Published in final edited form as:

Pediatr Neurol. 2017 October ; 75: 91–95. doi:10.1016/j.pediatrneurol.2017.05.025.

Defining Hand Stereotypies in Rett Syndrome: A Movement Disorders Perspective

Marisela E. Dy, MD^{1,2,3}, Jeff L. Waugh, MD, PhD^{1,2,3}, Nutan Sharma, MD, PhD^{1,2,3}, Heather O'Leary¹, Kush Kapur, PhD^{1,3}, Alissa M. D'Gama, PhD³, Mustafa Sahin, MD, PhD^{1,3}, David K. Urion, MD^{1,3}, and Walter E. Kaufmann, MD, PhD^{1,3,4}

¹Boston Children's Hospital

²Massachusetts General Hospital

³Harvard Medical School

⁴Greenwood Genetic Center

Introduction

Rett syndrome¹ (RTT, OMIM #312750) is a neurodevelopmental disorder that typically affects females, though it can rarely occur in males. Patients with RTT develop repetitive hand movements called hand stereotypies (HS), which are a primary diagnostic criterion for

Corresponding Author: Marisela E. Dy, MD, 300 Longwood Ave, Fegan 11, Boston, MA 02215, Phone: 617-355-8235, Fax: 617-730-0279, Marisela.dy@childrens.harvard.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author Contribution (Roles):

Marisela E. Dy: 1.A. Conception B. Organization C. Execution 2.A. Design B. Execution 3.A: Writing of the first draft.
Jeff L. Waugh: 1.A. Conception B. Organization C. Execution 2.A. Design B. Execution 3.B. Review and Critique
Nutan Sharma: 1.A. Conception B. Organization C. Execution 2.A. Design B. Execution 3.B. Review and Critique
Heather O'Leary: 1.A. Conception B. Organization C: Execution 3.B. Review and Critique
Kush Kapur: 2A. Design B. Execution C. Review and Critique 3.B. Review and Critique
Alissa D' Gama: 1.A. Conception B. Organization C: Execution 3.B. Review and Critique
Mustafa Sahin: 1.A. Conception B. Organization C: Execution 3.B. Review and Critique
David K. Urion: 1.A. Conception B. Organization C: Execution 3.B. Review and Critique
Walter E. Kaufmann: 1.A. Conception B. Organization C. Execution 2.A. Execution C. Review and Critique 3.B. Review and Critique

Declaration of Conflicting Interests:

Alissa M. D'Gama received research support by award Number T32GM007753 from the National Institute of General Medical Sciences.

Walter E. Kaufmann is a consultant to Neuren, Edison, Newron, EryDel, Marinus, Anavex, GW Pharmaceuticals and Echo Pharmaceuticals. He has received funding to his institution from Novartis, Ipsen, Eloxx, and Neuren.

Mustafa Sahin received research support from Roche, Pfizer, Novartis, Neuren. He is also on the Scientific Advisory Board of Sage Therapeutics.

The mecasermin trial was supported by RettSyndrome.org (Grant 2907), the Translational Research Program at Boston Children's Hospital, Boston Children's Hospital Intellectual and Developmental Disabilities Research Center P30 HD18655, the Harvard Catalyst–The Harvard Clinical and Translational Science Center (National Institutes of Health Grant 1 UL1 RR 025758-01), and Ipsen Pharmaceuticals.

Nutan Sharma, Jeff L. Waugh, Heather O'Leary, Kush Kapur, and David K. Urion declare that no specific funding was received for this work and that there are no conflicts of interest relevant to this study.

Ethical Approval: Parents or legal guardians provided informed consent. Collection of clinical videos was approved by the Boston Children's Hospital Institutional Review Board (IRB) as part of the larger IGF-1 study.

RTT.²⁻⁴ The HS in RTT tend to be continuous, include mouthing, mainly midline, and can involve the use of objects.⁵ HS may precede the loss of hand function, and appear to evolve over time.⁶⁻⁹ In older individuals with RTT, parkinsonism limits the expression of HS.^{3,4,10} It is unknown whether the underlying mechanism driving the stereotypy truly resolves. In addition to HS, patients with RTT have a breadth of other less well characterized stereotypies that include body rocking, and other lower extremity movements.^{11,12} Stereotypies in RTT are phenotypically heterogeneous, varying in location, frequency and severity, making it challenging to assess them systematically. For the purposes of this study, we focused only on HS. The value of categorizing patients with Rett syndrome based on their hand stereotypies may provide insight into the underlying pathophysiology and/or provide prognostic information.

