Growth failure and outcome in Rett syndrome: Specific growth references
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Growth failure and outcome in Rett syndrome
Specific growth references

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ABSTRACT

Objectives: Prominent growth failure typifies Rett syndrome (RTT). Our aims were to 1) develop RTT growth charts for clinical and research settings, 2) compare growth in children with RTT with that of unaffected children, and 3) compare growth patterns among RTT genotypes and phenotypes.

Methods: A cohort of the RTT Rare Diseases Clinical Research Network observational study participants was recruited, and cross-sectional and longitudinal growth data and comprehensive clinical information were collected. A reliability study confirmed interobserver consistency. Reference curves for height, weight, head circumference, and body mass index (BMI), generated using a semiparametric model with goodness-of-fit tests, were compared with normative values using Student’s t test adjusted for multiple comparisons. Genotype and phenotype subgroups were compared using analysis of variance and linear regression.

Results: Growth charts for classic and atypical RTT were created from 9,749 observations of 816 female participants. Mean growth in classic RTT decreased below that for the normative population at 1 month for head circumference, 6 months for weight, and 17 months for length. Mean BMI was similar in those with RTT and the normative population. Pubertal increases in height and weight were absent in classic RTT. Classic RTT was associated with more growth failure than atypical RTT. In classic RTT, poor growth was associated with worse development, higher disease severity, and certain MECP2 mutations (pre-C-terminal truncation, large deletion, T158M, R168X, R255X, and R270X).

Conclusions: RTT-specific growth references will allow effective screening for disease and treatment monitoring. Growth failure occurs less frequently in girls with RTT with better development, less morbidity typically associated with RTT, and late truncation mutations. Neurology® 2012;79:1653–1661

GLOSSARY

ANOVA = analysis of variance; BMI = body mass index; CSS = Clinical Severity Score; EDF = equivalent degrees of freedom; FDR = false discovery rate; FOC = fronto-occipital head circumference; MBA = Motor Behavioral Assessment; non-RTT = participants possessing MECP2 mutation but without Rett syndrome; RNHS = Rett Natural History Study; RTT = Rett syndrome.

Growth failure is a prominent feature in Rett syndrome (RTT); however, no RTT-specific growth charts exist. Many comorbid disorders have an impact on growth in RTT, such as oropharyngeal and gastrointestinal dysfunction, scoliosis, seizures, and osteopenia. The pattern of growth in female patients with RTT trends well below the lowest centile on standard growth references,1 which fail to differentiate a normal RTT growth pattern from one caused by malnutrition or illness.

Disease-specific standards screen for disease2–13 and measure the effect of therapeutic interventions designed to improve nutrition and neurologic function.14,15 With more than 200 mutation sites identified in the methyl-CpG-binding protein 2 gene (MECP2), the clinical...
severity in RTT varies widely. Associations exist among specific mutations and functional outcomes such as ambulation, hand use, and language. No study has generated accurate RTT growth references or adequately examined the associations between the degree of growth failure and genotype or clinical severity.

The aim of this study was to develop RTT-specific growth references for clinical and research use. The secondary objectives were to 1) compare the patterns of growth between patients with RTT and the normative population and 2) examine the effects of secular changes, disease severity, and MECP2 mutation on growth.

**METHODS Participants and data collection.** Participants with classic RTT and atypical RTT and MECP2-positive patients without clinical RTT (non-RTT) were recruited from 2006 to 2011 through the multicenter RTT Natural History Study (RNHS) at 1 of 7 sites and evaluated every 6–12 months as described previously. Diagnosis of classic and atypical RTT was based on consensus criteria and was confirmed by an RNHS neurologist or geneticist. All participants had MECP2 testing; participants with clinical RTT were included despite absence of a mutation. Evaluation included fronto-occipital head circumference (FOC), weight, height, or length using standardized techniques, and 2 quantitative scales of developmental abilities and disease severity, the Motor Behavioral Assessment (MBA) and Clinical Severity Score (CSS) (appendix e-2). Interoperator and intraoperator reliability was excellent (within 3 mm or 0.3 kg). To analyze secular trends, supplemental retrospective data were collected for participants seen by A.K.P. before the RNHS.

All female participants with classic and atypical RTT were included. Male participants (n = 20) were excluded, and non-RTT female participants (n = 31) were excluded from growth chart construction because of the paucity of subjects but were retained for comparison of adult measurements. No participants were excluded based on premature birth or secondary medical conditions; however, data on comorbidities were collected. Corrected age was used for premature participants until 2 years of age. A recruitment goal of 750 participants ensured at least 30 participants in each category. These participants were compared among each category using analysis of variance (ANOVA) adjusted for multiple comparisons using the Tukey-Kramer test. Growth velocity (from baseline to 6 years), time to growth nadir, and measurements at key age ranges (0–2, 2–7, 7–12, 12–17, and >17 years) were compared among different genotypes.

