

The Developmental Plateau in Rett Syndrome: New Insights from the Natural History Study to Inform Novel Interventional Study Designs

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Poster 302

Aims

This study evaluated whether developmental milestone gain or regain in a developmental plateau population (age 26 years) from a trial-anchored RHNS analysis cohort could support a natural-history-informed null hypothesis and a plateau-anchored, baseline-adjusted aggregate responder analysis framework for use in future interventional studies

Background

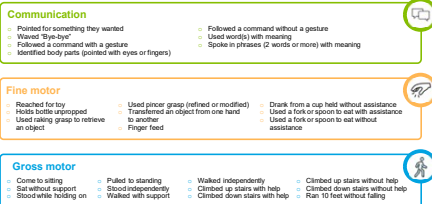
- RTT is a rare neurodevelopmental disorder characterized by heterogeneous developmental trajectories, including variable gain, loss, retention and occasional regain of developmental milestones^{1,2}
- Heterogeneity complicates interpretation of treatment-associated change in interventional studies, particularly when baseline function and developmental history differ across participants³⁻⁶
- PACOC approaches preserve individualized participant interpretation but do not inherently support prespecified group-level inference or powered aggregate analyses⁷
- Trial design challenges are compounded when evaluating an investigational gene therapy for RTT due to ethical and methodological concerns with sham controls (e.g., lumbar puncture without active agent), potential functional unblinding from required immunosuppression, and delayed-treatment control designs that may expose participants to unjust harm by postponing intervention during critical neurodevelopmental windows⁸⁻¹⁴
- The US Rett Syndrome Natural History Study (RHNS) >1800 participants with RTT and RTT-related disorders provides longitudinal data on developmental milestone trajectories;¹⁵⁻¹⁶ recent analyses indicated a clear developmental plateau beyond 6 years of age, with minimal spontaneous milestone gain/regain¹⁷
- The aims were to use the RHNS dataset to confirm a plateau in a trial-like analysis cohort; evaluate whether clinical, genotypic, and sociodemographic factors affect incidence of milestone gain in the plateau population; develop a plateau-anchored, baseline-adjusted aggregate responder analysis framework that uses an appropriate natural-history-informed single null hypothesis; and validate this null using 10,000 simulated control cohorts using the RHNS dataset

Methods

Study design

- Cohort analysis of RHNS data using cumulative incidence of developmental milestone gain, loss, and regain over time
- Participants were female with typical RTT and confirmed MECP2 mutation; inclusion/exclusion criteria were aligned to those typically used in interventional RTT trials
- Developmental milestone selection
 - Starting from 151 potential developmental milestones captured in the RHNS protocols (MECP2, 2006-2014; MECP2, 2015-2021)¹⁸ RHNS study principal investigators, RTT specialists, and caregivers identified milestones that were linked to activities of daily living and that were independently meaningful based on caregiver concept elicitation work
 - Finally, milestones with higher likelihood of spontaneous gain in an untreated population were also excluded, resulting in a selected set of 28 milestones for analysis (Figure 1)

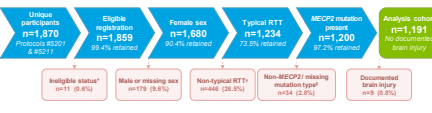
Figure 1: 28 developmental milestones that reflect meaningful functional gains to caregivers, with low likelihood of being achieved without treatment, used in the study analysis



Analysis cohort selection

- Parameters closely matching typical interventional RTT trial inclusion/exclusion criteria were applied to the RHNS dataset¹⁹ to select a trial-aligned analysis cohort representative of potential study participants (Figure 2)

Figure 2: Inclusion flow of RHNS population for developmental plateau analyses



Accounting for prognostic variables

- Prespecified prognostic covariates, identified a priori through literature review and endorsed by RHNS study PIs, were evaluated across sociodemographic, genetic, comorbidity, and birth characteristics to assess their impact on developmental milestone gain

Statistical analyses

- Cumulative incidence analyses were used to estimate the proportion of individuals who gained, lost, or regained developmental milestones as a factor of age and time, with gain defined from birth to first event, loss as the first loss after gain, and regain as the first regain after loss
- Multivariable Cox proportional hazards models were used to evaluate the effect of prespecified covariates on milestone gain, with results reported as hazard ratios (95% CIs) and p-values adjusted for multiple comparisons using Bonferroni correction

Designing aggregate responder analysis: Plateau-Anchored, Baseline-Adjusted (PABA) aggregate responder analysis

- RHNS cumulative incidence estimates were used to construct the PABA aggregate responder framework by defining milestone eligibility and deriving a conservative natural-history-informed null threshold. The highest observed spontaneous gain rate after age 6 years was 3% which, at N=15, corresponded to 0.45 expected spontaneous responders; however, as responder rate must be discrete, one spontaneous responder (6.7%) was selected as the null threshold and evaluated across feasible sample sizes and responder counts using power calculations

