# Characterizing the Journey of Rett Syndrome in the United States Using the Rett Natural History Study Database

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## INTRODUCTION

- Rett syndrome (RTT) is a severe neurodevelopmental disorder that almost exclusively affects females.[1] RTT is clinically diagnosed based on the manifestation of key signs and symptoms, such as loss of hand function and language skills, with an average age of diagnosis of 2.5 years[2]
- Individuals with RTT often require lifelong care due to a variety of symptoms ranging from mild to severe, including neurological, gastrointestinal, cardiac, endocrine, and orthopedic disorders[3]
- Treatment options for RTT include both pharmacological and supportive therapies and are focused on managing symptoms of the disease. There is limited real-world information related to patterns of treatment use among individuals with RTT[4]
- Previous literature has reported a significant association between the severity of RTT and mortality among individuals with classic RTT[5]
- In addition to high disease burden, RTT is associated with substantial humanistic burden, impacting quality of life (QoL) for both individuals with RTT and their caregivers[6,7]
- This poster describes the methodology behind a study that will aim to illustrate the burden of RTT by characterizing females with RTT in the United States and their disease journey with respect to treatment patterns, changes in RTT clinical severity measures, RTT-related complications and outcomes, and changes in participant and caregiver QoL measures

## METHODS

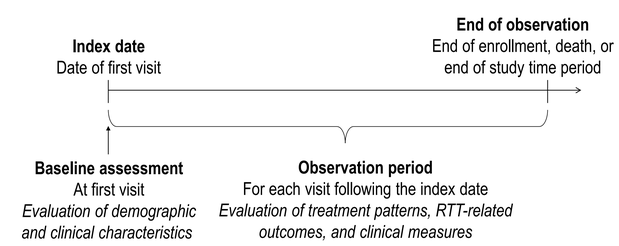
### Data Source

- Data from the 5211 Natural History of Rett Syndrome & Related Disorders (5211 RNHS) study will be used to address the study objectives
- The 5211 RNHS study is a US-based, multicenter, 5-year, observational registry study that spanned from November 2015 to July 2021, including both cross-sectional and longitudinal data from individuals with genetically confirmed or clinically diagnosed RTT. Participants were evaluated at diagnosis (first visit) and followed up every 6–12 months until end of study enrollment, death, or end of study time period
- The 5211 RNHS study data include diagnosis information, demographic and socioeconomic data, treatment/medication logs, death and other RTT-related complication records, clinical severity measures including Clinical Severity Score (CSS) and Motor Behavioral Assessment (MBA) score, participant QoL measures including the Child Health Questionnaire-Parent Form 50 (CHQ-PF50), and caregiver QoL measures including the 36-item Short Form Health Survey (SF-36)

### Study Design and Population

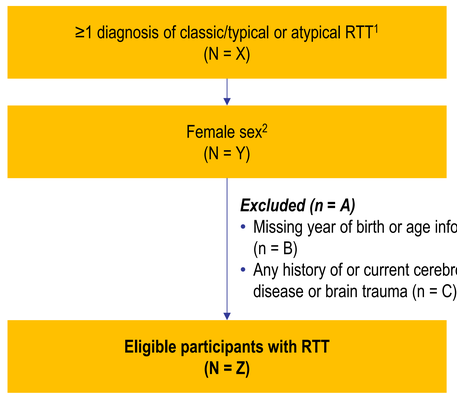
- A longitudinal, retrospective, cohort study will be used to address all study objectives (**Figure 1**)
- Female participants in the 5211 RNHS study data with a diagnosis of classic/typical or atypical RTT will be included (**Figure 2**). Participants will be included regardless of *MECP2* mutation status
  - Participants will be excluded if their data are missing year of birth or age information or if they have any history of or current cerebrovascular disease or brain trauma
- The study period will be defined as the period from November 2015 to July 2021, covering the entire evaluation period of the 5211 RNHS study
- The index date will be defined as the date of first visit, and the baseline assessment of participant demographic and clinical characteristics will be evaluated on the index date
- The observation period will be defined as the period from the index date (exclusive) to the earliest of end of study enrollment, death, or end of study time period. Treatment patterns, RTT-related complications and outcomes, clinical severity measures, and participant and caregiver QoL measures will be assessed over the observation period
- Individuals will be further stratified into pediatric (<18 years of age) and adult (≥18 years of age) subgroups and classic/typical RTT and atypical RTT subgroups

**Figure 1. Study design scheme**




RTT, Rett syndrome

**Figure 2. Participant disposition**




RTT, Rett syndrome

### Study Assessments

- Baseline demographic and clinical characteristics will include age, race and ethnicity, maternal and paternal age, *MECP2* mutation status, pubertal status, congenital anomaly/birth defect, select clinical manifestations/ functional characteristics, and age of onset of regression (**Table 1**)
- Treatment patterns will include the proportion of participants receiving pharmacologic agents and supportive therapy, duration of treatment for each therapy, and reasons for discontinuation
- Clinical severity measures will include CSS and MBA scores; QoL measures will include CHQ-PF50 and SF-36 scores
- RTT-related complications and outcomes will include death (including cause of death), gastrostomy tube surgery, and hospitalization or emergency room visit