The associations of the severity of common RTT characteristics in childhood with adult measurements were examined using linear regression. Characteristics included scoliosis severity (scoliosis), periodic breathing (hyperventilation), repetitive hand movements (stereotypies), seizure severity (seizure), ability to speak after regression (language) and communicate wants through nonverbal means (nonverbal), and age at which the following occurred or were acquired: hand use, ambulation, sitting unsupported (sitting), and regression of verbal and motor skills (regression). Puberty onset based on Tanner staging was compared with race-specific standards. Associations of age of pubertal onset with growth, RTT characteristics, and genotypes were examined. Patients were categorized based on proportion of FOC to somatic size. Associations of these proportions with diagnoses, secular trends, RTT characteristics, genotype, and pubertal onset were examined using ANOVA.

Analyses were performed using SAS version 9.1 (SAS Inc., Cary, NC), SPSS version 15.0 (SPSS Inc., Chicago, IL), and LMSChartmaker. A value of p < 0.05 was considered significant for all tests, and FDR < 0.05 was used to correct results for growth chart comparison.
RESULTS Of 878 female participants, 8 RNHS and 54 supplemental participants were excluded because of unconfirmed diagnoses. The remaining participants, 726 with classic RTT and 90 with atypical RTT, were followed up to 3.25 years (mean 1.5 years).

Demographics. Participants were mostly Caucasian and non-Hispanic (table 2). Birth year ranged from 1945 to 2008. Nearly all lived at home, and none born after 1997 lived in a group home or institution. Two-thirds were diagnosed before age 4 years, and half were enrolled by age 10.

Mutation frequencies. Among 816 participants, 751 (92%) had mutations in MECP2, including 689 with classic RTT (95%) and 62 with atypical RTT (69%). The 8 common point mutations made up 56% of classic RTT and 37% of atypical RTT mutations (table 1).

Measurements. Overall, 9,749 observations were recorded, averaging 12 per individual: 9,240 weight, 6,178 FOC, and 6,937 BMI; the majority (90.6%) were for participants with classic RTT. The number of observations decreased with age but remained greater than 40 per year in classic RTT (table e-1). Height measurements included 44% recumbent, 50% standing, and 6% calculated from segmental measurements. After 3 years of age, the majority were measured standing. Measurement type did not affect average height before 5.5 years, beyond which average height or length was shorter in participants measured recumbent. After 2.5 years, CSS was higher for participants measured recumbent.

Summary statistics. Birth. Mean birth measurements in participants with both classic and atypical RTT were similar to those in the normative population (data not shown).

Adulthood. Adult RTT measurements were homogeneously distributed from normal (obese in the cases of weight and BMI) to extremely low (table 3). Average adult age was 25.4 years. Final adult height, weight, BMI, and FOC for participants with classic and atypical RTT were lower than those for non-RTT participants ($p < 0.001$); however, no difference existed between those with classic and atypical RTT.

Growth references. The LMS method generated classic RTT charts with empirical data evenly distributed at younger ages and moderately dense at older ages. At ± 3 SD the charts tended to overestimate weight

<table>
<thead>
<tr>
<th>Classification</th>
<th>Mutation</th>
<th>Classic RTT (n = 726)</th>
<th>Atypical RTT (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Type or location</td>
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<td></td>
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<tr>
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<td>3</td>
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<tr>
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<td>11.0</td>
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</tr>
<tr>
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<td>5.1</td>
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</table>

* Data could not be collected on all participants for all demographic categories.
Patterns of growth in classic RTT. Weight. The mean weight trajectory for classic RTT diverged below the normative pattern at age 6 months (figure 1). Mean weight was lower than the normative at 13 months ($p = 0.04$, FDR $= 0.05$). By age 12.5 years, mean weight was equal to the normative second percentile. Weight distribution was wider than that in unaffected children, and between 7 and 12 years, 6.4% were above the 98th percentile. By 18 years, 71% of participants were below the second percentile on the normative reference. When participants were examined individually, 80% fell below the second percentile for weight at some point during development; only 51% of participants declined in weight velocity $>1.3$ SD.

Height. Mean RTT height fell below the normative mean by 17 months ($p = 0.02$, FDR $= 0.03$) (figure 1). By age 12 years, mean height was $<2$ SD. The distribution of height was also wide; between 12 and 17 years, 7.9% of participants were taller than the 98th percentile. By 18 years, 84.5% of adults were below the second percentile for height. Individual height velocity fell $>1.3$ SD in 41% of participants, and 87.5% were below the second percentile for height at some point.