Trial control cohort simulations

- Using RHNS participants in the developmental plateau (age 26 years) cohort, bootstrap simulations (10,000 iterations) were used to generate trial-like untreated cohorts (N=15; 1-year follow-up) via repeated sampling of the RHNS analysis cohort under prespecified assumptions
- Simulations evaluated spontaneous milestone gain and regain in untreated cohorts, assuming a conservative null hypothesis of 1 spontaneous responder per cohort (6.7%) and assessed the probability of exceeding the null threshold for responder rate and event rate in untreated cohorts
- Each milestone was assessed to determine the minimum time-since-loss at which spontaneous regain falls below the defined null threshold

Results

Cohort profile and demographics

- The RHNS dataset comprises 1870 individuals. Parameters closely matching the inclusion/exclusion criteria typically used in interventional RTT trials were applied to select the analysis cohort (Figure 2)
- 1191 (63.7%) participants were included, with a mean (SD) age at first study visit of 10.2 (9.3) years (Table 1)

Table 1: Cohort profile and demographics

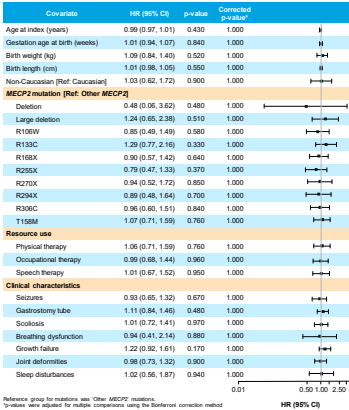
	Cohort (N=1191)
Protocol, n (%)	
MECP2 only	570 (47.9)
MECP2 only	309 (25.9)
Both	312 (26.2)
Age at index (years)	
Mean (SD)	10.2 (9.3)
Median (IQR)	6.4 (3.5, 14.3)
Min-Max	0.7-66.5
Categorical age at index (years), n (%)	
<4	353 (29.6)
4-5	135 (11.3)
5-9	110 (9.2)
10-14	110 (9.2)
15-19	69 (5.8)
20-24	51 (4.3)
25-29	24 (2.0)
30-34	16 (1.3)
35-39	14 (1.2)
≥40	14 (1.2)
Race, n (%)	
White	855 (71.8)
American Indian or Alaskan Native	27 (2.3)
Native Hawaiian or other Pacific Islander	7 (0.6)
Asian	64 (5.4)
Black or African American	62 (5.2)
Other	7 (0.6)
Missing	246 (20.7)
Mutation, n (%)	
R106W	36 (3.0)
R133C	68 (5.8)
T168M	127 (10.7)
R168X	131 (11.0)
R255X	114 (9.6)
R270X	74 (6.2)
R284X	79 (6.6)
R309C	89 (7.5)
Deletion	253 (21.2)
Large deletion	91 (7.6)
Missing	75 (6.3)
Clinical characteristics, n (%)	
Seizures	1003 (84.2)
Gastrostomy placement	470 (39.5)
Scoliosis	922 (77.4)
Breathing dysfunction	1179 (99.0)
Growth failure	832 (69.4)
Joint deformities	461 (38.7)
Sleep disturbances	1090 (91.5)

*Covariates not mutually exclusive; †includes unknown or related and those with no response for at least categories

Prognostic factors

- No consistent significant predictors of gain/regain were identified across the 28 milestones, such as "finger feed" (Figure 4)
- HRs were generally close to 1, with no consistent direction or magnitude of effect observed

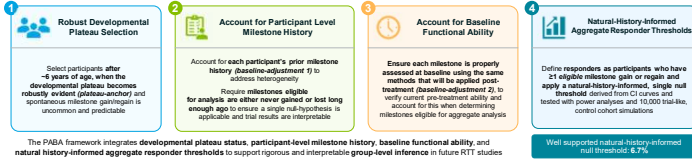
Figure 4: Association between covariates and milestone gain in multivariable Cox proportional hazards model for the milestone "finger feed"



Conclusions

- RHNS data demonstrate a clear developmental plateau in the typical RTT population beginning at 6 years of age, after which spontaneous milestone gain or regain is highly unlikely and more predictable, supporting a stable population to serve as the plateau-anchored for interventional studies
- Before 6 years of age, milestone gain, loss, and regain were more variable and less predictable, with spontaneous first-time gain for a single milestone as high as 97%; inclusion of younger participants without explicit age accounting could increase background spontaneous gain and thereby increase type I error
- Time-since-loss parameters were important for interpretation of milestone regain because spontaneous regain likelihood varied as a function of time since milestone loss

