

# Gross Motor Profile in Rett Syndrome as Determined by Video Analysis

## Authors

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## Key words

- Rett syndrome
- gross motor function
- mobility
- movement disorder
- *MECP2* mutation
- phenotype

## Abstract

▼ Movement impairment is a fundamental but variable component of the Rett syndrome phenotype. This study used video supplemented by parent report data to describe the gross motor profile in females with Rett syndrome (n=99) and to investigate the impact of age, genotype, scoliosis and hand stereotypies. Factor analysis enabled the calculation of general and complex gross motor skills scores. Most subjects were able to sit, slightly less than half were able to walk and a minority were able to transfer without assist-

ance. General gross motor skills declined with age and were poorer in those who had surgically treated scoliosis but not conservatively managed scoliosis. Complex gross motor skills did not decline with age and were better in those without scoliosis. Those with a p.R133C, p.R294X, or a p.R255X mutation appear to have better motor skills overall than those with a p.R270X or large deletion mutation. Motor scores were not related to the frequency of hand stereotypies. This information is useful for the clinician and family when planning support strategies and interventions.

## Introduction

▼ The onset of Rett syndrome (RTT) in early childhood is characterised by a gradual or sudden loss of speech and hand function followed by a slow loss of acquired gross motor skills [12,13,32]. The syndrome is characterised by a number of movement disorders including hand stereotypies, gait disturbance and dystonia [9]. It has an incidence of 1:8500 girls by the age of 15 years [23] and is associated primarily with mutations in the *MECP2* gene [2]. Although most subjects are severely functionally dependent there is considerable clinical variability [7,12]. Mutations affecting the nuclear localisation signal (NLS) of the transcription repression domain appear to lead to more severe [8,15] and late truncating mutations to milder clinical presentations [6,8,28].

Cross-sectional studies of subjects with RTT suggest that most can sit independently [5], approximately half can walk [5,16,21], gross motor abilities improve until adolescence and decline thereafter [3,5], and there are difficulties with the performance of transitional movements [3,5,21]. However, details on the breadth of the motor skills are not clear and relationships

between mobility and factors such as genotype and other features such as scoliosis and hand stereotypies are not available.

Broadly based on activities of daily living as conceptualised in the WeeFIM measure [26], we recently developed a video assessment tool to assess multiple features of the RTT phenotype [10], and found some evidence to support its inter-rater reliability, content validity and social validity. In this study, we characterised gross motor function in naturalistic settings in a series of girls and young women with RTT using the aforementioned tool, and evaluated relationships with age, the *MECP2* mutation and other features of RTT including scoliosis and frequency of hand stereotypies. There was also an opportunity to assess the concurrent validity of the video tool by examining the relationship between gross motor function and information on functional status (WeeFIM scores) collected from another source (i.e., a separately administered questionnaire).

## Materials and Methods

▼ The Australian Rett Syndrome Database (ARSD) is a population-based register of confirmed RTT

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cases with data collected from family and clinician questionnaires [24]. In 2004, all families whose children were subjects in the ARSD were invited to participate in the video study [10]. Video data were available for 99 females (median age 14.1 years; range 1.5–27.9 years) with a clinical diagnosis of RTT. Twenty-seven girls were younger than 8 years, 15 were 8 < 13 years and 28 were 13 < 19 years. There were 29 women  $\geq$  19 years.

Families who agreed to participate were sent a filming protocol presented as a pamphlet entitled “A guide for parents: what you need to capture on your video”, a demonstration video, a blank video and a parent report checklist [10]. The filming protocol was developed with the input of health professionals with relevant experience in the areas covered. The demonstration video featuring 4 subjects with Rett syndrome of varying ages and functional ability had been developed to accompany and to supplement the filming protocol in providing guidance to families in making the video of their own daughter. We asked families to film natural function of a list of activities within a familiar environment. The list of activities was broadly based on activities of daily living and included aspects of oromotor function, mobility, hand function and movements, personal care and communication. This paper describes the gross motor mobility items shown on the videos.

