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## The heart of Rett syndrome: A quantitative analysis of cardiac repolarization

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# The Heart of Rett Syndrome: A Quantitative Analysis of Cardiac Repolarization

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## Abstract

**Background:** Rett syndrome (RTT) is a developmental encephalopathy disorder that is associated with a high incidence of sudden death presumably from cardiorespiratory etiologies. Electrocardiogram (ECG) abnormalities, such as prolonged heart-rate corrected QT (QTc) interval, are markers of cardiac repolarization and are associated with potentially lethal ventricular arrhythmias. This study investigates the cardiac repolarization characteristics of RTT patients, including QTc and T-wave morphology characteristics.

**Methods:** A retrospective quantitative analysis on 110 RTT patients and 124 age and sex-matched healthy controls was conducted.

**Results:** RTT patients had longer QTc, more abnormal T-wave morphology, and greater heterogeneity of cardiac repolarization parameters compared to controls. Even RTT patients without prolonged QTc had more abnormal ECG and T-wave characteristics than controls. Among RTT patients, *MECP2* patients had prolonged QTc compared to *CDKL5* and *FOXG1* patients. A subset of five RTT patients who died had normal QTc, but more abnormal T-wave morphology than the remaining RTT patients.

**Conclusions:** Cardiac repolarization abnormalities are present in RTT patients, even without long QTc. T-wave morphology is related to RTT genotype and may be predictive of mortality. These findings could be used to help the management and monitoring of RTT patients.

**Keywords:** Rett syndrome; Long QT; Abnormal T wave; T-wave analysis; Electrocardiogram; Cardiac repolarization; Ventricular repolarization

## Introduction

Rett syndrome (RTT) is an X-linked developmental encephalopathy with a prevalence of about 1 in 10,000 females [1]. Both typical RTT and atypical RTT fall under the term RTT. Mutations of *MECP2* are found in most patients. Atypical RTT encompasses monogenic disorders such as *FOXG1* syndrome, *CDKL5* deficiency disorder, *MECP2* duplication syndrome, and *MECP2*-related severe neonatal encephalopathy as well as other developmental encephalopathies associated with pathogenic variants in *GABBRG2*, *NTNG1*, *SMC1A*, and *MEF2C* [2, 3].

RTT patients have an overall mortality rate of 1.2% per year, of which 20-26% are sudden and unexpected, and up to 35% are suspected to be cardiorespiratory arrests. The etiologies of cardiorespiratory arrest have yet to be fully elucidated. Leading potential causes include seizure (i.e., sudden unexpected death in epilepsy), autonomic dysfunction, or cardiac arrhythmias [4].

Multiple cardiac abnormalities have been associated with RTT including subclinical biventricular myocardial dysfunction, reduced heart rate (HR) variability, cardiac arrhythmias, and abnormal cardiac repolarization on electrocardiogram (ECG) (such as prolonged heart rate corrected QT (QTc) interval and nonspecific T-wave abnormalities) [5-11]. Since prolonged QTc and increased heterogeneity of cardiac repolarization are associated with an increased risk of life-threatening ventricular arrhythmias, they may be associated with sudden death in RTT [12, 13]. However, QTc measurements are variable in RTT while T-wave abnormalities have only been qualitatively described as nonspecific in one small case series of RTT [9, 14]. Automated identification of electrocardiographic features of abnormal cardiac repolarization may be important for risk stratification and surveillance of RTT patients. We sought to compare quantitative morphological features of the T wave including flatness, asymmetry, and notching between RTT patients and normal controls. We also investigated the re-