FOC. Mean FOC for RTT fell below the normative mean by 1 month ($p < 0.0001$, FDR $< 0.0001$) (figure 2). By 2 years, mean FOC was $<2$ SD; no individual had an FOC above the 98th percentile thereafter. At 18 years, 81% were below the second percentile. Individual FOC velocity fell $>1.3$ SD in 44%, and 86% had a minimum FOC below the second percentile at some point.

BMI. The mean BMI trajectory for children with RTT fell slightly below that for normal children at 4–5 months, but mean RTT BMI was similar to the normative mean after 9 months (figure 2). At 18 years, the average BMI was 20, compared with 21 for normal women. The distribution was wide with 36% below the normative second percentile and 19% above the 98th percentile at some point in development, typically between 12 and 17 years. Despite normal average BMI, growth failure was evident in BMI velocity, which fell $>1.3$ SD in 57% of participants.

Classic vs atypical RTT. No differences in average measurements were found between participants with classic and atypical RTT. Growth patterns were different ($p < 0.01$), with a higher proportion of participants with atypical RTT exhibiting either preserved somatic growth with microcephaly or normal growth (patterns 2 and 5) (figure e-1A).

Based on secular trends. Mean standardized weight was lower in participants born before 1997 ($M = -1.86$), compared with those born during or after 1997 ($M = -1.42$, $p = 0.05$). A higher proportion of participants born during or after 1997 exhibited growth pattern 2, preserved somatic growth with microcephaly ($p < 0.001$) (figure e-1B).

Rett syndrome characteristics. Functional limitations, including overall severity, hand use, ambulation, nonverbal communication, scoliosis, seizures, stereotypes, hyperventilation, sitting, and regression were associated with lower adult measurements (table e-2), but verbal language was not. Growth proportions were associated with overall disease severity.
Height in Rett syndrome falls below the normative population at 21 months, and weight is lower at 13 months. Pubertal growth spurt is attenuated.

hand use, ambulation, scoliosis, seizures, sitting ($p < 0.001$) but not with language, stereotypies, hyperventilation, or regression. Preserved somatic growth, with or without microcephaly, was associated with better outcome (patterns 2 and 5) (figure e-1, C–H).

Genotype and growth. Two- to 7-year age range and mutation ($n = 494$). Weight was higher in participants with C-terminal truncation than in those with pre-C-terminal truncation, large deletion, no mutation, T158M, R168X, and R255X ($p < 0.001$). BMI was also higher in those with late truncation than in those with either early truncation or large deletion ($p = 0.001$). Head circumference was higher in those with the R294X point mutation than in those with R255X and R270X point mutations ($p = 0.001$).

Seven- to 12-year age range and mutation ($n = 272$). Head circumference was smaller in participants with pre-C-terminal truncation than in the other missense and no mutation groups, and smaller in those with large deletion than in those with no mutation ($p < 0.05$).

Adult ($n = 169$). No significant difference in final average adult measurements existed among mutation types.
Growth velocity and mutation. The decline in standardized weight from baseline to 6 years was lower in participants with C-terminal truncation than in those with pre-C-terminal truncation, large deletion, other missense, T158M, R255X, and R270X ($p < 0.001$). Average weight velocity was lower for those with R270X than for those with R306C and R133C ($p < 0.001$). BMI velocity was higher in those with C-terminal truncation than in those with large deletion, other missense, R294X, and R270X ($p = 0.001$). Head circumference velocity was lower in those with pre-C-terminal truncation than in the C-terminal truncation group ($p < 0.05$).

Age at minimum SD score and mutation. Participants with pre-C-terminal truncation and large deletion reached their minimum standardized weight at an earlier age than those with C-terminal truncation ($p < 0.05$). Likewise, those with pre-C-terminal truncation reached their minimum BMI before those with C-terminal truncation ($p < 0.05$). The pre-C-terminal truncation group reached minimum FOC before the other missense group, and those with R270X reached their FOC nadir before those with

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Head circumference in Rett syndrome falls below the normative population at 1 month of age. Average BMI is similar to normative population, but distribution is wider.

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**Figure 2** Head circumference and body mass index (BMI) in unaffected children (orange) and children with classic Rett syndrome (blue)
R294X and R133C ($p < 0.05$). None of these associations was influenced by age of the participants at the final measurement.

**Puberty and growth in classic RTT.** Age of pubertal onset ($n = 66$) ranged from 5.1 to 16.6 years and was associated with final height, weight, and BMI ($p < 0.001$) but not with any measures of disease severity or specific MECP2 mutations. Normal pubertal onset adjusted for race occurred in 85%, with precocious puberty in 12% and late-onset puberty in 3%. Patterns of growth varied with age of pubertal onset ($p < 0.001$). Average age of pubertal onset was $8.8 \pm 0.9$ years in participants with normal growth (pattern 5), $9.3 \pm 1.7$ years in those with microcephaly and preserved somatic growth (pattern 2), $10.2 \pm 0.8$ years in those with microcephaly and mild somatic growth failure (pattern 3), and $11.5 \pm 1.7$ years in those with microcephaly and global somatic growth failure (pattern 1) (figure e-1I).

