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Characteristic behaviors associated with gait of individuals with Rett syndrome

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ABSTRACT

Background: Individuals with Rett syndrome (RTT) exhibit impaired motor performance and gait performance, leading to decreased quality of life. Currently, there is no robust observational instrument to identify gait characteristics in RTT. Current scales are limited as individuals with intellectual disorders may be unable to understand instructions. Our primary purpose was to utilize video analysis to characterize the behaviors associated with walking in individuals with RTT and explore the relationship between behaviors during overground and during treadmill walking.

Methods: Fourteen independently ambulatory females with RTT were video-taped and observed during overground and treadmill walking. Their gait was codified into an observational checklist to reveal prominent features associated with gait in this population.

Results: Participants exhibited similar rates of freezing, veering, and hand stereotypies between overground and treadmill walking; however, freeze duration was shortened during treadmill walking. Toe walking was prominently exhibited during overground, but not treadmill walking. During both walking modes, participants required extensive external motivation to maintain their walking patterns.

Conclusions: Results identify several gait characteristics observable during overground and treadmill walking. In general, participants behaved similarly during overground and treadmill walking. We conclude that both overground and treadmill walking are appropriate tools to evaluate gait in this population.

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Ataxia of gait; clinical decision-making; neurodevelopmental disorder; rehabilitation; Rett syndrome

➤ **IMPLICATIONS FOR REHABILITATION**

- Locomotor rehabilitation may increase the quantity of walking performed by the patients, which can alleviate negative effects of the sedentary lifestyle commonly observed in patients with Rett syndrome (RTT).
- Video analysis of natural walking can be an effective tool to characterize gait in patients with RTT which does not require particular instructions which may not be fully understood.
- Both overground and treadmill walking are appropriate means of evaluating gait in individuals with RTT.

Introduction

Rett syndrome (RTT) is a neurodevelopmental disorder that affects approximately one in 10,000 live female births. Typically, RTT is the result of a mutation in the methyl-CpG-binding protein 2 (MECP2) gene. Individuals with RTT display an apparently healthy developmental progression until age 6–18 months, after which they stall, and later regress in motor, language, and social skills [1]. Among the most reported motor dysfunctions are early hypotonia evolving into hypertonia and stereotypic hand motions, as well as ataxic gait and postural control difficulties. Previous investigation has found that approximately only half of those with RTT can walk with assistance, and 75% of ambulatory individuals with RTT can walk without assistance [2]. Presumably, these mobility deficits lead to poorer physical fitness and overall health status. Moreover, it has been reported that there is an association between spatio-temporal gait characteristics and level of physical fitness in individuals with intellectual disabilities (ID), further suggesting that poor gait control is related to low physical fitness [3]. As there is no current cure for RTT, developing protocols that can effectively improve gait are important for enhancing mobility of individuals with RTT. Previously, it has been reported that improving the walking ability of patients with RTT would decrease spasticity, control development of foot anatomical deformities, and promote a degree personal independence [4–7]. Downs et al. [6] suggested that promoting an active lifestyle, including a walking program, may lead to health benefits and improved quality of life.

A number of reports have described some of the gait characteristics associated with females with RTT. These behaviors include ataxia, toe walking, hand wringing while walking [4,8], stiff-legged walking [9,10], freezing of gait (FOG) [11], dysrhythmic gait, and lateral and backwards stepping [12,13]. Downs et al. [13] provided an important contribution in the characterization of the motor activities that can be accomplished by those with RTT, when they reported the results of a video-based movement analyses protocol, emphasizing activities in a natural environment. This study investigated a number of gait activities, such as walking on a sloped surface, turning 180°, or stepping over an obstacle, and the level of assistance required to accomplish the task. However,

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kinematic details or descriptions of the behaviors displayed while performing these tasks were not part of their evaluation.