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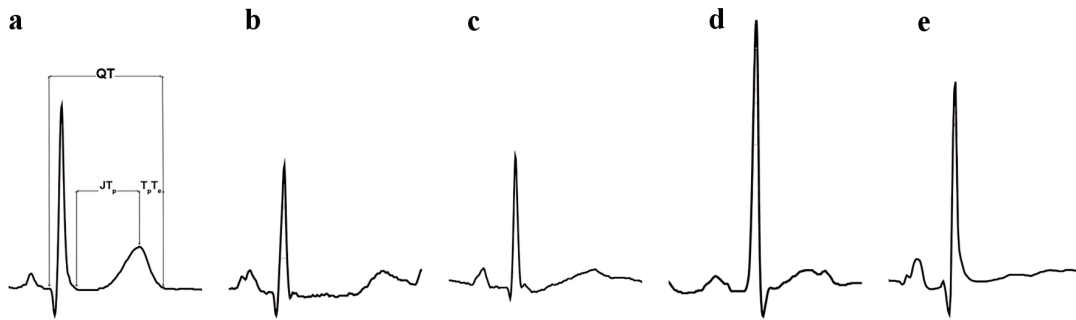
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**Figure 1.** Depiction of the electrocardiographic measurements along with T-wave morphology characteristics seen in the study's RTT patients. (a) Normal T wave. (b) Prolonged QT with prolonged JTp. (c) Asymmetric T wave. (d) Notched T wave. (e) Flat T wave. This ECG had the highest morphology combination score (MCS). ECG: electrocardiogram; RTT: Rett syndrome; JTp: time from the J point to the peak of the T wave.

relationship of these morphologic measures and QTc with genotype and mortality in RTT patients.

## Materials and Methods

### Patients

This study was approved by the Institutional Board Review at Washington University School of Medicine and Rush Medical College. Informed consent was waived by the Institutional Board Review at Washington University School of Medicine and Rush Medical College. All research was performed in accordance with the Declaration of Helsinki. Female RTT patients at St. Louis Children's Hospital and Rush University Children's Hospital, who had at least one ECG performed from January 2006 to January 2020 were included. Medical records were reviewed to obtain demographic, genotype, and mortality data. None of the patients received anti-arrhythmic medications. Details regarding all other medications at the time of ECG were not available from the chart review. The age and sex-matched controls were patients referred to the Cardiology Clinic at St. Louis Children's Hospital for chest pain or syncope, who subsequently were found to have no cardiac disease.

### ECG analysis

We retrospectively analyzed ECGs of clinical female RTT patients obtained from St. Louis Children's Hospital and Rush University Children's Hospital, which were collected between January 2006 and January 2020. Both institutions utilize MUSE Cardiology Information System (GE Healthcare, Waukesha, WI) to record and interpret ECGs. The QTGuard Plus Software (GE Healthcare, Milwaukee, WI) was used to analyze the digital ECG files, determine the QTc according to Bazett's formula (QT divided by the square root of the previous RR interval,  $QT/\sqrt{RR}$ ; ms), and generate morphology parameters related to flatness, asymmetry, and notching of the T wave

as previously described [15]. A  $QTc \geq 460$  ms was considered prolonged. A median beat for each lead of the surface 12-lead ECG was formed. These median beats were then transformed to median beats on XYZ orthogonal leads. The principal component analysis (PCA) was then applied to the ST-T segment of the XYZ median beats forming orthogonal PCA leads describing the spatial direction of the ST-T loop. As a result, there are three PCA leads used for analysis. The T wave of the first PCA lead is a geometrical representation of the optimal projection of the heart dipole vector during the ST-T segment. This lead was used to derive the flatness, asymmetry, and notch score of the T wave for each ECG. The flatness score is based on the inverse kurtosis of the area unit of the T wave with a higher score corresponding to a flatter T wave. The asymmetry score is based on the difference in the slope and duration of the ascending and descending limbs of the T wave. The lower the asymmetry score, the more symmetric the T wave. The presence of notching is based on the radius of curvature of the T wave, where values  $> 0$  correspond with the presence of notching. The morphology combination score (MCS) was calculated by summing the three morphology scores with the coefficient of each score determined by linear regression; flatness had the highest coefficient, and a higher score indicates more abnormal morphology (Fig. 1). The heterogeneity of repolarization was represented by the principal component analysis ratio 2 (PCA-2) defined as the ratio of the second PCA lead to the first PCA lead. A higher PCA-2 indicates increased cardiac repolarization heterogeneity. Other ECG parameters determined by QT Guard Plus Software include HR (beats per minute (bpm)), QT interval, heart-rate corrected QT interval using Bazett's formula, time from the J point to the peak of the T wave (JTp, ms), and time from the peak of the T wave to the end of the T wave (TpTe, ms) (Fig. 1).