Most studies have characterized HS by direct cross-sectional observations. However, delineations using video analysis have also been reported.^{4,11-14} Only one study was a complete blinded review,⁵ whereas in another study the initial evaluation was blinded, with subsequent adjustments based on reviewing frequently to ensure consistency.⁴ Previous studies have focused on descriptions of the features of the HS, associations with *MECP2* mutations, changes over time, relationship with behavioral abnormalities, and comparison with HS in other disorders.^{4,5,14-17} This body of literature highlights multiple methodological issues. Prior attempts to characterize HS have been made in using either a single rater with a coding system,¹¹⁻¹² or having different raters define their own operational definitions based on video review.¹⁴ In the study with a completely blinded review, the focus was a comparison of HS between individuals with RTT and autism spectrum disorder. In addition, other studies have used categories without clearly defined terms;¹⁸ only a recent study looking at anxiety and HS provided operational definitions of the abnormal movements.¹⁴ We endeavored to develop a protocol for the systematic characterization of HS. Our objective was to better define types and features of HS in RTT for their systematic assessment in observational and intervention studies.

Methods

Participants

27 girls with RTT participated in a phase 2 randomized controlled trial with mecasermin (recombinant human IGF-1; NC T01777542). Clinical assessment with video recording was performed prior to their first subcutaneous injection of drug/placebo. Trial recruitment and implementation were performed at Boston Children's Hospital. Subjects met diagnostic criteria for classic RTT,² harbored a *MECP2* mutation, and were in the post regression phase.¹⁹ The subjects ranged in age from 2 years 10 months to 11 years 4 months (average age = 6 years 4 months). The most common *MECP2* mutations observed were T158M (n=5), R133C (n=5), R294X (n=4), and R168X (n=4). Other mutations included R270X, R133P, exon4a-4b del, c.519_522delTAAG, c.140 G>C, c.1163-1197del, c.1157-1200del, and T158M and c.1143_1160del (one subject with each mutation). Parents or legal guardians provided informed consent. Collection of clinical videos was approved by the Boston Children's Hospital Institutional Review Board (IRB) as part of the larger IGF-1 study.

Video analyses and operational definitions

Videotaped recordings were reviewed by three raters (HMO, MED, AG) to isolate two 5-minute periods within each video that included the two most common HS for each subject. Three of the twenty seven subjects were excluded from the analyses: one subject had a casted arm and two subjects had restrained arms, precluding visual assessment. Table 1 depicts operational definitions designed by one of the raters (MED), which included modifications to the operational definitions reported by Quest *et. al.*¹⁴

Videos were rated according to nominal (initial protocol) categories derived from prior studies (see Table 1).^{4,11,12,14–16,20,21} The two most frequent HS seen were labeled as HS1 and HS2. HS1 was the most frequent of the two hand stereotypes representative in the five-minute window. HS2 was the second most frequently occurring HS within the five-minute window. Poor inter-rater agreement using previously-reported categories convinced us that refinement and simplification of these categories was required. The operational definitions were revised based on position of HS in relation to the body: midline versus peripheral versus mouthing. In the first simplified protocol, “Midline” was defined as HS within the medial plane of the body. “Peripheral” was defined as HS located away from the body. “Mouthing” was defined as any instances where any part of the hand/fingers were in the mouth, including nail biting and licking of the fingers. “Midline” and “Peripheral” HS were further stratified into “Simple” or “Complex.” “Simple” was defined as a single type of hand movement. “Complex” was defined as a subject having more than one type of hand movement. A second iteration of the protocol further refined the “Midline” label with a more precise definition, subsequently labeled as “Central.” The final simplified protocol incorporated “Mouthing” into the “Central” region rather than as a discrete entity, as there were instances where the mouthing hand was simultaneously involved in a different type of movement (see Figure 1A). “Central” hand movements were operationally defined as those performed within a rhomboid bounded by the nose, the bilateral acromioclavicular joints, and the navel (see Figure 1B). “Peripheral” hand movements were re-defined as those located outside of the region defined as “Central.” In addition, in the final simplified protocol, the left and right hands were scored independently rather than together.

Results

Videos were independently reviewed by three movement disorder specialists (MED, JLW, NS), one of them who participated in the selection of video segments (MED), using the two iterations of the protocol mentioned in Methods (see also Table 1 and Figure 1). Kappa statistics was used to determine level of rater agreement for each iteration of the protocol.

Ratings with nominal categories (initial protocol)

Kappa statistics for the multiple raters with the initial categories demonstrated a 20.7 percent overall agreement ($p < 0.0001$, SE 0.0512) for HS1 and 28.2 percent overall agreement ($p < 0.0001$, SE 0.0001) for HS2 (See Table 2). Considering this low level of agreement, we hypothesized that classifying HS on the basis of location and complexity, as well as coding each hand separately, would increase inter-rater agreement. Further refinement of the scale included having established terminology for the categories as described in Methods.