**Table 1. Study assessments**

| Outcome | Variables |
|---|---|
| **Baseline characteristics** | |
| Demographic characteristics | • Age<br>• Race and ethnicity<br>• Maternal age<br>• Paternal age |
| Clinical characteristics | • *MECP2* mutation status<br>• Pubertal status<br>• Congenital anomaly/birth defect<br>• Clinical manifestations<br>◦ Hand stereotypies, scoliosis, respiratory dysfunction, epilepsy, language disorders, fractures, gastroesophageal reflux, gall bladder dysfunction, constipation, feeding problems, sleep disturbances, autonomic symptoms<br>• Functional characteristics<br>◦ Ambulation, gross motor function, communication |
| **Treatment patterns** | |
| Pharmacologic therapies | • Proportion of participants receiving pharmacologic therapies<br>◦ Antiepileptic drugs: pyrrolidines, benzodiazepines, valproic acid, carboxamides, triazines, fructose derivatives, sulfonamides, gabapentinoids<br>◦ Sedatives/hypnotics: phenobarbital, zolpidem, midazolam, triazolam, zaleplon<br>◦ Nutritional supplements: levocarnitine<br>◦ Prokinetic agents: metoclopramide<br>◦ Antiarrhythmic drugs (if available)<br>• Duration of pharmacologic treatment (time from medication start date to reported medication stop date)<br>• Reasons for discontinuation, per pharmacologic class |
| Supportive therapies | • Proportion of participants receiving supportive therapies<br>◦ Feeding assistance<br>◦ Behavioral therapy<br>◦ Physical therapy<br>◦ Speech-language therapy<br>◦ Occupational therapy<br>◦ Vision therapy<br>◦ Scoliosis treatment |
| **RTT-related complications and outcomes** | |
| Death | • Cause of death |
| Hospitalization or emergency room visit | |
| Gastrostomy tube surgery | |
| **Clinical severity and QoL measures** | |
| Clinical severity | • CSS<br>• MBA |
| QoL | • CHQ-PF50<br>• SF-36 |

CHQ-PF50, Child Health Questionnaire-Parent Form 50; CSS, Clinical Severity Score; MBA, Motor Behavioral Assessment; QoL, quality of life; RTT, Rett syndrome; SF-36, 36-item Short Form Health Survey

### Statistical Analysis

- Baseline demographic and clinical characteristics, treatment patterns, and RTT-related complications and outcomes will be described using means, standard deviations (SDs), and medians for continuous variables, and frequencies and proportions for categorical variables
- Contingent on data availability, rates of hospitalization and emergency room visits will be assessed per person-year
- Total scores of the CSS, MBA, CHQ-PF50, and SF-36 will be described on the index date and every 6 months during the observation period using means, SDs, and medians. Changes in total scores will be estimated using longitudinal mixed-effects models. Mean change in score per year will be calculated along with 95% confidence intervals

## DISCUSSION

### Study Strengths

- The 5211 RNHS is an ideal data source for this analysis given that detailed clinical and humanistic information has been reported longitudinally in a cohort-design study among participants with RTT. Generally, such endpoints of interest are difficult to examine or are largely missing in secondary data sources, such as administrative claims databases or electronic healthcare records
- Analyses using the most recent 5 years of data provide a contemporary perspective of outcomes of interest in participants with RTT

### Study Limitations

- This analysis relies on self-reported data to evaluate certain endpoints of interest over time, such as the CHQ-PF50 and SF-36. Therefore, some outcomes may be subject to response bias and potential misspecification
- Time on and off treatment between participants' visits cannot be captured in the data, so the durations of treatment estimated in this study may not reflect the true duration of treatment for therapies of interest
- QoL measures, including the CHQ-PF50 and SF-36, are generic instruments designed for general pediatric and caregiver populations, respectively, and are not specific to individuals with RTT and their caregivers. As such, the measure may not be sensitive to the specific type of burden associated with RTT and thus may not capture the full extent of such burden
- Findings may not be generalizable to the RTT population in the United States beyond the races/ethnicities represented in this study

## CONCLUSIONS

- Given the paucity of literature characterizing the RTT population and their associated disease burden, this study will address this knowledge gap by providing a comprehensive overview of individuals with RTT, particularly by examining the progression of clinical severity and QoL over time
- In addition, this study will add to the body of existing literature by examining the progression of QoL over time among caregivers of individuals with RTT, which, to the best of our knowledge, has not been reported in prior studies

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### DISCLOSURES

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