### Statistical analysis

All values were reported as means and standard deviations (SDs). Continuous variables were compared using a Mann-Whitney U test for two group comparisons. A Chi-square test or Fisher's exact test was used to compare proportions. ECG and T wave characteristics, due to repeat measurements per

**Table 1.** Baseline and Electrocardiographic Characteristics

	Control (n = 124)	All RTT (n = 110)	<i>MECP2</i> (n = 78)	<i>CDKL5</i> (n = 8)	<i>FOXP1</i> (n = 3)	Clinical RTT (n = 21)	P control vs. all RTT
Long QT	6 (4.8)	55 (50)	45 (57.6)	1 (12.5)	0 (0)	9 (42.8)	< 0.001
Mean age, years	9.3 (5.2)	11.7 (8.5)	10.7 (7.6)	5.9 (5.4)	4.1 (2.5)	18 (9.6)	< 0.001
Heart rate, bpm	87.1 (24.1)	95 (21.8)	94 (20.9)	110.6 (14.4)	123 (14.3)	92.6 (24.9)	< 0.001
QTc, ms	422.8 (19.3)	445.6 (31.6)	448.1 (32.8)	430.2 (17.6)	430.4 (12.8)	440.8 (28.8)	< 0.001

Values are counts (%) or means (SD). QTc: corrected QT; SD: standard deviation; RTT: Rett syndrome; bpm: beats per minute.

subject, were modeled using mixed random effect models with heterogeneous variance structure. Fixed effects comprised RTT status, genotype, mortality status, age, long QT status, and the interactions between RTT status and long QT status. Random effects included subjects. Degrees of freedom were adjusted with Kenward-Roger's method. P values for *post-hoc* pair-wise comparisons were adjusted using Tukey's method. Analyses were performed in SAS (Version 9.4; SAS Institute, Cary, NC).

## Results

### Baseline characteristics

A total of 110 unique female RTT patients with 577 ECGs were analyzed. The mean age of the RTT group was 9.3 (SD = 5.2) years. Seventy-eight patients (71%) had *MECP2* mutations, eight patients (7%) had *CDKL5* mutations, and three patients (3%) had *FOXP1* mutations. The remaining 21 patients (19%) were diagnosed clinically; they either did not have genetic testing results available or they did not have known pathogenic RTT mutations. There were five deaths (5/110, 5%) in the RTT group. Ages at death ranged from 12 to 36 years. Two of the mortalities had *MECP2* mutations, while the remaining three patients were classified as clinical RTT. One deceased patient had multiple ECGs with long QTc, but the cause of death was respiratory failure. The cause of death of the other four patients could not be determined. The control group comprised 124 subjects, who had 140 ECGs (Table 1).

### Electrocardiographic characteristics

All groups had normal QRS duration. RTT patients had a higher HR than controls. They also had longer QTc intervals compared to controls (445.6 (SD = 31.6) ms vs. 422.8 (SD = 19.3) ms;  $P < 0.001$ ). The *MECP2* group had the longest mean QTc (448.1 ms (SD = 32.8 ms)) (Table 1). Fifty-five (50%) RTT patients had a prolonged QTc on at least one ECG. Forty-five of these patients (82%) had *MECP2* mutations. These 45 patients constituted 41% (45/110) of the RTT group. Thirty-eight patients (38/110, 35%) had two or more ECGs with long QTc. Figure 2 details the percentage of RTT patients with repeated prolonged QTc on ECG. Among the common *MECP2* mutations (R106W, R133c, R168X, R255X, R270X,

R294XX, R306C, R306H, T158M), there was no difference in the proportion of patients with repeated prolonged QTc on ECG ( $P = 0.37$ ) (Table 1).

### T-wave parameters

The TpTe interval and the corrected JTp interval were longer in the RTT group but without reaching statistical significance. The MCS score was higher in the RTT group (97.8 (SD = 59) vs. 60.7 (SD = 24.6);  $P < 0.001$ ). T waves in RTT patients were more flat, asymmetric, and had higher notch score when compared to the T waves of controls. PCA-2 percentages were higher in RTT patients than in controls (25.5 (SD = 13.2) vs. 17.3 (SD = 9.1);  $P < 0.001$ ) (Table 2).