For all examples of each gross motor item demonstrated by each subject, the best ability demonstrated was coded to represent the skill level for that subject. The motor items, which were coded, described sitting (on the floor, a chair and a stool); standing (for 3, 10 and 20 s); transfers (sitting to standing, standing up from the floor, and bending down to touch or pick up an object on the floor and returning to standing); and walking, side-stepping, turning 180°, walking along a slope, stepping over an obstacle and running. Coding categories included performed with no assistance; minimal assistance (a requirement for light support or the holding of one hand to perform the activity); moderate assistance (requiring two-hand or trunk support to perform the activity); or maximal assistance (requiring a composite of support to balance, transfer weight and move legs appropriately for the task or if unable to perform the skill). Information contained in the parent report checklist was used to replace missing video data [10]. The videos were scored by an experienced physiotherapist who was blind to the *MECP2* genotype.

The molecular techniques used to identify pathogenic mutations in the *MECP2* gene have been described previously [25]. A *MECP2* mutation was identified in 73 of the 96 (76.0%) subjects who had genetic testing. The ARSD 2004 follow-up questionnaire was used as an additional data source [18] to describe scoliosis, hand stereotypies and WeeFIM ratings. The score developed by Kerr et al. [19] and modified by Colvin et al. [7] was used to describe the severity of scoliosis, with scores of 0 denoting no scoliosis, 1 denoting scoliosis without surgery, and 2 denoting scoliosis treated with surgery. The frequency of hand stereotypies was assessed on a 9-point Likert scale ranging from never to all the time. WeeFIM scores were used to describe independent function [26]. Ethical approval for the study was provided by the Ethics Committee of the Women's and Children's Health Services in Western Australia.

### Data analysis

Age was grouped into four categories representing the pre-school and early school years, primary school, adolescent and adult years, respectively. Gamma tests of association were used

to assess the relationship between age category and level of assistance required for each skill on data provided by the video and parent report checklist. Missing data were imputed using a linear regression model [31] for factor analysis. Principal components analysis was performed to reduce the set of 15 sitting, standing, transfer and walking items into a smaller number of independent variables with extraction of factors having eigenvalues greater than one. After varimax rotation, Z-scores for the extracted factors were calculated for each subject and the internal consistency of the factors was analysed with Cronbach's  $\alpha$ . The relationships between mobility scores and other variables were analysed with linear regression, Spearman correlation, t test and ANOVA as appropriate. All analyses were undertaken using Stata 9 [30].

## Results

### Subjects

More subjects presented with classical (n=79, 79.8%) than atypical (n=20, 20.2%) RTT. Thirty-four (35.1%) subjects were reported to have no scoliosis, whilst 39 (40.2%) were reported to have conservatively managed scoliosis and 24 (24.7%) to have had surgically treated scoliosis. The mean WeeFIM score was 29.02 (95% CI 26.80, 31.24) out of a total possible score of 126. Participants who provided a video were similar in age, genotype and WeeFIM scores to those in the Australian population-based cohort who did not provide a video, but were more likely to have classical rather than atypical RTT [10].

### Description of individual motor skills

Performance on 15 gross motor skills was coded from the video observations and the parent report checklist (with an average of over 70% of data provided from the video for each item). The percentage of subjects who could perform each item is shown in **Table 1**. For all items except sitting on a chair with a back, the level of assistance required to perform the task increased with age group (**Table 1**). As seen in **Table 2** more of those with p.R133C (4/5), p.R168X (5/6), p.R294X(8/10) and p.R306C(3/4) were able to walk compared particularly with those with large deletions (0/5). With standing those with p.R133C, p.R255X, p.R294X, p.R306C and p.T158M performed best compared with those with C terminal deletions, p.R270X and large deletions. Those with p.R168X were intermediate in their capacities.

### Development of motor profiles

Principal components analysis of the 15 items resulted in the extraction of two factors that accounted for 74.5% of total data variance (**Table 3**). Ten items describing sitting, standing, walking, side stepping, turning 180° and sit to stand loaded strongly on factor one which was named ‘General Gross Motor Skills’ because it related to a range of basic skills. Five items of moving from the floor to standing, picking up an object from the floor from standing, stepping over an obstacle, walking along a slope, and running loaded strongly on factor two. These motor skills are more difficult and the factor was named ‘Complex Gross Motor Skills’. The Cronbach's  $\alpha$  coefficient for ‘General Gross Motor’ was 0.96 and for ‘Complex Gross Motor Skills’ it was 0.89.