Currently, there are no robust observational instruments that can be used by medical professionals or researchers to identify the range of behaviors exhibited by those with RTT. This hinders the clinician's ability to effectively evaluate regression of these individuals' gait over time. Furthermore, evaluating the effectiveness of any physical therapy or pharmaceutical treatment is also compromised by a lack of an easy-to-administer survey to evaluate the gait in those with RTT. An instrument that can be quickly and easily administered in a clinical setting and does not require either the patient's or their caregivers' input would be valuable to both clinicians and researchers working with females with RTT.

Robust checklists and scales currently exist to characterize gait in other disabled adult or pediatric populations. For example, the multiple sclerosis walking scale-12 can identify the impact of MS on walking capabilities. Unfortunately, this scale requires patient ratings and, therefore, cannot be used in patients with ID such as in RTT [14]. Similarly, Parkinson's disease and post-stroke testing batteries such as the ambulatory capacity measure (ACM), Clinical Gait and Balance Scale (GABA), Walking Handicap Scale (WHS), and timed get up and go (TUG) have been employed to measure the progression of gait disturbances [15–17]. Unfortunately, a majority of these batteries are also disqualifying of those with severe ID.

In patient populations with ID, the findings of the assessment tool must not be influenced by a patient's inability to understand the task's directions. Due to this, Hale et al. [18] suggested that identifying characteristics during natural gait was an ideal way to perform these measurements in patients with ID. Hale et al. utilized the modified gait abnormality rating scale (GARS-M) to identify gait parameters of individuals with Down syndrome, nonsyndromic ID, and other comorbidities. The therapists watched for variability, guardedness, staggering, foot contact, hip range of motion, shoulder extension, and arm-heel strike synchronicity. Specifically, in RTT, the Rett Syndrome Motor Evaluation Scale (RESMES) has been previously suggested as a tool to assess locomotor function in RTT [19]. This scale utilizes six sections to identify the ability to locomote independently. The scale identifies how long the patient can stand or walk with varying levels of physical assistance among other items. More recently, Rodocanachi Roidi et al. [20] have identified that the RESMES is related to disease severity as well as spasticity and hand dysfunction. The RESMES is a well-researched and useful tool in measuring the physical capabilities of children with RTT; however, it is not designed to identify behavioral features exhibited during gait that may influence these capabilities [19,20]. By using a scale such as the RESMES in conjunction with an observational instrument that can be utilized to identify gait characteristics in individuals with RTT, therapists and clinicians can more accurately identify the efficacy of pharmacological or physical interventions on RTT gait. A recent study investigating the parental perception of the care that their daughters with RTT received, reported that fathers expressed the desire to receive additional information about their daughters' walking characteristics and clinical progression. An observational instrument such as the one used in the current study could be used in conjunction with addition sources to provide such information [21].

A majority of previous investigations into the biomechanics of RTT posture and gait have used video-based surveillance analysis. Conversely, our lab has recently published among the first investigations of RTT gait using laboratory-based techniques, including motion capture and center of pressure analysis [10,22]. Our group has identified differences in spatiotemporal and kinematic components of gait between overground and treadmill walking, as well as throughout a range of increasing treadmill speeds. These indicate an ability for RTT patients to adapt to changes in their task through utilizing sensory feedback. Smith-Hicks et al. [23] used an instrumented walkway to record spatio-temporal measures of gait in females with RTT before and after pharmacological intervention; however, due to a small sample size, the group did not perform any statistical comparisons.

While biomechanical analysis of gait in RTT is critical for improving understanding of the motor dysfunctions in these patients, there are features of RTT gait that cannot be fully described using typical biomechanical analysis methods. While motion capture can identify the presence and duration of a freeze during gait, there are features of these instances that may be better described using observational video analysis, such as changes in gaze or apparent attentional focus.

To characterize the nature of gait in RTT, we performed video observational analysis of a sample of females with RTT while they walked both overground and on a treadmill. This study had three primary objectives: (1) characterize the range of behaviors associated with walking in a sample of individuals with RTT, (2) explore the possible relationships existing between the behaviors exhibited during overground walking with those observed during treadmill walking, and (3) initiate the development of an observational-based instrument that identifies the predominant behaviors that can be further refined by clinicians and researchers to characterize gait in females with RTT.