### Sub-group comparisons of QTc and T-wave parameters

#### RTT mortality comparisons

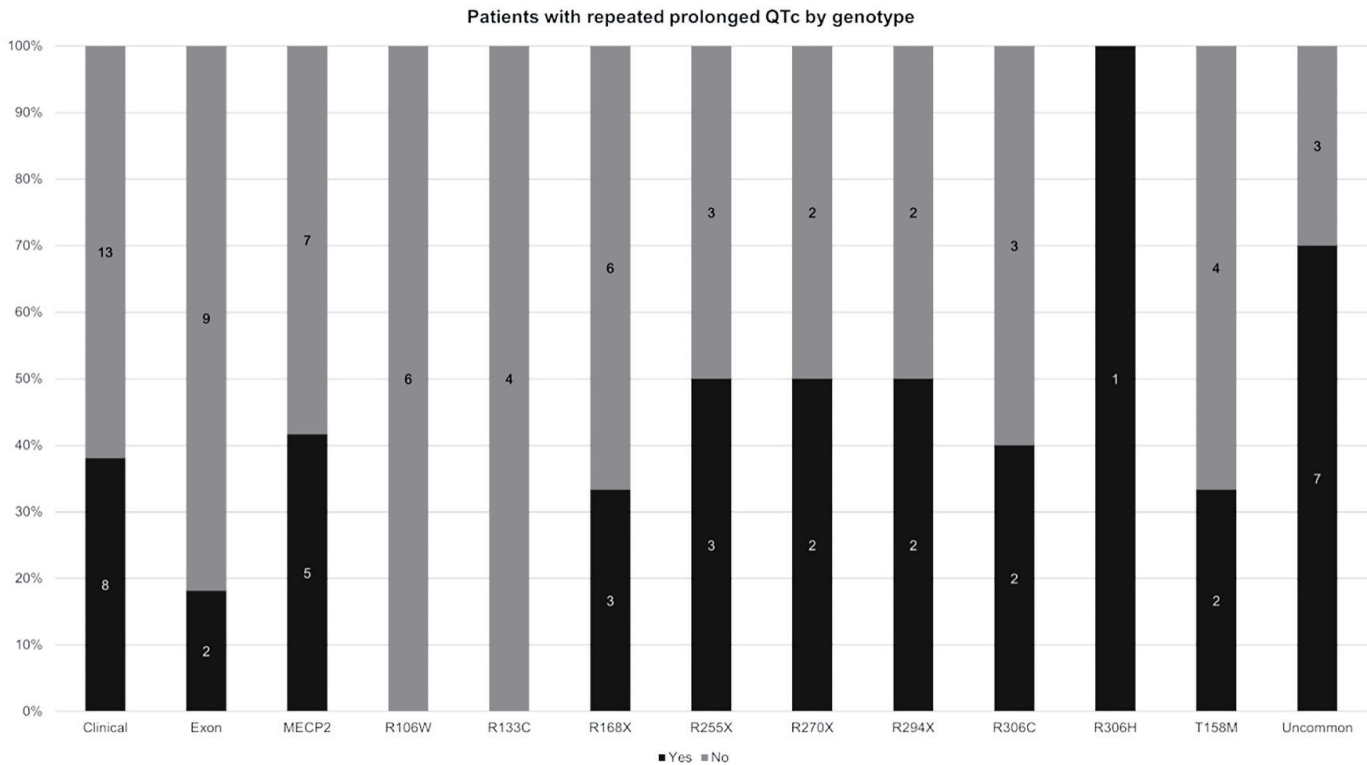
The QTc was not statistically different between deceased RTT and living RTT patients. The JTp interval was longer in deceased patients (192 (SD = 36.7) ms vs. 206.3 (SD = 44) ms;  $P < 0.029$ ). The T wave in deceased patients was significantly flatter, more asymmetric, and more notched. Therefore, the MCS score for deceased patients was higher compared to living patients (127.3 (SD = 75.7) vs. 94.8 (SD = 56.2);  $P = 0.001$ ) (Table 3).

#### Normal QTc group comparisons

RTT patients, who had normal QTc, still had significant differences in other T-wave parameters than normal QTc controls. In the RTT group, both JTp and TpTe lengthened significantly in long QT RTT patients when compared to normal QT RTT patients (Table 4).

