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Functional Outcomes in Rett Syndrome

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Abstract

Aim—To relate functional outcomes to mutation type and age at evaluation in patients with Rett syndrome (RTT).

Method—We identified 96 RTT patients with mutations in the *MECP2* (methyl-CpG-binding protein 2) gene. Chart analysis, clinical evaluation, and functional measures were completed.

Results—Among 11 mutation groups, a statistically significant group effect of mutation type was observed for self-care, upper extremity function, and mobility, on standardized measures administered by Occupational and Physical Therapists. Patients with R133C and uncommon mutations tended to perform best on upper extremity and self-care items, whereas patients with R133C, R306C and R294X had the highest scores on the mobility items. The worst performers on upper extremity and self-care items were patients with large deletions, R255X, R168X, and T158M mutations. The lowest scores for mobility were found in patients with T158M, R255X, R168X, and R270X mutations. On categorical variables as reported by parents at the time of initial evaluation, patients with R133C and R294X were most likely to have hand use, those with R133C, R294X, R306C and small deletions were most likely to be ambulatory, and those with R133C were most likely to be verbal.

Interpretation—Functional performance in RTT patients may relate to the type of mutation. Knowledge of these relationships is useful for developing appropriate rehabilitation strategies and prognosis.

Keywords

Rett syndrome; function; mutation groups

Rett syndrome (RTT) is a genetic disorder affecting between 1 in 10,000 to 22,000 females.

[1] Early development is apparently normal followed by a period of developmental arrest

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with deterioration in motor skills, cognition, hand function, and speech.[2] Genetic linkage studies have mapped the location of the disease trait to the Xq28 region of the X chromosome with mutations in three of the four exons of the methyl CpG binding protein 2 (*MECP2*) gene that are found in 90–95% of individuals with RTT.[3, 4]

The ability to perform detailed genetic analysis has revealed more than 200 mutations in the *MECP2* gene with eight common missense and truncating mutations (R106W, R133C, T158M, R168X, R255X, R270X, R294X, and R306C) accounting for a majority of patients with RTT.[5] Small deletions in exon 4, large deletions in exons 3 or 4, and a group of uncommon mutations have also been identified in patients with RTT. Taken together, these specific mutations and deletions account for the genetic defect in 70 to 80% of patients with the clinical features of RTT.[6]

Most previous studies have not had the ability to differentiate the clinical effects of specific mutations in the *MECP2* gene on function.[7, 8, 9, 10] An exception is the report by Neul in which a clinical severity scale based on history, exam, and family responses was administered to a cross sectional cohort of RTT patients over a 14 year interval.[11] This investigation and others like it have relied on scoring systems based on history and exam to make correlations between genotype and phenotype.[12]

This study provides information about the relationship between specific mutations in the *MECP2* gene and function based on skill assessments in addition to parent report and neurologic examination. The inclusion of data about task performance, as measured by physical and occupational therapists, is a unique contribution.

Written informed consent was obtained for all participants. The Johns Hopkins University School of Medicine Institutional Review Board approved the study protocol.

METHOD

Case Selection and Data Collection

A cross sectional cohort of 96 RTT patients who met clinical criteria with mutations in the *MECP2* gene was evaluated at the Kennedy Krieger Institute (KKI) over a 5 year period between July 2004 and June 2009. Those patients without a mutation in the *MECP2* gene but atypical features of RTT were not included. The relationship between outcomes and mutation type was assessed for 11 groups of frequent and uncommon mutations. Evaluation age was categorized as < 5 years, 6 to 10 years, and > 11 years for analyses based on the different stages of the disease as described by Hagberg et al. [13]

MECP2 gene testing

Patient blood samples were analyzed for mutations in the *MECP2* gene including sequencing of exon 1, and by multiplex ligation-dependent probe amplification analysis to identify large deletions or duplications.[1, 14]

Functional analysis

Functional abilities were assessed with instruments developed to provide detailed descriptions of upper and lower extremity skills over multiple domains by trained physical and occupational therapists.

The Functional Independence Measure for Children (WeeFIM) was used to determine the level of independence in the domains of eating, grooming, upper body dressing, lower body dressing, toileting, bathing, mobility, transfers, and stairs.[15] Each item is scored from 1 to 7 based on the individual's ability to perform a skill with 1 indicating total dependence and 7 indicating total independence. A total score for self-care and for mobility was calculated.