Materials and methods

Participants in this investigation included 14 females with a mean age of 9.2 years with a standard deviation of ±5.4. All participants had been diagnosed with typical RTT using the criteria proposed by Neul et al. and had a pathogenic mutation in the MECP2 gene [1]. All participants currently receive treatment at the Baylor College of Medicine through the Blue Bird Circle Rett Center in Houston, TX. Inclusion criteria included orthotic-free independent walking ability and not taking any medications that may have influenced movement control or muscle tone. The Institutional Review Boards at both the University of Houston and the Baylor College of Medicine approved the study. The parents of the participants provided consent for their daughters to participate in the study. Table 1 provides the age of each of the participants.

Participants performed several trials of overground walking across an instrumented walkway 4.27 m long × 61 cm wide (GAITRite®), followed by several minutes of treadmill walking. During the treadmill protocol, walking was initiated at 0.1 m/s and increased by 0.1 m/s approximately every 20 s. A full description of the experimental protocol can be found in Layne et al. [22,24]. During the two walking protocols, digital cameras were positioned around the walkway and treadmill so that the full range of exhibited behaviors during walking were captured for later analysis.

The initial task was to view the videos obtained during the walking tasks and identify various behaviors that the participants exhibited during walking. That process involved two research analysts that independently viewed the videos and recorded every behavior they observed. After each of the analysts tabulated the

Table 1. A listing of the participants ages at the time of gait assessment.

Participant	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age	4	8	19	5	4	16	20	5	6	8	6	12	8	8

Table 2. Percentage of participants who exhibited identified behaviors during overground and treadmill walking.

RETT Syndrome Behavioral Gait Analysis Scale		
Gait variables	Overground – % of participants	Treadmill – % of participants
Freezing	85.7	78.6
Veering	78.6	78.6
Toe walking	42.9	14.3
Foot dragging	7.1	7.1
Freeze and gaze direction change	64.3	42.9
Freeze and rotate	57.1	0.0
Freeze and clap	35.7	0.0
Freeze and wringing	35.7	0.0
Parkinsonian shuffling	21.4	21.4
Marching in place[a]	28.6	na
Initiation freeze[a]	35.7	na
Retropulsion steps[a]	42.9	na
Anteropulsion steps[a]	14.3	na
Hand clapping while walking	35.7	28.6
Hand wringing while walking	42.9	57.1
External interactions	Overground – % of participants	Treadmill – % of participants
Hand holding	71.4	78.4
Shoulder touching	57.1	85.7
Verbal encouragement	100.0	92.9

[a]Overground only.

observed behaviors, there was 84.5% agreement between the two analysts. Disagreements between the two analyses were submitted to a third analyst. This analyst independently viewed the activities in question and supported one or the other analyst's evaluation. In this way, a final dataset of behaviors was developed and used for further analysis.

Table 2 displays the range of behaviors exhibited by at least one of the participants at some point during overground or treadmill walking (see section "Results"). As can be noted, some variables identify whether a participant ever exhibited a given behavior during either treadmill or overground walking. These tabulations were then converted to the percent of participants who exhibited the behavior. Additionally, there are several variables which are calculated from observed variables as well as three variables identified as interactions with either research assistants or parents that stood alongside either the overground gait mat or treadmill. As FOG was the identified as the most prevalent behavior, we obtained four additional variables associated with FOG. These behaviors were (1) freeze and gaze direction change, (2) freeze and rotate, (3) freeze and clap, and (4) freeze and rotate. These four behaviors promoted greater insight into the behaviors associated with the gait of individuals with RTT.