**Table 1** Levels of assistance (%) for each motor item for the whole group and the relationships with age-group.

	Level of assistance – whole group				Relationship between level of assistance and age group, p value
	None (%)	Minimal (%)	Moderate (%)	Maximal (%)	
<b>sitting</b>					
sit on the floor	73.8	3.6	1.2	21.4	<0.001
sit on chair with a back*	62.1	5.8	30.1	1.9	0.068
sit on a stool	70.7	8.5	9.8	11	0.012
<b>standing</b>					
standing 3 s	38.5	7.3	28.1	26	0.001
standing 10 s	34.5	4.6	29.9	31	0.005
standing 20 s	30.4	6.3	25.3	38	0.07
<b>transfers</b>					
sit to stand	20.4	13.6	39.8	26.1	0.001
sitting on floor to standing	8.6	5.2	36.2	50	0.019
bending to touch the floor and returning to standing	13.5	1.9	0	84.6	<0.001
<b>walking</b>					
walking 10 m	42.7	3.1	24	30.2	0.022
able to side-step	42	4.9	3.7	49.4	0.011
able to turn 180°	43	2.3	16.3	38.4	0.014
able to step over an obstacle	23.1	7.7	10.8	58.5	0.002
able to walk on a slope	24.2	9.7	12.9	53.2	0.025
able to run	13.5	0	0	86.5	0.001

\*Ability to sit in a wheelchair was coded as moderate assistance. Many videos showed sitting in a wheelchair to demonstrate sitting in a chair and the best ability is unlikely to be represented by the percentage shown in this table

**Table 2** Number and percentage of subjects for each mutation performed each motor skill with no assistance on the video (n = 57<sup>a</sup>).

	C-terminal deletions n=7 (7.3%)	R133C n=5 (5.2%)	R168X n=8 (8.3%)	R255X n=5 (5.2%)	R270X n=7 (7.3%)	R294X n=10 (10.4%)	R306C n=4 (4.2%)	T158M n=6 (6.2%)	Large Deletions n=5 (5.2%)
sitting on the floor	5/6 (83.3%)	4/4 (100%)	6/6 (100%)	3/4 (75%)	2/4 (50%)	7/7 (100%)	4/4 (100%)	3/4 (75%)	3/5 (60%)
sitting on a chair	6/7 (85.7%)	5/5 (100%)	8/8 (100%)	5/5 (100%)	7/7 (100%)	10/10 (100%)	4/4 (100%)	6/6 (100%)	4/5 (80%)
sitting on a stool	3/3 (100%)	4/5 (80%)	5/6 (83.3%)	3/4 (75%)	3/7 (42.9%)	8/8 (100%)	4/4 (100%)	5/5 (100%)	3/5 (60%)
transfer sitting to standing	2/7 (28.6%)	3/5 (60%)	1/6 (16.7%)	2/4 (50%)	1/6 (16.7%)	5/10 (50%)	3/4 (75%)	1/5 (20%)	0/4 (0%)
standing 3 s	2/7 (28.6%)	4/5 (80%)	4/8 (50%)	3/4 (75%)	2/6 (33.3%)	7/10 (70%)	4/4 (100%)	4/5 (80%)	0/5 (0%)
standing 10 s	2/7 (28.6%)	3/5 (60%)	3/6 (50%)	3/4 (75%)	2/6 (33.3%)	7/9 (77.8%)	3/3 (100%)	4/5 (80%)	0/5 (0%)
standing 20 s	1/6 (16.7%)	3/4 (75%)	3/5 (60%)	3/4 (75%)	1/6 (16.7%)	5/8 (62.5%)	3/3 (100%)	3/4 (75%)	0/5 (0%)
walking	2/7 (28.6%)	4/5 (80%)	5/6 (83.3%)	3/5 (60%)	1/6 (16.7%)	8/10 (80%)	3/4 (75%)	3/5 (60%)	0/5 (0%)
side-stepping	2/5 (40%)	3/5 (60%)	3/6 (50%)	3/5 (60%)	1/5 (20%)	5/7 (71.4%)	3/3 (100%)	3/6 (50%)	0/4 (0%)
turning 180°	2/6 (33.3%)	4/5 (80%)	3/6 (50%)	2/3 (66.7%)	1/4 (25%)	7/9 (77.8%)	3/3 (100%)	3/5 (60%)	0/4 (0%)
transfer floor to standing	2/45 (0%)	0/1 (0%)	1/5 (20%)	1/3 (33.3%)	0/4 (0%)	2/4 (50%)	3/4 (75%)	1/4 (25%)	0/3 (0%)
bending down and returning to stand	2/5 (40%)	1/1 (100%)	0/2 (0%)	1/3 (33.3%)	0/4 (0%)	2/6 (33.3%)	0/0 (0%)	0/1 (0%)	0/2 (00%)
stepping over an obstacle	2/4 (50%)	2/4 (50%)	1/4 (25.0%)	1/3 (33.3%)	0/3 (0.0%)	4/6 (66.7%)	2/2 (100.0%)	0/6 (0.0%)	0/4 (0.0%)
walking up or down a slope	1/4 (25%)	1/3 (33.3%)	2/4 (50.0%)	1/2 (50.0%)	1/4 (25.0%)	4/6 (66.7%)	2/2 (100.0%)	1/5 (20.0%)	0/5 (0.0%)
running	1/4 (25%)	1/3 (33.3%)	1/4 (25.0%)	0/3 (0.0%)	0/5 (0.0%)	2/6 (33.3%)	2/2 (100.0%)	1/6 (16.7%)	0 (0.0%)