Measurement tools developed by the Kennedy Krieger Institute (KKI) staff for internal use were used in conjunction with the WeeFIM in order to describe more discrete and subtle deficiencies in function. The KKI Physical Abilities and Mobility Scale (PAMS) provided supplemental information on quality of movements.[16] The PAMS includes 20 items which are scored based on a 5-point scale which rates a skill from "unable to complete" to "able to complete in a normal manner" with higher scores indicating less severe involvement. This scale was validated on a sample of 107 children and adolescents admitted to an inpatient rehabilitation unit. Preliminary evaluation of reliability and validity was good with an internal consistency of 0.97. Correlations with the WeeFIM ranged from 0.53 to 0.91. The highest correlation was between the WeeFIM motor and PAMS total score and was sensitive to change with physical therapy intervention.

The KKI Upper Extremity Measurement Scale (UEMS) evaluates primarily play, feeding, reaching, and grasping patterns.[17] There are 20 items that were scored on a 5-point scale on the UEMS with higher scores indicating less severe involvement. The UEMS was validated on a sample of 97 children and adolescents admitted to an inpatient rehabilitation unit. Preliminary evaluation of reliability and validity showed an internal consistency of 0.95. Correlations with WeeFIM were moderate-high, ranging from 0.59 to 0.82. The highest correlation was between UEMS total score and WeeFIM total. Scores of all UEMS items and total score improved significantly with occupational therapy intervention. Both the PAMS and the UEMS scores are expressed as a total score out of 100 possible points.

In addition to standardized measures administered on the day of the evaluation, parents were asked to rate their child on hand use, ambulation, and verbal communication skills.

Statistical analysis

The relationship between the performance on functional measures and type of mutation was examined using analysis of variance. These analyses were repeated using age group instead of type of mutation as the independent variable. For those outcomes showing statistically significant group effect, post-hoc analyses were performed to examine differences among specific mutations, with correction for multiple comparisons using Tukey's Honestly Significant Difference correction (HSD). Chi square analyses were conducted to examine group differences in the likelihood of impairment in verbal skills, hand use, and ambulation. Patients with missing data points for an outcome instrument were excluded from the analyses for that particular measure.

All information collected was coded to protect confidentiality and entered into SPSS 22.0 for analysis.

RESULTS

Participants

96 female patients with RTT were sequentially evaluated by study team members. They were grouped for analysis of differences in functional outcomes according to mutation. Groups included the eight most common mutations (R133C, R294X, R106W, T158M, R306C, R270X, R255X, R168X), which accounted for 70% of the total. Patients with large deletions, small deletions, and uncommon mutations were also included in the analysis for a total of 11 groups. The type and frequency of genetic mutations and the age at evaluation are listed in Table 1. No difference in mean age at examination among mutation groups was observed ($p=.75$)

Therapist-assessed Mobility

A significant effect of mutation type was found for functions involving the use of lower extremities, as measured by therapists on the PAMS ($p < .05$). Post-hoc analysis suggested that patients with R133C had significantly higher scores than patients with T158M. Overall group means on this measure ranging from lowest to highest are depicted in Figure 1.

A significant group difference was also found for level of independence on the WeeFIM mobility scale ($p < .05$). Post-hoc analyses again showed that patients with R133C were more independent than those with T158M ($p < .05$). Overall group means on this measure ranging from lowest to highest are depicted in Figure 2.

Therapist-assessed Self-care and Upper Extremity Skills

A main effect of mutation group was found for upper extremity skills as measured by Occupational Therapists on the UEMS ($p < .01$). Patients with uncommon mutations had significantly better scores than those with large mutations, and patients with R133C had significantly better scores than those with large mutations, T158M, and R255X mutations (all $p < .05$). Overall group means on this measure ranging from lowest to highest are depicted in Figure 3.

A significant group effect was also found regarding functional independence related to self-care activities as measured by the WeeFIM ($p < .05$). Post-hoc analysis revealed that patients with either uncommon mutations or R133C were significantly more independent in self-care abilities (all $p < .05$) than those with T158M, R168X, and R255X. Overall group means on this measure ranging from lowest to highest are depicted in Figure 4.

Age group was not significantly related to outcome on any of the outcome measures administered.

Parent-reported abilities

Similar to the therapist-administered measures, Chi-square analysis also suggested an effect of group across parent-reported skills of hand use ($p < .005$), verbal ability ($p < .005$), and ambulation ($p < .05$). The overall percentages of each group with the designated skill are presented in Table 1.