If a participant was observed to produce a specific behavior, they were coded with a one (1) and a zero (0) if the behavior was never observed. Given the prevalence of FOG, we also calculated the number of gait freezes as a percentage of the total walking time and the number of seconds of the longest freeze during both overground and treadmill walking. After using the Kolmogorov–Smirnov test to confirm the normality of the data of the last two variables, we conducted two sample *t*-tests to assess if there were significant differences between overground and treadmill walking.

To explore the relationships between the most prevalent behaviors of freezing, veering, hand clapping, and wringing during overground and treadmill walking, we tabulated the number of participants who displayed the behavior during both walking modes, in one or the other, or never displayed the behavior. We used Pearson's product moment correlations to assess the degree of relationship between participant age, presence of freezing, freeze count of those who did freeze, the number of freezes as a percentage of the total walking time, and presence of crossing the midline, hand wringing, and hand clapping, for both treadmill and overground walking. Additionally, the number of freezes and the duration of the longest freeze during both treadmill and overground walking were tabulated. We again used Pearson's *R* correlations to assess the relationship between treadmill and overground FOG as a percentage of totaling walking time and longest freeze duration. Finally, we assessed the relationship between the two most prevalent hand stereotypies; clapping and hand wringing, on both the treadmill and during overground walking using Pearson's *R* correlations. These techniques enabled us to more fully characterize the behaviors associated with the gait of females with RTT.

Results

With few exceptions, the variables reported below were exhibited during both treadmill and overground walking. Variables that were only exhibited during overground walking were "marching in place", "initiation freeze", "retropulsion steps", and "anteropulsion steps", as the motorized treadmill prevented these behaviors from occurring (see Table 2). Freezing on the treadmill occurred when the participant ceased walking and drifted backward until either external encouragement caused them to reengage in walking or they reached the backward limits of the treadmill harness, which would then trigger a return to walking.

Table 2 details the percentage of participants who displayed these behaviors during overground and treadmill walking. As can readily be seen, veering and FOG were the two behaviors most often exhibited during both walking conditions. It should be noted that the variables associated with FOG and additional behaviors, for example, FOG and clapping or FOG and rotate- are subsets of the freezing total. Therefore, while 12 of 14 (85.7%) participants during overground walking and 11 of 14 (78.6%) during treadmill walking froze at some point during the protocol, fewer displayed the subset of behaviors associated with FOG. The percentage of participants who displayed toe walking during overground testing was 42.9% but decreased to 14.3% during treadmill walking. Three external interaction variables were regularly observed with the encouragement provided by those interactions often necessary to keep the participants on task.

Table 3. Tabulation of freeze counts and duration of longest freeze during treadmill and overground walking.

	Treadmill walking		Overground walking	
Participant	Freeze count	Longest freeze duration (s)	Freeze count	Longest freeze duration (s)
1	4	6	4	17
2	0	0	11	6
3	15	7	0	6
4	20	4	0	0
5	6	5	2	6
6	4	5	8	6
7	5	5	0	0
8	7	4	3	6
9	6	3	3	6
10	13	12	4	6
11	3	2	1	6
12	15	5	4	6
13	0	0	2	6
14	3	3	1	6
R	0.58		0.28	

The average FOG as a percentage of total walking time during overground testing was 5.08% (SD = 3.85), while for treadmill walking the average was 2.43% (SD = 1.93). The *t*-tests between overground and treadmill for the variable FOG as a percentage of the total walking time revealed a significant difference between the two conditions (*t*-stat = 2.175, $p < 0.024$). The Pearson *R* correlation between overground and treadmill walking for this variable was −0.143. The average longest freeze during overground walking was 6.36 s (SD = 3.46) and 4.36 s (SD = 3.00) during treadmill walking. There was a significant difference between treadmill and overground average freeze duration (*t*-stat = 1.77, $p < 0.049$). The tabulation of the number of freeze counts and the duration of the longest freeze for each participant is displayed in Table 3. This table also contains the Pearson *R* correlation between the two variables for both treadmill and overground walking. There is a moderate positive correlation between the number of freeze counts and the longest freeze during treadmill (0.58) but a low association during overground (0.28) walking.

