but an increasing trend was noted in CSS and CHQ-PF50 PsS scores over time.

**Relationship between mutation type, clinical status, and QOL.** For baseline clinical status and CHQ-PF50 summary scores, we examined whether they differed by *MECP2* mutations after adjustment for age at enrollment. As shown in table 3, CSS scores were different among *MECP2* mutation types ( $p = <0.0001$  and  $p = <0.024$  from the type 3 test). Compared with participants with other mutation types, those with R133C had clinically less severe disease, showing lower scores for both the CSS and

**Table 2** Summary statistics for clinical severity scores and CHQ-PF50 summary scores

Total score	Visit	No.	Median (range)	Mean (SD)	Spearman rank correlation
<b>Clinical severity</b>					
<b>CSS</b>	Baseline	242	24.0 (7.0 to 40.0)	24.1 (7.2)	0.623 <sup>a</sup>
	Year 1	194	24.0 (7.0 to 40.0)	24.2 (7.6)	0.736 <sup>a</sup>
	Year 2	156	24.0 (9.0 to 42.0)	24.3 (7.9)	0.755 <sup>a</sup>
<b>MBA</b>	Baseline	242	53.5 (13.0 to 87.0)	53.0 (13.6)	
	Year 1	194	51.0 (13.0 to 84.0)	51.0 (13.8)	
	Year 2	157	55.0 (20.0 to 81.0)	53.0 (14.3)	
<b>CHQ-PF50</b>					
<b>Physical</b>	Baseline	186	13.1 (−8.5 to 59.4)	16.9 (16.2)	0.252 <sup>a</sup>
	Year 1	152	11.9 (−5.0 to 57.6)	15.8 (15.3)	0.220 <sup>a</sup>
	Year 2	104	14.6 (−7.7 to 54.9)	17.2 (14.3)	0.105
<b>Psychosocial</b>	Baseline	186	45.3 (12.6 to 70.0)	45.4 (11.2)	
	Year 1	152	47.8 (19.7 to 66.5)	46.2 (10.3)	
	Year 2	104	47.3 (19.6 to 72.6)	47.0 (10.7)	

Abbreviations: CHQ-PF50 = Child Health Questionnaire 50; CSS = Clinical Severity Scale; MBA = Motor Behavior Analysis.

<sup>a</sup> $p < 0.05$ .

**Table 3** Age-adjusted estimates for mutation variable with clinical severity scores or CHQ-PF50 summary scores as dependent variables

	Clinical severity				CHQ-PF50			
	CSS		MBA		PhS		PsS	
<i>MECP2</i> mutation	PE (SE)	p Value	PE (SE)	p Value	PE (SE)	p Value	PE (SE)	p Value
C316T (R106W)	6.72 (3.05)	0.028 <sup>a</sup>	3.68 (6.10)	0.548	1.48 (9.64)	0.878	10.58 (6.54)	0.107
C397T (R133C)	−5.17 (1.92)	0.008 <sup>a</sup>	−11.06 (3.84)	0.004 <sup>a</sup>	10.75 (5.12)	0.037 <sup>a</sup>	0.20 (3.47)	0.955
C473T (T158M)	0.30 (1.57)	0.850	−2.12 (3.14)	0.499	1.52 (4.33)	0.725	1.58 (2.94)	0.590
C502T (R168X)	0.69 (1.64)	0.676	−5.38 (3.29)	0.103	−1.81 (4.67)	0.700	0.85 (3.17)	0.788
C763T (R255X)	1.81 (1.58)	0.254	−2.11 (3.16)	0.505	−1.97 (4.47)	0.660	8.05 (3.03)	0.009 <sup>a</sup>
C808T (R270X)	6.88 (1.92)	0.001 <sup>a</sup>	2.93 (3.85)	0.447	−5.11 (5.45)	0.350	7.62 (3.70)	0.041 <sup>a</sup>
C880T (R294X)	−5.25 (1.83)	0.005 <sup>a</sup>	−5.13 (3.67)	0.164	2.45 (5.12)	0.632	−6.24 (3.47)	0.074
C916T (R306C)	−3.46 (1.88)	0.067	−4.38 (3.77)	0.246	5.14 (5.50)	0.351	4.53 (3.73)	0.226
Large-scale deletion	1.98 (1.80)	0.273	2.42 (3.60)	0.501	0.69 (5.12)	0.893	5.64 (3.47)	0.106
C-terminal	−2.59 (1.72)	0.135	−1.74 (3.45)	0.615	−7.72 (4.85)	0.113	0.42 (3.29)	0.898
No mutation	−3.14 (2.02)	0.122	−11.06 (4.05)	0.007 <sup>a</sup>	6.94 (5.45)	0.205	7.34 (3.70)	0.106
Other mutation types	Referent		Referent		Referent		Referent	
Type 3 test		<0.0001 <sup>a</sup>		0.0240 <sup>a</sup>		0.2154		0.0136 <sup>a</sup>