DISCUSSION

A difference in the ability to perform functional tasks was observed in patients who met established criteria for RTT and had a mutation in the *MECP2* gene identified by molecular analysis. Physical and occupational therapists with experience in evaluating RTT patients used scales with graded task specific items across multiple domains to make their assessments. The observed difference across mutation types is in agreement with other reports in regard to the genetic categories that are associated with the least and most affected phenotypes. [11, 18] Patients could generally be stratified according to mutation type across measures, with the R133C being the least affected across domains. For mobility, children with T158M were generally more affected than other mutation types, with R133C being least impaired. For self-care and upper extremity use, children with large deletions, R168X, and R255X were most affected, while children who had uncommon mutations or R133C mutations were least impaired. These relationships were present despite the younger average age at assessment reported in our study compared to the study by Neul.[11

The observation of similar groupings of best and worst performance supports the initiation of targeted interventions at an early age for patients with *MECP2* mutations in the higher risk categories. While the best and worst functional performance may be predicted based on some of the mutation types, a predictable pattern among the remaining mutations was not found when functional abilities fell in the midrange. Our findings support the clinical observation that RTT patients present with a varied phenotype during childhood, and suggest that this may in part be related to the underlying genetic defect, in addition to X inactivation and other epigenetic factors which were not evaluated in this study. [19, 20]

The use of functional outcomes scales to assess RTT patients is a unique aspect of this report. These instruments include items that evaluate specific skills required for upper and lower extremity function, self-care abilities, and mobility. Performance on these tasks was assessed through interviews with the families of these patients and evaluations by a therapist. Since some tools from the evaluation chosen for this study are not age normed, the ability to determine the effects of age at time of examination on performance of tasks was limited.

In regard to the association of functional outcomes with mutation location, our findings are in accordance with studies that reported unique consequences associated with specific sites in the *MECP2* gene with variability within mutation types. [11, 18, 21] This suggests that analysis of clinical outcomes in RTT should take into account additional factors contributing to genomic abnormalities that may be contributing to the severity of clinical manifestations. Although a large number of RTT patients were studied, there were small numbers of subjects within in each mutation group for analysis. A meta analysis including more studies

could lead to the improved ability to provide counseling to families, develop tailored treatment plans, and perhaps insight into the pathologic underpinnings of the clinical severity in this disorder.

While the use of functional outcome measures is a strength of this study, the available standardized measures (e.g. WeeFIM) have limitations in that they are not well normed for younger children, and have significant floor effects. Future studies using a variety of age-normed and standardized measurement tools that can capture a broader range of ability levels are needed to further delineate differences in functional abilities by mutation type in these children as well as the effects of intervention.

SUMMARY

The analysis of the influence of genetic defect on development of functional skills in RTT is complicated by the different ages at examination and the severity of phenotype. On one end of the scale are RTT patients with minor neurologic manifestations throughout childhood with maintenance of the ability to walk, speak, and use their hands to some extent. In contrast, there are patients who never learn to walk or speak and have global developmental delay or arrest in development during childhood. Although functional performance in RTT patients can be related in general to the type of genetic defect, the specific needs of each patient must be considered when structuring an early intervention rehabilitation program. This should be based on therapist assessment at initial evaluation and adjusted as per assessment on subsequent visits. Understanding the relationship between mutations in the *MECP2* gene, age effects, and functional skills may illuminate aspects of the genetic mechanisms underlying this disorder, enhance the ability to counsel families, and assist in developing appropriate rehabilitation strategies for improving mobility, speech, and self-care.

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Figure 1.
Physical Abilities and Mobility Scale (PAMS) ordered from lowest to highest scores.

Figure 2.
WeeFIM Mobility ordered from lowest to highest total scores.

Figure 3.
Upper Extremity Measurement Scale (UEMS) ordered from lowest to highest total scores.

Figure 4.
WeeFIM Self-Care ordered from lowest to highest total scores.

Genetic defect and age at evaluation and preserved ability at time of initial assessment

TABLE 1

Type of genetic defect	Number	%	Mean age at evaluation (% CI)	% with retained skill at initial evaluation		
				Hand use	Verbal	Ambulation
R106W	5	5.2	7.8 (4.7–10.9)	0%	20%	40%
R133C	11	11.5	4.6 (3.5–5.8)	73%	55%	73%
T158M	14	14.8	5.3 (1.5–9.2)	13%	13%	29%
R168X	8	8.3	7.0 (4.1–9.9)	0%	0%	29%
R255X	8	8.3	6.7 (3.4–9.9)	13%	0%	38%
R270X	8	8.3	5.1 (2.7–7.5)	25%	13%	50%
R294X	6	6.3	7.6 (2.9–7.5)	50%	17%	100%
R306C	7	7.3	7.5 (4.5–10.5)	29%	0%	86%
large deletions	4	4.2	7.2 (–8.9–15.4)	16%	0%	74%
small deletions	19	19.8	5.7 (3.9–7.5)	0%	0%	50%
uncommon mutations	6	6.3	6.1 (2.3–9.9)	33%	0%	50%
Total	96	100	6.2 (5.4–7.0)	23%	10%	57%