<sup>a</sup>Data for subjects with p.R106W (n = 3), p.R306H (n = 2), other mutations (n = 11), no mutation (n = 23) or not tested (n = 3) not shown in table

### General and complex gross motor skills factor scores

Z-Scores for each factor are presented in **Table 4** with higher scores representing greater abilities. General gross motor scores in girls who were <13 years were higher than those  $\geq 13$  years ( $p=0.01$ ), but there was no significant difference between the complex motor skills scores of these two groups ( $p=0.34$ ).

General gross motor scores of women  $\geq 19$  years were lower than of girls <8 years ( $p=0.01$ ) or  $8 < 13$  years ( $p=0.03$ ). The scores of girls younger than 8 years were not significantly different from those at  $8 < 13$  years ( $p=0.60$ ) or  $13 < 19$  years ( $p=0.21$ ), and scores of girls  $13 < 19$  years were not significantly different from those of women  $\geq 19$  years ( $p=0.19$ ). There was no significant difference in the complex motor skills score across the age groups ( $p=0.61$ ).

### Relationship between motor profiles and genotype

General and complex gross motor skills Z-scores corrected for age are shown for the main individual mutations (**Fig. 1, 2**). Those with individual mutations p.R133C, p.R294X or p.R255X appear to have better motor abilities overall than those with p.R270X or large deletions (**Fig. 1, 2**).

### Relationships between motor profiles and other factors

After adjusting for age, general gross motor scores in those who had scoliosis surgery were significantly worse compared to those without scoliosis ( $p < 0.001$ ) but not compared to those with conservatively managed scoliosis ( $p=0.10$ ). In contrast, complex motor skills were significantly worse both in the presence of conservatively treated scoliosis ( $p < 0.001$ ) and surgically treated scoliosis ( $p=0.001$ ) compared to those without scoliosis. There was no significant correlation between the frequency of hand stereotypies and the general ( $r_s = -0.167$ ,  $p=0.11$ ) or complex gross motor skills score ( $r_s = 0.123$ ,  $p=0.24$ ). However,

poorer WeeFIM scores correlated moderately with poorer general ( $r_s = 0.494$ ,  $p < 0.001$ ) and poorer complex gross motor skills ( $r_s = 0.328$ ,  $p=0.001$ ) scores.

### Discussion

Using a video assessment tool, gross motor function was examined in a large cohort of girls/women with RTT. Most subjects were able to sit, slightly less than half were able to walk or stand and a minority were able to transfer without assistance. Basic postural control (sitting balance) is a strength in RTT, some individuals walk despite voluntary motor control difficulties, and difficulty with transfers reflects the dramatic impact that RTT has on carrying out complex movements. Two distinct motor profiles were developed. The general gross motor factor score reflected abilities to sit, stand, walk, side step and turn, whilst walking, and transfer from sit to standing. The complex gross motor skills factor score represented more difficult tasks including moving from the floor to standing, picking up an object from the floor whilst standing, stepping over an obstacle, walking up a slope and running. Of particular interest is our finding that general but not complex gross motor ability decreased with age. General gross motor skills were poorer in those who had had scoliosis surgery and were best for those with p.R294X or p.R133C mutation. Complex gross motor skills were better in those without scoliosis and in those with a p.R133C, p.R294X, or, unexpectedly, a p.R255X mutation.