Abbreviations: CHQ-PF50 = Child Health Questionnaire 50; CSS = Clinical Severity Scale; MBA = Motor Behavior Analysis; PE = parameter estimate; PhS = Physical Summary; PsS = Psychosocial Summary.

<sup>a</sup> $p < 0.05$ .

MBA. The CHQ-PF50 PsS scores, but not the PhS scores, were different across all mutation types ( $p = 0.0136$ ). Participants with R133C showed significantly higher PhS scores than those with other mutations, which is consistent with the results from clinical severity analysis. This result implies that participants with an R133C mutation were clinically and physically better than those with other mutations. R270X carriers had better PsS scores and worse clinical status on the CSS than those with other mutation types.

The effect of clinical severity on CHQ-PF50 summary scores was examined after adjustment for *MECP2* and age at enrollment from cross-sectional analysis at each study visit and from longitudinal analysis (table 4). Worse clinical status from both the CSS and MBA was highly associated with lower PhS scores at each visit. For example, at the baseline, if 2 participants had the same age and mutation, a participant with 1 score higher in the MBA would have a 0.43 lower PhS score, but a participant with 1 score higher in the CSS would have a 0.91 lower PhS score. Whereas the MBA had no effect on the PsS scores, worse clinical status measured from the CSS was significantly associated with higher PsS. For example, at the baseline, if 2 participants had the same age and mutation, a patient with 1 score higher in the CSS would have a 0.26 higher PsS score. By longitudinal analysis using all the data from all study visits,

we examined the fixed effect of clinical severity on QOL. For any 2 participants, if their age and *MECP2* mutations were the same, a unit increase of the MBA score resulted in a 0.32 decrease in the PhS score and that of the CSS score resulted in a 0.69 decrease in the PhS score ( $p < 0.0001$ ). Conversely, a unit increase of the CSS score produced a 0.20 increase in the PsS score ( $p = 0.028$ ), but a unit increase in the MBA score would have no effect. This result is consistent with the cross-sectional analysis that worse clinical status measured from the CSS is highly associated with higher psychosocial function in the current sample.

**Relationship between motor assessment and psychosocial aspects of QOL.** In clinical practice, it has been noted that participants who have better motor function, such as walking and hand use, tend to exhibit more behavior problems including aggressive behaviors toward others, self-abusive behaviors, and risky behaviors such as walking into traffic or opening doors, which may lead to injury. Although both clinical severity scales assess the participant's motor function, only the MBA includes measures of behavior/social assessment. Our analysis showed a significant association of psychosocial function measured by the CHQ-PF50 with clinical severity measured by the CSS, but not by the MBA. In addition, we found an increasing trend of CHQ-PF50 PsS scores with ear-



**Table 4** Age- and mutation type-adjusted estimates for clinical severity with CHQ-PF50 summary scores as dependent variables at each visit

Clinical severity	Visit	No. observations used	PhS				PsS			
			Cross-sectional		Longitudinal		Cross-sectional		Longitudinal	
			PE (SE)	p Value	PE (SE)	p Value	PE (SE)	p Value	PE (SE)	p Value
MBA	Baseline	186	-0.43 (0.09)	<0.0001 <sup>a</sup>	-0.32 (0.06)	<0.0001 <sup>a</sup>	-0.00 (0.06)	0.967	-0.01 (0.04)	0.764
	12 mo	151	-0.34 (0.09)	0.001 <sup>a</sup>			0.02 (0.06)	0.765		
	24 mo	104	-0.35 (0.10)	0.001 <sup>a</sup>			0.08 (0.08)	0.371		
CSS	Baseline	186	-0.91 (0.18)	<0.0001 <sup>a</sup>	-0.69 (0.12)	<0.0001 <sup>a</sup>	0.26 (0.13)	0.043 <sup>a</sup>	0.20 (0.09)	0.028 <sup>a</sup>
	12 mo	151	-0.55 (0.18)	0.003 <sup>a</sup>			0.32 (0.12)	0.006 <sup>a</sup>		
	24 mo	104	-0.77 (0.18)	<0.0001 <sup>a</sup>			0.34 (0.15)	0.032 <sup>a</sup>		

Abbreviations: CHQ-PF50 = Child Health Questionnaire 50; CSS = Clinical Severity Scale; MBA = Motor Behavior Analysis; PE = parameter estimate; PhS = Physical Summary; PsS = Psychosocial Summary.