Table 4 presents the tabulation of the prevalent behaviors for each participant during overground and treadmill walking. All participants presented FOG in at least one of the walking modes. Of the 11 participants who displayed FOG during overground walking, nine also displayed FOG during treadmill walking. Five of the participants displayed FOG either during overground or treadmill walking, but not both. Nine participants veered during both overground and treadmill walking. Only three of the 14 participants veered only during overground or treadmill walking, but not during both conditions, while two never veered. During overground walking, 10 of the participants who froze also veered. During treadmill walking, all nine participants who froze also veered. Six of the 14 participants froze and veered during both treadmill and overground walking.

Ten of 14 participants displayed either hand clapping or wringing while walking in one of testing modes. Four of the five participants who clapped during overground walking also clapped during treadmill walking. Although eight participants displayed hand wringing during treadmill walking, only four of those also displayed wringing during overground walking. Only three of the 14 participants exhibited both clapping and wringing during overground walking. The same was true during treadmill walking. Four participants never displayed any repetitive hand motions during either walking mode. Finally, only two participants (participants 1 and 6) displayed all four behaviors during overground walking, while participants 1, 6, and 10 displayed the four tabulated behaviors during treadmill walking.

Table 4. Tabulation of prevalent behaviors by individual participants.

	Participants														
Behaviors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Sum
Overground freezing	1	1	0	0	1	1	0	1	1	1	1	1	1	1	11
Treadmill freezing	1	0	1	1	1	1	1	1	1	1	1	1	0	1	12
Overground veering	1	1	1	0	0	1	0	1	1	1	1	1	1	1	11
Treadmill veering	1	1	1	1	0	1	0	1	0	1	1	1	0	1	10
Overground clapping	1	0	1	0	0	1	0	0	0	1	0	1	0	0	5
Treadmill clapping	1	0	0	0	0	1	0	0	0	1	0	1	0	0	4
Overground wringing	1	1	1	0	0	1	0	0	0	0	0	0	0	1	5
Treadmill wringing	1	1	0	0	1	1	0	1	1	1	0	0	0	1	8

1 represents the participant exhibited the behavior, while 0 represents the behavior was never exhibited by the participant.

Table 5 displays summary data of the number of participants who displayed the prevalent behaviors as well as two simultaneously occurring behaviors during overground and treadmill walking. Although the small sample size limits interpretability, the data reflect that the walking mode does not appear to influence the likelihood of a behavior occurring independently or in combination with another behavior.

Table 6 displays the Pearson *R* correlations between the participants' ages and several prevalent behavioral activities demonstrated by our participants during gait. Most of the values reflect weak or no appreciable relationships between age and the behavior with the exception of a moderate correlation (–0.54) between the presence of FOG and age but only for overground walking. Finally, the Pearson *R* correlations between hand wringing and clapping during both treadmill and overground walking were, 0.23 and 0.37, respectively.

Discussion

Several investigators have described the general characteristics of gait exhibited by females with RTT. These include ataxic and rigid limb motion often accompanied with a wide-base of support, limited range of motion, toe walking, problems initiating, and FOG [8–11]. Many of our participants displayed several of these features in addition to other behaviors reported above. Overall, our participants demonstrated what can be characterized as ataxic gait.

There are several articles that have used different methodologies to provide data about some of the gait activities that individuals with RTT can accomplish and the degree of assistance that is required [13,25–27]. Although these reports provide important information that is of value for investigators and clinicians, these

Table 5. Relationships within walking modes.