The video footage collected for this study allowed us to examine gross motor function over a range of ages, clinical and genotypic variability, and locations throughout Australia. Unlike other studies [3, 5, 16, 21] our sample was sourced from a population-based register and was broadly representative of a national RTT population [10]. The assessed items were comprehensive and relevant to daily living, and by including details not previously described, we have been better able to characterise the gross motor phenotype. Furthermore, factor analysis enabled the calculation of composite motor scores that facilitated the investigation of relationships with other variables. The factor analysis supported the content and construct validity, and the internal reliability of our previously developed gross motor profile [10], and the correlation between the motor and WeeFIM scores supports its concurrent validity.

Despite the aforementioned strengths, there was limited power to be able to analyse specific mutations individually. Because of the cross-sectional nature of the study, there is the possibility of bias towards survivors with the most severely affected dying earlier. Therefore, our study may have provided a slightly more optimistic profile of the population than actually exists.

Consistent with other literature [5, 13, 16, 21], a broad range of abilities was found. As did Cass et al. [5] we found that slightly less than half of the subjects could walk with no assistance. We also observed a smaller proportion of subjects who could stand with no assistance compared with walking, representing the

**Table 3** Factor loadings for items included in the factor analysis.

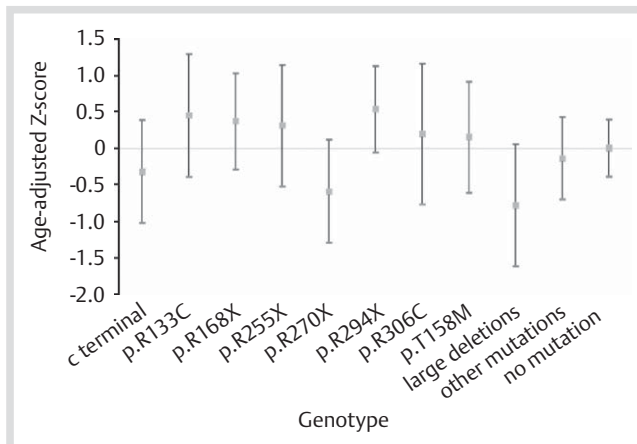
	Factor one	Factor two
sitting on the floor <sup>a</sup>	0.727	0.043
sitting on a chair <sup>a</sup>	0.805	0.193
sitting on a stool <sup>a</sup>	0.688	0.183
transfer sitting to standing <sup>a</sup>	0.669	0.511
standing 3 s <sup>a</sup>	0.834	0.453
standing 10 s <sup>a</sup>	0.831	0.380
standing 20 s <sup>a</sup>	0.673	0.404
walking <sup>a</sup>	0.801	0.520
side-stepping <sup>a</sup>	0.724	0.577
turning 180 ° <sup>a</sup>	0.752	0.562
transfer floor to standing <sup>b</sup>	0.452	0.684
bending to pick up object from floor and returning to stand <sup>b</sup>	0.144	0.838
stepping over an obstacle <sup>b</sup>	0.538	0.709
walking up or down a slope <sup>b</sup>	0.583	0.689
running <sup>b</sup>	0.120	0.851

<sup>a</sup>Items loading onto factor one and called "gross motor skills"

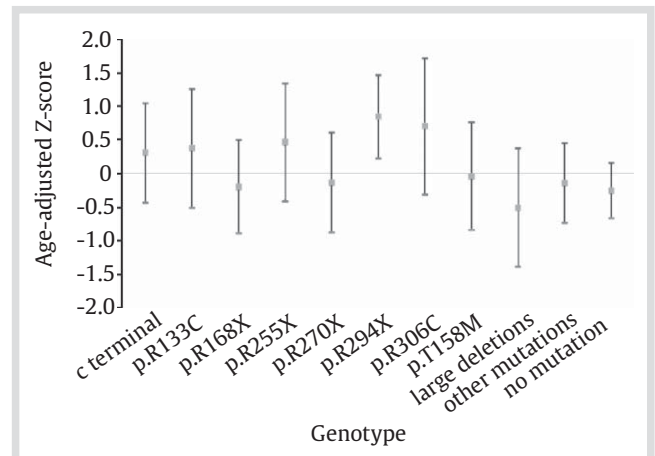
<sup>b</sup>Items loading onto factor two and called "complex motor skills"