#### RTT genotype comparisons

There was no statistically significant difference between the RTT genotypes on most of the ECG and T-wave parameters. Only the corrected JTp was significantly different across the three genotypes; the *MECP2* group had the longest interval



**Figure 2.** Distribution of patients with and without repeated prolonged QTc on ECG by RTT genotype. The black bar is the percentage of patients with repeated prolonged QTc on ECG. The gray bar is the percentage of patients without repeated prolonged QTc (i.e., patients with only one prolonged QTc on ECG or patients with no prolonged QTc on ECG). For each column, the percentage of patients with repeated prolonged QTc and the percentage of patients without repeated prolonged QTc add up to 100%. Clinical: clinical RTT as defined in the text; Uncommon: identified mutations besides R106W, R133C, R168X, R255X, R270X, R294x, R306C, R306H, T158M; QTc: corrected QT; ECG: electrocardiogram; RTT: Rett syndrome.

while the *FOXP1* group had the shortest interval (Supplementary Material 1, [www. cardiologyres.org](http://www.cardiologyres.org)).

## Discussion

This study with a large, longitudinal, and genetically diverse group of RTT patients confirms that RTT patients exhibit

longer QTc intervals than healthy controls. The prevalence of 50% of patients with at least one ECG with QT  $\geq$  460 ms is higher than previously reported [11]. However, this prolonged QT may reflect the background noise due to within-individual variation. Within-individual prolonged QT variation has been shown to be amplified when using Bazett's formula possibly due to its "overcorrection" of the QT at higher HR such as seen in RTT patients [16]. On the other hand, 35% of patients

**Table 2.** Comparison of T wave Analysis Characteristics

	Control (n = 124)	All RTT (n = 110)	<i>MECP2</i> (n = 78)	<i>CDKL5</i> (n = 8)	<i>FOXP1</i> (n = 3)	Clinical RTT (n = 21)	P control vs. all RTT
Corrected JTp, ms	189.6 (30.6)	193.3 (37.6)	196.3 (36.7)	156.7 (18.9)	144.5 (13.4)	195.1. (38.8)	0.169
TpTe, ms	91.3 (10.4)	96.4 (19.9)	96.6 (20.9)	89.9 (12)	94.8 (11.5)	93.3 (17.5)	0.343
MCS	60.7 (24.6)	97.8 (59)	106.4 (61.8)	55.1 (18.8)	50.3 (30.7)	78.1 (42)	< 0.001
Flatness score	27.3 (11.8)	35.6 (13.4)	37.3 (13.3)	23.4 (6.7)	19.9 (6.5)	33.1 (13.1)	0.005
Asymmetry score	15.6. (10.8)	25.9 (22.6)	28.3 (22.9)	16.9 (12.8)	11.3(10.4)	19.6 (22.2)	< 0.001
Notch score	0 (0.4)	2 (8.1)	2.5 (9.3)	0 (0)	0.38 (1.1)	0.2 (1)	0.002
PCA-2, %	19.2 (9.1)	25.5 (13.2)	25.2 (13)	25.6 (10.3)	31.2 (7.3)	26.1 (15.2)	< 0.001

Values are mean (SD). SD: standard deviation; RTT: Rett syndrome; MCS: morphology combination score; PCA-2: principal component analysis ratio; JTp: time from the J point to the peak of the T wave; TpTe: time from the peak of the T wave to the end of the T wave.



**Table 3.** QTc and T-wave Parameters by RTT Mortality

	RTT living (n = 105)	RTT deceased (n = 5)	P
QTc, ms	446.8. (29.9)	432.9 (43.1)	0.903
Corrected JTp, ms	192 (36.7)	206.3 (44)	0.029
TpTe, ms	96.7 (18.6)	93.6 (29.4)	0.391
MCS	94.8 (56.2)	127.3 (75.7)	0.001
Flatness score	35.2 (12.9)	39.4 (17.3)	0.038
Asymmetry score	24.9 (21.3)	35.6 (31.2)	< 0.001
Notch score	1.8 (8.11)	3.3 (8.3)	0.028
PCA-2, %	25.3 (12.6)	27 (18.3)	0.043