**DISCUSSION** Growth studies in RTT have been limited to small populations or specific anthropometric measurements, and most were performed before MECP2 mutations were discovered or used statistical methods insufficient for calculating $z$ scores. This study demonstrates that the patterns of growth in RTT are different from those in unaffected individuals. Functional gross motor, fine motor, and nonverbal language deficits, as well as the presence of seizures, scoliosis, and RTT behaviors earlier in life are associated with severity of growth failure in late childhood and adolescence. Research on acquired microcephaly suggests that sparing of somatic growth confers a better developmental outcome. We found that despite persistent microcephaly, preserved somatic growth occurs in 45% of girls with RTT and is associated with better development and lower seizure, scoliosis, and RTT behavior burden, contradicting dogma that “proportional” microcephaly conveys a protective effect. The resting metabolic rate is higher in patients with RTT than in those with other developmental disabilities, and intensive nutritional therapy improves growth outcomes. These findings suggest both that growth is an important outcome for clinical trials and that improved nutrition could moderate the association between growth and development.

No study has adequately examined BMI in RTT. One assessed BMI in large age clusters that precluded analysis of BMI velocity. Despite height and weight failure, mean BMI in classic RTT is similar to that of unaffected, healthy females. Because BMI distribution in RTT is wide, standard BMI values overestimate low BMI. Conversely, decreasing BMI velocity was a sensitive marker for weight failure when absolute values were normal. Notably, the normal pubertal increase in height or weight velocity was absent in RTT. Although height in normative references is invariably positively skewed, height in adults with RTT was negatively skewed, suggesting that few women with RTT are tall, whereas many are extremely short.

Mutation in MECP2 was associated with growth velocity, the crucial prerequisite of growth failure. Growth failure was more evident in those with mutations associated with greater clinical severity such as pre-C-terminal truncation and R270X than in mutations associated with a milder burden such as R306C, R133C, and C-terminal truncation. Conditional references based on genotype could aid in studying the factors contributing to growth failure in RTT and response to treatment.

Concern exists that disease-specific charts based on biased methodology or insubstantial data will become standards for a disorder. However, most individuals with RTT after age 7–8 years have measurements less than $–3$ SD compared with those for unaffected individuals. Statistical comparisons beyond $–3$ SD contain insufficient empirical data and are imprecise. This study addressed methodologic concerns by recruiting 7% of the RTT population in the United States, ranging in disease severity and coming from many racial, ethnic, and geographical backgrounds, through the International Rett Syndrome Foundation. Although not designed for longitudinal data, LMS produces precise curves and was selected from among 30 methods by the World Health Organization.

The benefit of the World Health Organization prescriptive standards based on normal, healthy, breastfed international populations remains unclear. Alternately, empirical data restricted to certain outcomes regarded as favorable could represent the standard for growth in the disorder. One limitation of this study is that quantitative measures of therapeutic or nutritional intervention were not incorporated. Gastrostomy tube supplementation affects growth, and other interventions such as physical therapy may as well. Several potential contributors to growth failure, such as nutrition, seizure disorder, anxiety, constipation, gastroesophageal reflux, and orthopedic issues, can be modified. The RNHS study is currently collecting information on these aspects of health care that will be included in subsequent analyses designed to identify prescriptive targets for normal growth.

Our growth charts will allow researchers to more precisely examine the effects of novel RTT treatments. Moreover, clinicians will be able to assess medical health and the effect of interventions. As
definitions of “healthy” individuals with RTT emerge from the natural history study, prescriptive standards of growth will provide objective data about how individual children with RTT should be growing. Comparison of aggressive and standard treatment of variables influencing growth could lend further insight into the interplay between nutrition, growth, and health in individuals with RTT.

AUTHOR CONTRIBUTIONS
Daniel C. Tarquinio: study conduct, data collection, manuscript preparation. Kathleen J. Motil: study conceptualization, study conduct, data collection, manuscript review. Wei Hou: statistical analysis, manuscript review. Hye-Seung Lee: study conduct, data collection and statistical analysis, manuscript review. Daniel G. Glaze: study conduct, data collection, manuscript review. Steven A. Skinner: study conduct, data collection, manuscript review. Jeffrey L. Neul: study conduct, data collection, manuscript review. Fran Annese: study conduct, data collection, manuscript review. Suzanne Geerts: study conduct, data collection, manuscript review. Jane B. Lane: study conceptualization, study conduct, data collection, manuscript preparation. Alan K. Percy: study conceptualization, study conduct, data collection, manuscript preparation.

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REFERENCES


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