<sup>a</sup>p < 0.05.

lier onset age of RTT stereotypes, which is measured as a part of the RTT behaviors/other neurologic symptoms subscale in the CSS. Thus, additional analyses were performed to see whether or not certain subscales either in the CSS or in the MBA had a major role in this finding. Table 5 summarizes the results.

Subscales from the MBA did not show any association. As for the CSS, scores for subscales involving motor function and age at onset of RTT stereotypes were consistent with findings from the total score, but the remainder of CSS subscales excluding those for motor function and age at onset of RTT stereotypes did not show any association with the PsS scores. This result implies that those with classic RTT who have worse motor function tend to have better psychosocial QOL; the CSS elucidated this relationship whereas the MBA did not. Earlier onset age of RTT stereotypes seems to make the association stronger, especially from the observations at 2 years of follow-up.

**Table 5** Age- and mutation type-adjusted estimates for clinical severity subscales with CHQ-PF50 PsS scores as dependent variables

Clinical severity	Subscale	Visit	Cross-sectional		Longitudinal	
			PE (SE)	p Value	PE (SE)	p Value
MBA	Motor	Baseline	0.16 (0.14)	0.235	0.09 (0.08)	0.261
		12 mo	0.21 (0.13)	0.121		
		24 mo	0.19 (0.17)	0.246		
	Behavior/Social	Baseline	-0.07 (0.12)	0.580	-0.09 (0.08)	0.254
		12 mo	-0.05 (0.12)	0.674		
		24 mo	0.13 (0.15)	0.410		
CSS	Motor and age at onset of RTT stereotypes	Baseline	0.45 (0.19)	0.020 <sup>a</sup>	0.33 (0.14)	0.015 <sup>a</sup>
		12 mo	0.45 (0.17)	0.009 <sup>a</sup>		
		24 mo	0.49 (0.24)	0.042 <sup>a</sup>		
	Excluding motor and age at onset of RTT stereotypes	Baseline	0.18 (0.22)	0.431	0.14 (0.14)	0.346
		12 mo	0.41 (0.22)	0.067		
		24 mo	0.45 (0.29)	0.127		
	Motor	Baseline	0.45 (0.20)	0.030 <sup>a</sup>	0.33 (0.15)	0.027 <sup>a</sup>
		12 mo	0.48 (0.18)	0.011 <sup>a</sup>		
		24 mo	0.47 (0.26)	0.070		
	Age at onset of RTT stereotypes	Baseline	1.94 (1.11)	0.083	1.86 (0.87)	0.034 <sup>a</sup>
		12 mo	1.81 (1.08)	0.095		
		24 mo	3.17 (1.49)	0.036 <sup>a</sup>		

Abbreviations: CHQ-PF50 = Child Health Questionnaire 50; CSS = Clinical Severity Scale; MBA = Motor Behavior Analysis; PE = parameter estimate; PsS = Psychosocial Summary; RTT = Rett syndrome.

<sup>a</sup>p < 0.05.

**DISCUSSION** This study examined the relationships among *MECP2* mutations, clinical severity, and psychosocial and physical aspects of QOL for individuals with classic RTT. QOL assessment, in general, has received increased attention in recent years with respect to its potential as a useful metric in the conduct of clinical trials. The CHQ-PF50 has been shown to perform effectively in the pediatric age range for both general medical problems<sup>11,12</sup> and disorders affecting the central and peripheral nervous systems. The latter include studies on individuals with cerebral palsy<sup>13,14</sup> and, more recently, for neurofibromatosis,<sup>15</sup> inherited peripheral neuropathies,<sup>16</sup> and very low birth weight preterm birth.<sup>17</sup> In each neurologic scenario, the CHQ-PF50 was able to detect adverse effects on QOL, suggesting that it could be a useful outcome measure for determining efficacy in clinical trials. This is particularly relevant to RTT as the emergence of credible pharmacologic interventions is widely anticipated.