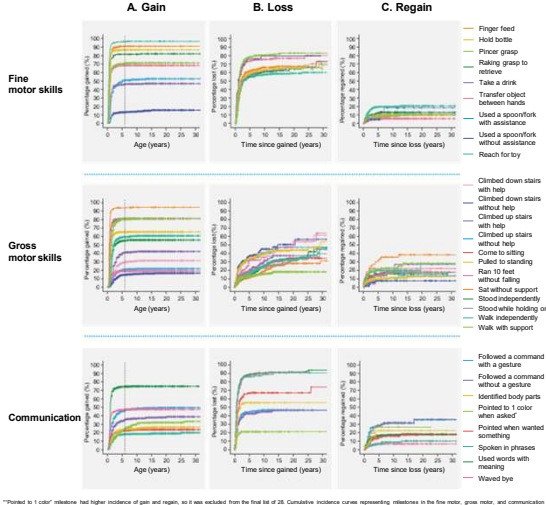
Figure 5: Novel PABA aggregate analysis framework applied to RTT as a use-case



Developmental plateau

- Relatively high and variable rates of spontaneous first-time milestone gain were observed in children before 6 years of age, with rates as high as 97% in the youngest participants; most regain occurred within several years after loss, with milestone-specific variation (Figure 3A-C)

Figure 3: Cumulative incidence of gain, loss, and regain across developmental milestones



*Marked as a "color" milestone that higher incidence of gain and regain, as it was excluded from the first set of 28. Cumulative incidence curves representing references in the fine motor, gross motor, and communication milestones are shown in the legend. Colored data points shown as circles. Colored lines shown as circles. Colored lines shown as circles. Colored lines shown as circles.

Sample size feasibility

- The incidence of spontaneous gain during the developmental plateau (age 26 years) was <3% (Figure 3)
- For a sample size of 15, a 3% natural-history responder rate corresponds to less than one expected spontaneous responder
- To equate to whole participant numbers, a conservative null hypothesis of one spontaneous responder (1/15=6.7%) was selected and found to provide robust power to detect treatment effects exceeding natural history expectations (Table 2)

Table 2: Power calculation indicates that a minimum of five responders would be required to reject the natural-history-informed null hypothesis with a sample size of 15

Sample size	Spontaneous responder (n)	Power
1	0.01	0.00
2	0.02	0.00
3	0.03	0.00
4	0.04	0.00
5	0.05	0.00
6	0.06	0.00
7	0.07	0.00
8	0.08	0.00
9	0.09	0.00
10	0.10	0.00
11	0.11	0.00
12	0.12	0.00
13	0.13	0.00
14	0.14	0.00
15	0.15	0.00

Colors indicate likelihood for acceptable power to reject null at treatment effect, that null values indicate moderate power, and green values indicate strong power. *This calculation is for a potential sample size of 15, considering a responder count of 0-15 individuals. Responder count reflects the number of participants with a participant event. Colored data points shown as circles. Colored lines shown as circles. Colored lines shown as circles.

Responder threshold

- Across 10,000 simulations (N=15; 26 years of age), only 1.8% of simulations had 22 responders (Table 3)
- Across 150,000 simulated participants, this equated to a spontaneous responder rate of 1.39%
- The gain/regain event rate was extremely low (around 0.02 events per person) supporting 21 gain/regain as a responder threshold for a sample size of 15

Table 3: Distribution of milestone gain/regain responses and events across 10,000 simulated trials (N=15; 26 years of age)

Responder count	N	Number of responders	Percentage of simulations
0	8113	0	81.13%
1	1699	1	16.99%
2	179	2	1.79%
3	27	3	0.27%
Average spontaneous responder rate		20.84	1.39%
Event count	N	Number of events	Percentage of simulations
0	8113	0	81.13%
1	1332	1	13.32%
2	385	2	3.85%
3	135	3	1.35%
4	35	4	0.35%
Average spontaneous event rate		26.53	1.69%

*This number is across 10,000 simulated trials that randomly sampled 10,000 participants in the developmental plateau (age 26 years) of age from the RHNS analysis cohort

Key takeaway

- A robust RTT developmental plateau was observed after age 6 years, supporting use of natural-history-informed null thresholds in an aggregate responder analysis
- Novel PABA analysis framework preserves individualized participant interpretation by enabling prespecified group-level inference in future RTT interventional studies (Figure 5)
- This framework aligns with recent FDA guidance on baseline control and supports application of a PABA analysis framework to RTT trial design in populations that are robustly in the plateau stage (6+ years) where spontaneous milestone gain or regain rates are rare and can be statistically accounted for
- Milestone eligibility is critical for interpreting milestone gain and regain in a trial setting, including accounting for time-since-loss, because spontaneous regain rates vary by duration since loss
- Including participants younger than age 6 years may increase spontaneous milestone gain/regain rates and inflate type I error risk, if not explicitly accounted for in the analysis framework

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*Accessed from RSF: ClinicalTrials.gov: NCT02738281; a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT. Cumulative incidence of milestone gain

Abbreviations: CI, confidence interval; FDA, Food and Drug Administration; HR, hazard ratio; IQR, interquartile range; MECP2, methyl-CpG-binding protein 2; PABA, Plateau-Anchored, Baseline-Adjusted

PACOC, patient-as-control control; RHNS, Rett Syndrome Natural History Study; SD, standard deviation

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