Overground					Treadmill				
	Freeze	Veer	Both	Neither		Freeze	Veer	Both	Neither
Freeze vs. veer	1	1	10	2	Freeze vs. veer	3	1	9	1
	Freeze	Clap	Both	Neither		Freeze	Clap	Both	Neither
Freeze vs. clap	6	1	5	2	Freeze vs. clap	8	0	4	2
	Freeze	Wring	Both	Neither		Freeze	Wring	Both	Neither
Freeze vs. wring	7	1	4	2	Freeze vs. wring	5	1	7	1
	Veer	Clap	Both	Neither		Veer	Clap	Both	Neither
Veer vs. clap	6	0	5	3	Veer vs. clap	6	0	4	4
	Veer	Wring	Both	Neither		Veer	Wring	Both	Neither
Veer vs. wring	6	0	5	3	Veer vs. wring	4	2	6	2
	Clap	Wring	Both	Neither		Clap	Wring	Both	Neither
Clap vs. wring	2	2	3	7	Clap vs. wring	1	5	3	5

The values represent the number of participants who displayed a given combination of behaviors. For example, during overground walking 10 participants both froze and veered while during treadmill walking nine participants participated in both behaviors. Additionally, two participants neither froze nor veered during overground and during treadmill walking only one participant did not display either behavior.

Table 6. Pearson's product moment correlation values between participant age and prevalent behavioral measures during overground and treadmill gait.

Walking mode	Presence of FOG	FOG count	# of FOG as % of total walking time	Crossing the midline	Clapping	Wringing
Overground	−0.54	−0.06	−0.10	0.008	0.37	0.25
Treadmill	0.09	0.07	−0.04	−0.42	0.10	−0.41

approaches are not designed to identify specific behaviors exhibited during walking in females with RTT. The cognitive impairment associated with RTT provides a rationale to establish measurements that can be obtained during natural gait, which does not require complicated instructions to be provided to the participant.

This investigation identified several features of RTT gait during overground walking that can be codified by a clinician or researcher with no specific training in gait evaluation. These features are identified in Table 2. Of the 11 participants that froze during overground walking, nine also froze while on the treadmill. The prevalence of freezing during both walking modes indicates that FOG is an important characteristic of walking in individuals with RTT. Gait initiation freezing has been previously reported [11,28], but to our knowledge this is the first laboratory-based report of FOG occurring during gait. Our data suggest that during FOG episodes, the underlying neurophysiological mechanisms responsible for the alternating flexion and extension lower limb pattern are interrupted in a way that results in FOG. Even the rhythmicity of lower limb motion promoted during walking on the motorized treadmill is not enough to completely prevent FOG.

Although freezing is associated with a motor behavior, the root cause of the freezing does not seem to be related to the basic underlying neurophysiological mechanisms directly related to the mechanisms associated with producing the pattern of lower limb motion. Rather, it is likely that FOG is related to our participants' inability to maintain attentional focus while walking. As displayed in Table 2, FOG in combination with changes in gaze direction was often displayed and is suggestive of shifts in attentional focus. As described by Almuhtaseb et al. [29], the interrelation between cognition and gait may be a significant contributor in individuals with ID. Walking requires the cognitive processes of attentional focus, planning, and memory [30], and there is evidence that executive functioning in individuals with ID is interrelated with deficits in motor behavior [31]. Models of FOG that emphasize the role of cognition propose that diverted attention is associated with an interruption of the functioning of the locomotor mechanisms, thereby resulting in freezing [32].

A total of 12 participants froze during treadmill walking, which we found to be somewhat surprising. We had hypothesized that few participants would freeze during treadmill walking since the motorized treadmill and its continuously moving belt would make it more difficult to freeze than during overground walking. Our data suggest that the feedback received from the feet and lower limbs is enhanced by walking on a motorized treadmill, and thereby supports the neurophysiological mechanisms responsible for the alternating flexion and extension lower limb pattern, is not enough to prevent FOG episodes. Interestingly, previous work by our group has reported that treadmill locomotion does result in less variable temporal gait measures (i.e., stride times), indicating that these participants did respond to the sensory feedback generated during treadmill walking by altering their behavior relative to overground walking [22]. This further suggests that the inability to maintain focus interferes with the mechanisms directly associated with limb motion during episodes of FOG.