Therefore, in the present study, both cross-sectional and longitudinal analyses showed that higher scores on the CSS and MBA significantly de-

creased the CHQ-PF50 physical summary scores. This result suggests that worse clinical status is associated with worse QOL in the physical domain. This finding is not surprising, given that more severe motor impairments most likely impair the ability to carry out motor functions, thereby negatively influencing the physical QOL. However, we also found that higher scores on the CSS were related to better scores on the CHQ-PF50 psychosocial domain, which suggests that participants with worse clinical status tend to have better psychosocial functioning. This finding may seem somewhat counterintuitive. However, it may be that severe clinical impairments (such as very low motor functioning) inhibit those individuals with RTT from being able to engage in negative behaviors such as aggression or self-injury that would otherwise adversely affect their psychosocial QOL. In fact, our in-depth investigation highlighted the fact that worse motor functioning along with earlier age at onset of RTT stereotypies was the area of clinical status that accounted for higher CHQ-PF50 PsS scores. In addition, we did not find any change over time in measurements of clinical severity and QOL during the 2-year course of the study. This may be because developmental change is slow in RTT and may suggest that investigators should lengthen follow-up time for studies.

Family life satisfaction in RTT families has not been reported. A single study from 2006 found that the most important predictors of physical and mental health in mothers of children with Rett syndrome were child behavior, caregiver demands, and family function.<sup>20</sup>

The CHQ-PF50 assesses Family Cohesion, which is independent of the composite physical and psychosocial scores. Family Cohesion correlates significantly with the PsS score but not with the PhS score. As such, the degree of motor impairment does not seem to affect family cohesion. The CHQ-PF50 does not capture parental stress directly. Rather, it looks at tension, conflict, and the ability of families to get along with one another, which might be perceived as causing stress. It has been suggested that early diagnosis may lead to better services, access to resources, or expectations of outcome. The principal advocacy group, the International Rett Syndrome Foundation, may fill the needs of families with children with recently diagnosed RTT to an extent not available previously, which might decrease family stress for some. We have no evidence to support this idea, however. One feature of RTT that is almost universal and could affect family QOL is sleep dysfunction, which would affect families across the spectrum of involvement.

Our findings may have implications for the applicability of the measures used in this study for individ-

uals with RTT. Overall clinical status scores on both the CSS and the MBA showed significant relationships with the physical QOL score on the CHQ-PF50. This result probably suggests that both clinical status measures and the CHQ-PF50 perform well in this population. However, only the CSS was related to the psychosocial QOL score on the CHQ-PF50, which implies that the CSS, rather than the MBA, more strongly assesses clinical status factors that correlate with the psychosocial components of QOL. Conversely, it may be that the CHQ-PF50, which is a general measure of QOL, does not appropriately measure this construct in the population with RTT, particularly given the surprising finding that worse motor functioning on the CSS was related to better psychosocial QOL. For future research, it may be useful to develop RTT-specific measures of QOL.

The current study has several limitations worth noting. In this study, the CHQ-PF50 questionnaires were completed by parents, not the participants, which may increase the bias in the measurements. However, in that individuals with RTT have significant cognitive and fine motor impairments, the completion of this questionnaire by participants is not feasible. Another limitation of the current study is that statistical analyses were correlational in nature. Thus, we cannot determine whether a causal relation exists between the study variables.

Nevertheless, for children and adolescents with RTT, QOL is significantly related to clinical severity. Whereas poorer physical QOL is related to greater clinical severity, better psychosocial QOL is related to greater motor impairment. Conversely, poorer psychosocial QOL is related to better scores on our measure of clinical severity. As clinical trials in RTT emerge, the CHQ-PF50 may represent one of the important outcome measures.

## AUTHOR CONTRIBUTIONS

J.B. Lane: study conceptualization, study conduct, data collection, manuscript preparation. Dr. Lee: study conceptualization, study conduct, data collection and statistical analysis, manuscript preparation. Dr. Smith: study conceptualization, manuscript preparation. P. Cheng: data analysis, manuscript preparation. Dr. Percy: study conceptualization, study conduct, data collection, manuscript preparation. Dr. Glaze: study conduct, data collection, manuscript review. Dr. Neul: study conduct, data collection, manuscript review. Dr. Motil: study conduct, manuscript review. J.O. Barrish: study conduct, data collection, manuscript review. Dr. Skinner: study conduct, data collection, manuscript review. F. Annese: study conduct, data collection, manuscript review. L. McNair: study conduct, data collection, manuscript review. J. Graham: study conduct, data collection, manuscript review. Dr. Khwaja: study conduct, data collection, manuscript review. K. Barnes: study conduct, data collection, manuscript review. Dr. Krischer: study conceptualization, statistical analysis, manuscript preparation.

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## DISCLOSURE

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