Values are mean (SD). QTc: corrected QT; SD: standard deviation; RTT: Rett syndrome; MCS: morphology combination score; PCA-2: principal component analysis ratio; JTp: time from the J point to the peak of the T wave; TpTe: time from the peak of the T wave to the end of the T wave.

had long QTc on two or more ECGs, which may reflect the true prevalence of prolonged QTc in RTT. Previously, certain *MECP2* mutations have been associated with long QT (e.g., *R255X*, *T158M*) [10, 11]. We did not replicate that finding in our report. Among the common *MECP2* mutations, the *R270X* and *R294X* groups had a higher proportion of repeated prolonged QTc on ECG patients than the *R255X* and *T158M* groups. However, overall, there was no statistical difference in the proportion of repeated prolonged QTc among the common *MECP2* groups.

Persistently prolonged QTc, especially at 500 ms and above, has been associated with increased risk of malignant ventricular tachyarrhythmias [17]. However, ventricular tachycardia has only been documented in only one deceased patient with RTT. While this patient also had prolonged QTc, whether an episode of ventricular tachycardia preceded the demise and whether an arrhythmia was the direct cause the death could not be confirmed [8]. Moreover, most reported Holter data thus far have not shown frequent ventricular arrhythmias in RTT patients [6, 18, 19]. One deceased patient in our cohort did have long QTc on multiple ECGs, but the patient died due to acute respiratory failure. Since there is currently no accurate data on the incidence of sudden cardiac arrhythmic death in RTT, long-term and continuous cardiac monitoring with minimally invasive (e.g., implantable loop recorders) or wearable sensors may help further assess the relationship between long QT, arrhythmias, and outcomes.

Other components of the QT such as increased JTp and increased TpTe intervals have been identified as risk factors for sudden cardiac deaths in various populations [20, 21]. Increased TpTe is thought to represent increased heterogeneity of transmural cardiac repolarization that is associated with cardiac arrhythmogenicity [13]. In our study, both intervals were longer in RTT without reaching statistical significance. The observed long JTp is congruent with the persistence of late sodium channel current in mouse models of RTT [22, 23]. Interestingly, while deceased RTT patients had similar QTc and TpTe, they had significantly longer JTp than living RTT

**Table 4.** QTc and T-Wave Parameters Between Control With QTc < 460 ms and RTT With QTc < 460 ms

	Control (n = 118)	RTT (n = 55)	P
QTc, ms	420.55 (16.82)	431.31 (19.82)	< 0.001
Corrected JTp, ms	189.14 (30.39)	188.12 (36.43)	0.117
TpTe, ms	90.91 (10.31)	95.37 (18.91)	0.186
MCS	59.86 (24.34)	89.61 (54.29)	< 0.001
Flatness score	27.03 (11.80)	33.71 (13.39)	0.007
Asymmetry score	15.11 (10.57)	23.72 (21.95)	< 0.001
Notch score	0.04 (0.42)	1.32 (6.23)	0.004
PCA-2, %	18.65 (8.36)	25.37 (13.35)	< 0.001

Values are means (SD). QTc: corrected QT; SD: standard deviation; RTT: Rett syndrome; MCS: morphology combination score; PCA-2: principal component analysis ratio; JTp: time from the J point to the peak of the T wave; TpTe: time from the peak of the T wave to the end of the T wave.

patients. The long JTp is driven mostly by the *MECP2* and clinical groups, which account for all the mortalities. Measurements of JTp may be clinically more relevant in RTT.

This study further characterizes the qualitatively described abnormal T wave in RTT with quantitative scores [9]. These intuitive to visualize quantitative scores may not only guide the visual assessment of T-wave morphology but also help reduce the variability of the manual assessment of T-wave morphology especially in longitudinal measurements [24]. These scores have helped diagnosing long QT syndrome [15, 25]. Moreover, they have been independently associated with mortality in the general population [26]. These findings suggest the morphology of the T wave on ECG to be an important parameter to monitor in RTT patients. Since these scores can be implemented in ECG applications, they may help develop clinically meaningful risk-stratification criteria for sudden cardiac death in RTT. Finally, applications of other novel T-wave characterization methods may uncover other T-wave morphologies that are more sensitive for arrhythmic risk stratification [27].

