



Behavioral Disorders in Rett Syndrome

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Background:

Rett syndrome (RTT) is a complex neurodevelopmental disorder with a significant behavioral component. A few previous studies have evaluated behavioral characteristics in small cohorts of individuals with RTT, but behavioral profiles based on large datasets have not been described. Behaviors frequently observed in RTT include inappropriate laughing and/or screaming episodes, nighttime unrest, hyperventilation, breath holding, self-injury, anxiety and abnormal mood [1], [2], [3], [4], [5], [6]. Despite their apparent high frequency, the prevalence of internalizing and externalizing behaviors in RTT and their optimal treatment in RTT have not been fully determined. Although literature on the subject is lacking, clinical experience and natural history study data demonstrate that anxiety symptoms in RTT may be severe enough to require treatment with anxiolytic medications, such as selective serotonin reuptake inhibitors (SSRI) and benzodiazepines. We have previously examined the profiles of anxious behavior in a sample of girls with RTT using standardized questionnaires, but biomarker correlates have not been evaluated, and correlations with estimates of intellectual functioning have not been performed [7]. Our study would be the first in RTT to identify behavioral profiles using a Big Data approach, to define the behavioral construct of anxiety and associated behaviors in RTT, and to correlate these manifestations with intellectual ability and participant and caretaker quality of life.

Methods:

Utilizing data from the RTT5201 Rett Natural History Study (RNHS) protocol, we will characterize behavioral profiles and response to commonly used behavioral medications using a Big Data approach and standard analytical strategies. New participants with RTT will also be recruited. Participants' parents will complete the Anxiety Depression and Mood Scale (ADAMS), a psychiatric disorders screening instrument normed in intellectual disability; the Rett Syndrome Behaviour Questionnaire (RSBQ), a novel checklist of behavioral and emotional features commonly seen in RTT; the Aberrant Behavior Checklist-Community (ABC-C), a standardized behavior rating scale; the Child Health Questionnaire (CHQ), a standardized quality of life measure; and the Optum SF-36v2 Health Survey (SF36v2), a standardized assessment to evaluate caretaker physical and mental quality of life. We will also conduct cognitive assessments using the newly RTT-adapted Mullen Scales of Early Learning (MSEL) and survey current and past medication use, including medication dose, indication and reported side effects. In addition, we will study standard anxiety biomarkers, including autonomic parameters (heart rate variability, vagal tone, and electrodermal activity) and HPA axis parameters (salivary cortisol levels). The expressive language and self-awareness limitations in RTT make accurately diagnosing anxiety, or the behavioral construct we call anxiety in the general population, very difficult. Objective biomarkers can provide additional evidence (or verification), that the behaviors we label as anxiety in RTT are comparable to those in the general population with anxiety. Scores from the ADAMS, RSBQ, and ABC-C will be correlated to standard anxiety biomarker measurements to delineate RTT behaviors with a higher probability of corresponding to the behavioral construct termed anxiety in typically developing individuals and in other disorders associated with intellectual disability. Further, associations between anxiety-

related behavioral and biomarker data and levels of cognitive impairment will be explored. Impact of anxiety parameters on participant quality of life, as measured by the CHQ, and caretaker quality of life, as measured by the SF36v2, will also be examined.

Preliminary results:

We have gathered longitudinal data from 1,073 females with classic or variant RTT, including age, methyl-CpG-binding protein (MECP2) mutation type, medication use (class and indication), total scores on two clinical severity measures (Clinical Severity Score [CSS] and Motor Behavioral Assessment [MBA]), and their Likert-type scale scores for a variety of clinical features including some considered anxiety-related (e.g., hyperventilation). We identified 161 subjects (15.0%) who were being treated with medication for anxiety and described their clinical features. Analyses delineated distinctive features of this population: relatively high prevalence, better motor function, lower overall severity of behavioral problems, high frequency and early use of SSRIs. Our preliminary data is limited due to a lack of psychiatric diagnostic records. The individuals described are those being treated with medication for an indication of anxiety, identified through medication logs. The methodological limitations in identifying affected individuals may have resulted in decreased prevalence and bias towards more severe cases. However, our anxiety-related data are supported by additional preliminary analyses of the RNHS data, including the CHQ and MBA, in which approximately 30-40% of parents reported one or more of the following regarding their child: felt lonely, felt like crying, had poor eye/social contact or lacked sustained interest, at least some of the time, indicating, a significantly higher prevalence of internalizing disorders in this population. The latter category of behaviors includes anxiety, depression, and social withdrawal, in the RNHS cohort.

Conclusions:

Our overall goal is to better define the diagnostic label of anxiety in RTT, by delineating its behavioral and biomarker correlates, as a basis for improved clinical care and future treatment trials. as it naturally induces immune responses that cause tumor remission and increased survival in mouse models (Fox et al 2013, Fox et al 2015), highlighting the feasibility of using live *T. gondii* in a therapeutic setting. In summary, the combination of *T. gondii*'s ability to cross biological barriers, synthesize proteins locally and deliver them into mammalian brain cells offers a unique platform to develop a synthetic biology-based solution to the challenges of protein delivery for Rett Syndrome therapy. We engineered a strain of *T. gondii* that expresses MeCP2 fused to an endogenous parasite secretory sequence. This transgenic line synthesizes and delivers MeCP2 into neuronal cells in culture. We showed that this parasite MeCP2 behaves like a functional MeCP2. Under this grant we propose to investigate the effects that MeCP2-secreting *T. gondii* have on mice models of Rett Syndrome and assess their potential as a therapeutic strategy for the treatment of Rett symptoms by MeCP2 delivery.