In addition to attentional deficits as a major contributor to the incidence of freezing, anxiety associated with the unfamiliar circumstances associated with data collection may have also contributed to this phenomenon. Although assessment always included family members in the environment, unfamiliarity with the research staff, treadmill and GAITrite naturally contributed to a level of increased anxiety in our participants. Martens et al. [33] report that anxiety may contribute to FOG as a result of overloading the ability of the basal ganglia to simultaneously process multiple sensorimotor, cognitive, and emotional inputs. One function of the basal ganglia is to integrate limbic and motor activity, and thus, provide a mechanism by which emotional input, including anxiety, can disrupt motor activity and thereby contribute to FOG. The subcategories of freezing, for example, freezing and clapping, are also likely to result from attentional or anxiety-induced causes.

Veering was also prevalent during both overground and treadmill walking. Several authors have reported that precise foot placement during walking is dependent on where gaze is directed [34,35]. It is also likely that the amount of veering observed in our participants was related to attentional issues as opposed to underlying physical problems. The initiation freezes we occasionally observed are consistent with a report by Isaias et al. [28] that indicated that the temporal organization of the motor activities associated with gait initiation was significantly impaired relative to healthy individuals. As expected, initiation freezes were not observed during treadmill walking as our participants were already positioned on the treadmill and immediately began to walk in response to belt motion.

One core diagnostic criterion to confirm RTT is the presence of stereotypic, repetitive hand motions [4,36]. Referring to Table 2, hand stereotypies never occurred during a FOG episode on the treadmill. This suggests that FOG experienced on the treadmill seemed to interfere with the production of hand stereotypies. However, hand stereotypies were often observed while participants were walking, i.e., not during a FOG episode, during both treadmill and overground walking. In fact, the number of individuals displaying hand stereotypies was greater during treadmill walking. Based on the data, it is reasonable to assert that if an individual with RTT typically displays stereotypical hand movements those movements will also be expressed during walking. Walking and hand stereotypies are the outcome of distinct underlying neurophysiological processes that do not appear to interfere with each other.

Not surprisingly, in addition to freezing and veering, the data indicate that freely ambulating individuals with RTT generally require a great amount of coaxing from external agents to maintain walking, even on a motorized treadmill. Almost all of our participants required verbal encouragement on both walking modes and a large proportion required either occasional hand holding or touches on the shoulder. Although these external behaviors are independent of the participant, we have included them as we believe they are an important component necessary to fully characterize the gait of individuals with RTT. A reasonable goal of a treadmill training program may be to reduce the amount of external feedback necessary to maintain a basic walking mode, thus making it important to chart this feedback.

Relationships between overground and treadmill variables

To gain greater insight into whether the walking mode influenced the presence of some of the most common behaviors we observed, i.e., veering, FOG and hand stereotypies, we examined the prevalence of these variables on the treadmill and during overground walking (Tables 3 and 4). The prevalence of FOG during overground and treadmill locomotion has been discussed above. Nine of the participants who veered during overground also veered during treadmill walking. This indicates that the treadmill does not influence the likelihood of veering despite the fact that during treadmill walking, veering often led to walking off the treadmill belt, requiring restarting of walking. Our supposition is that both veering and FOG are likely related to attentional factors.

We also assessed relationships between hand stereotypies during both treadmill and overground walking (Table 4). These data indicate that although 71% of participants did exhibit either clapping or wringing during one of the walking modes, participants who clap are not necessarily likely to wring their hands. The low correlations between the presence of wringing and clapping during both overground and treadmill walking reinforce this point. These data may indicate that the underlying neurophysiological mechanisms associated with the two behaviors are not identical. This contention is supported by the data presented by Stallworth et al. [36], who reported that fewer participants with a classic RTT diagnosis displayed hand wringing relative to clapping/tapping. Conversely, Carter et al. [37] reported that 59% of 144 individuals with RTT were observed to wring their hands while only 27.1% clapped. Although the reported relative prevalence of these two hand stereotypies are different in these two reports, both indicate that an individual with RTT who displays one behavior may not be likely to display the other, again suggesting the underlying mechanisms supporting these two behaviors may be somewhat distinct. Interestingly, Stallworth et al. [36] reported that mouthing of the hands was observed in upwards of 35% of their sample of 922 individuals diagnosed with classic RTT [36]. In the current study, mouthing of the hands was never observed during either overground or treadmill walking.