**Table 4** General and complex gross motor skills Z-scores by age-group.

	<8 years (n=27)	8<13 years (n=15)	13<19 years (n=28)	$\geq 19$ years (n=29)
general				
mean $\pm$ SEM	0.25 $\pm$ 0.15	0.40 $\pm$ 0.28	-0.04 $\pm$ 0.18	-0.40 $\pm$ 0.21
complex				
mean $\pm$ SEM	0.12 $\pm$ 0.23	0.10 $\pm$ 0.23	-0.08 $\pm$ 0.21	-0.09 $\pm$ 0.14



**Fig. 1** Age-adjusted general gross motor Z-scores (mean and 95% confidence interval) by genotype.



**Fig. 2** Age-adjusted complex gross motor skills Z-scores (mean and 95% confidence interval) by genotype.

subjects who walked on their toes and, although upright, were unable to stand on a stable base of support. Not previously described in the literature, fewer girls/women could walk on a slope, step over an obstacle or run, skills which require greater planning, balance and co-ordination.

The majority of children required assistance and some required lifting when getting in and out of a chair at mealtime and getting up from the floor to a chair or to an upright position. Larsson et al. [21] found that nearly half of their group could complete the transitional movement of sitting to standing [21], but the level of assistance was not specified. The difficulties with transitions that we identified may illustrate the motor impairment of dyspraxia as well as altered muscle tone and poor balance and co-ordination [11]. It is likely that dyspraxia becomes more evident with complex tasks such as transitions, and such difficulties are likely to represent an important burden to families. Rehabilitation of transitional skills has been recommended [14,22] and systematic examination of treatment could represent a promising area for future intervention.

Consistent with the literature [5,13], general gross motor skills decreased with increasing age. Additionally, we assessed complex motor skills and found that abilities did not deteriorate with age in those who achieved these skills. For example, if a child can bend to touch the floor or run, then they might well retain those skills and this would be important information for families. Alternatively, there may be a floor effect and changes with age were not detectable. Our study, like those to which we previously referred, is cross-sectional and the findings should be confirmed in a prospective study with video data collected longitudinally.

Those who had surgery for scoliosis had lower motor scores although we do not know if the poorer motor skills preceded or followed the surgical procedure, and longitudinal data is required to determine any relationships. Characteristic hand stereotypies may be a dramatic feature in RTT and it is reassuring that this behaviour does not affect the level of motor development.

Although it was difficult to assess for statistically significant differences between individual mutations because of power limitations, mutations p.R294X and p.R133C had the highest scores both for the general and complex domains. This was in keeping with the results we obtained for the individual items. However those with p.R306C also fared better with the complex motor skills as well as in standing and walking. Milder levels of severity

of RTT have been shown in those with the p.R133C and p.R306C mutations [4,6,20,27,28] with the p.R306C shown to be relatively advantaged in the motor compared with the language area in the most recently published study [27]. A similar milder phenotype has been demonstrated with p.R294X [4,8] with gross motor function a particular strength and a protective effect against the development of scoliosis [1]. What was less evident from these video results was the better functioning associated with C terminal deletions which has been previously noted by our own group [4] and others [27,29]. The p.R255X and p.R270X mutations in the NLS region are generally deemed to be "severe" [4,8,15]. Interestingly, we found, however, in this study that the p.R255X actually had reasonably good scores although low scores were obtained by those with the p.R270X mutation. It is possible that in those who are older we are seeing a survivor effect with those most severely affected by NLS mutations already having died [17]. It did require considerable effort and a major contribution from families to obtain video material filmed according to a specific protocol on almost 100 Australian cases. However when attempting to disentangle the effects of individual mutations an even larger sample would be preferable. Our descriptive and exploratory study has provided a rich bank of information that could be used by clinicians caring for those with RTT to assist with the management of key issues [5]. This information can be linked with other data sources in the ARSD to further describe the phenotype in this rare condition and could also be used as a base for the development of interventions such as facilitating transitions or walking abilities. In future research, we plan to investigate the relationships between motor abilities and the other domains illustrated on the videotapes including feeding, communication and hand function and also collect longitudinal data. With the inclusion of data relating to genetic characteristics, this will have the potential for greater characterisation and understanding of RTT.

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