In this study, we found that T waves are significantly more abnormal in RTT when compared to controls even when the QTc is normal. This finding suggests an intrinsic abnormal cardiac repolarization phenotype in RTT. This finding is important clinically since populations without long QT but with T-wave abnormalities that are similar to the abnormalities seen in congenital long QT syndrome appear to have increased arrhythmic risk. For example, in patients with bradycardia, those with T waves that resemble the T wave of congenital long QT syndrome type 2 are more at risk for developing ventricular tachycardia torsade de pointes. Future comparison with a matched pediatric cohort of long QT syndrome may explain the current perceived arrhythmic risk and further help risk stratify RTT patients.

RTT patients have sub-clinical myocardial dysfunction on echocardiograms [5]. T-wave abnormalities found in RTT may also reflect structural and mechanical abnormalities as seen in

channelopathy and cardiomyopathy patients [28]. Repeated echocardiography with tissue Doppler/strain analysis and potentially cardiac magnetic resonance imaging (MRI) when the echocardiogram is abnormal may help further characterize the cardiac phenotype of RTT.

### Limitations

This retrospective observational study was underpowered to perform mortality and genotype related analysis. The small number of patients in certain groups also precluded the analysis of the effects that physiologically significant interactions between groups (e.g., sex, mortality, and genotype) have on cardiac repolarizations. Moreover, the study lacked information on other confounding risk factors for abnormal cardiac repolarization such as concomitant medications, blood electrolytes, disease severity, epilepsy, or autonomic dysfunction. Serotonin reuptake inhibitors have been associated with long QT in RTT patients [11]. RTT patients frequently take antiepileptic drugs, some of which may be QT prolonging. On the other hand, sodium channel blocking agents have been shown to shorten QT in mice with *MECP2* mutations [22, 23, 29]. Future studies evaluating the effects of antiepileptic drugs with sodium channel blocking properties and sodium channel blocker anti-arrhythmic medications on the abnormal cardiac repolarization of RTT patients should be pursued. Sudden death with epilepsy may occur in RTT. However, it is challenging to determine what is and is not a seizure in RTT patients. It would also be challenging to study the role of epilepsy in sudden death in RTT patients due its repetitive remission and relapsing nature over the lifespan of RTT patients. Finally, RTT patients' autonomic dysfunction (e.g., reduced HR variability), has strongly been implicated as the major cause of sudden death in RTT [30]. Reduced HR variability reflecting the increased sympathetic activation and/or decrease in parasympathetic activation has been associated with prolonged QTc in RTT patients. Reduced HR variability has also been associated with increased cardiac repolarization heterogeneity and cardiac arrhythmias in many different populations. Future studies investigating the effects of changes in HR variability such as during natural circadian oscillation or when provoked (e.g., change in body position, cardiac pacing, or medications) have on QT duration and other parameters of cardiac repolarization are needed to elucidate the pathophysiology of autonomic dysfunction *vis-a-vis* cardiac repolarization and cardiac arrhythmic death in RTT.

### Conclusions

RTT patients have abnormal cardiac repolarization including long QTc, increased heterogeneity of cardiac repolarization, and abnormal T-wave morphology. Further longitudinal characterizations of these markers may help in better understanding of the RTT cardiac electrophysiologic phenotypes leading to helpful risk stratification for malignant cardiac arrhythmias of these patients.

## Supplementary Material

**Suppl 1.** QTc and T-wave parameters by genotype.

### Acknowledgments

None to declare.

### Financial Disclosure

None to declare.

### Conflict of Interest

Each author declares that they do not have any competing interests pertaining to this study.

### Author Contributions

All authors planned, conceived and designed the study. MPC and HHN acquired the data. HHN analyzed the data. MPC, MCJ, WAS, and HHN interpreted the electrophysiology data. RCR, JLW, PTH, CMB, DMMA, and HMK interpreted the clinical and genetic data. MPC wrote the first draft of the manuscript. All authors critically reviewed and edited the manuscript. All authors agreed to the submission of the manuscript.

### Data Availability

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

### Abbreviations

RTT: Rett syndrome; ECG: electrocardiogram; PCA: principal component analysis; MCS: morphology combination score

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