The analyses examining the relationship between age and prevalent behaviors exhibited by our participants during walking reflect that there is little association between age and the observed behaviors with the exception of a moderate negative correlation between age and the presence of FOG. Examination of the data revealed that our two oldest (age 19 and 20) participants were primarily responsible for this negative correlation as neither displayed freezing during overground walking. While inconclusive based upon the relatively small sample size, this potential relationship should be assessed more completely in future investigations.

Strengths of this investigation include a relatively large sample size with a reasonably large age distribution of females with RTT that served as our participants. This enabled us, to some degree, to explore associations between observed behaviors and age. We also identified relationships between FOG, which was displayed by the vast majority of our participants during both treadmill and overground walking and other prevalent behavior. The finding that hand stereotypies never occurred during FOG incidents during treadmill walking, provides an interesting area of exploration for future research. The ability to assess gait during both overground and treadmill walking provides a broader perspective regarding the behaviors exhibited by individuals with RTT. Combined with our laboratory's previous work [10,22], it is clear, that despite small differences in some gait variables, treadmill gait is a reasonable approximation of overground walking. This may suggest that treadmill gait training has the potential to advance the walking ability of those with RTT, including improvements in fluency, as a result of the continuous, and steady motion of the treadmill belt. Future studies should explore whether bouts of treadmill walking that reinforce improved fluency [10,22], transfer to overground locomotion. Additionally, our group has initiated the development of an easy to administer assessment instrument that can be used to provide a more complete picture of RTT gait behaviors. Such an instrument can be used to initially assess gait and be used in subsequent assessments to determine if interventions, be they pharmacological or behavioral, are resulting in improved lower limb gait patterns as well as a reduction in the extraneous behaviors identified in this investigation.

Limitations of this investigation include a limited number of participants within certain age ranges. Had there been additional participants, the ability to assess the possibility that certain observed behaviors were closely associated with age, would have been strengthened. As such, our current correlational analyses have limited generalizability. Future studies will aid in the further development of our behavioral assessment instrument and increase the participant sample size so that additional analyses can be conducted and thereby increase our ability to make more definitive statements regarding participant age and behaviors associate with gait of individuals with RTT. While assessing gait in a laboratory setting provides substantial and important information, future studies using a more fully developed behavioral assessment instrument in the participants' home setting will provide valuable additional information.

In conclusion, this study aimed to identify and tabulate the prevalence of behaviors displayed during overground and treadmill walking in a sample of females diagnosed with classic RTT based upon video evidence. It was found that FOG, veering, and hand stereotypies were commonly observed during both walking modes. We also characterized the actions of the caregivers and research assistants that were most often necessary to stimulate continued walking among our sample of participants. Although these were not the identifiable actions of our participants, we believe these external interactions are a fundamental feature required to characterize the gait of females with RTT. Many of the most prominently displayed behaviors were not influenced by walking mode, which suggest that both treadmill and overground walking can be used to evaluate the behaviors displayed during the gait of individuals with RTT. Each walking mode provides advantages and disadvantages relative to each other, so the choice of which mode to use certainly depends upon the reason the individual's gait is being assessed. We believe the observational instrument we used is effective in identifying the most prevalent behaviors associated with walking of those with RTT and can easily be adopted and adapted by others to help monitor disability progression and/or efficacy of pharmacological or physical therapy intervention, at least as it relates to mobility.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, CSL, upon reasonable request.

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