Ratings with simplified categories (final simplified protocol)

Ten videos were chosen at random for secondary review. The same reviewers independently viewed the videos using the final simplified protocol (MED, JLW, NS). Each hand was scored separately. The kappa statistics for each hand (Right/Left) and the two most frequent HS (HS1, HS2) were higher, demonstrating greater agreement. For HS1 Left, the level of agreement was 50.8%, ($p < 0.0001$, SE 0.1183), whereas for HS1 Right, the level of agreement was 42.2 % ($p < 0.001$, SE 0.1155). The level of agreement for the second most common HS of the left hand (HS2 Left) was 21.2% ($p = 0.0351$, SE 0.1160), whereas the level of agreement for HS2 Right was 29.5% ($p = 0.0077$, SE 0.1212). Although there was significant agreement among reviewers for HS1 Left and HS1 Right, it was not significant for HS2 for either hand. Overall, inter-rater agreement improved with protocol refinement, but remained unacceptably low (See Table 2).

Discussion

The present study aimed to systematically characterize and quantify HS, using a blind rating protocol. Despite our iterative and systematic efforts to develop systematic nomenclature that could be used by caregivers, researchers, and other health care specialists, the level of agreement among raters was at best 50%. Phenotypical variability in HS makes standardized evaluation a challenge.

Previous publications have used definitions based on categorical descriptions of HS and other associated features.^{14–16,20,21} Our results are similar to previous reports with respect to recognition of the heterogeneity.^{5,11} However, our data differ from Goldman & Temudo,⁵ where an 80–100% level of agreement was achieved based on a blinded review of videos comparing stereotypies between RTT and autism spectrum disorder. The attempts were at a consensus, not efforts to independently review and rate. In addition, the focus was on comparing profiles of RTT and autism. It was concluded that stereotypies in RTT tended to be midline, continuous, and rather complex similar to previous studies.^{5,10} Earlier reports also described asymmetric, non-midline hand movements.²² In Quest *et al.*, raters developed individualized operational definitions and had slightly different definitions of hand tapping.¹⁴

In our initial categorization, we used modified terminology employed in previous studies, achieving a low level of agreement. We simplified the protocol and achieved 50% level of agreement, but only for the most frequent HS. We speculate that our level of agreement was low because HS in RTT are very heterogeneous. Our data shows the importance of standardized terminology in phenotypic descriptions of patients, since refinement of definitions increased inter-rater agreement. However, even with standardized terminology and fairly well-described characteristics, inter-rater agreement was much lower than expected. Our data also demonstrates that HS in RTT do not break cleanly into neatly defined categories, thereby making it difficult to have standardized terminology in phenotypic descriptions of HS in patients with RTT.

Our results demonstrate the difficulty in creating operational definitions of HS in RTT. Despite our prior experience systematically characterizing abnormal movements in children,

and our iterative approach to improving our operational definitions, the phenotypical variability in RTT-related HS defied our attempts at characterization. The goal of defining HS in a manner that can be used among all health care providers, parents, and caregivers remains worthwhile, but appears unlikely to be achieved simply through improved definitions. Certainly, improved definitions could become important if HS are to become an outcome measure or biomarker for research determining efficacy of drugs targeting this major phenotype of RTT.

Our findings suggest that certain clinical phenomena in RTT, in this case HS, could be better delineated and quantified using objective measures such as actigraphy. The need for objective assessments in RTT is underscored by our work attempting to identify early detection markers for the disorder, which suggest an optimal approach would require automated communication output and movement pattern analyses.^{23,24} Previous reports have demonstrated that it is possible to use automated analyses for body rocking and hand flapping,²⁵ as well as for HS.²⁶ Automated analyses have also been used for gait assessment in other disorders such as Parkinson disease and multiple sclerosis.^{27,28} Complex video tracking would also be needed to correctly assess the presence or absence of the wide range of HS, even using a simplified protocol such as the one we created. Simpler actigraphy measures could certainly capture the presence or absence of movement, and may be able to classify (with machine learning) certain movement patterns, but most certainly fall short of an automated version of a clinical scale for classifying HS or other abnormal movements. While emphasizing newer technologies, it is critical not to forget that the focus of these efforts is to improve hand function and quality of life. Thus, any categorization or measurement of HS has to ultimately reflect hand function.

Acknowledgments

Our sincerest appreciation is extended to all of the children and their parents whose participation was vital to this research. This work was done at Boston Children's Hospital, Massachusetts General Hospital, and Harvard Medical School. This work has been presented at the 14th Rett Syndrome Symposium in June 2016. Marisela Dy was funded by Rettsyndrome.org under the U54 HD 061222 NIH grant.

Funding (Financial Disclosure):

Mustafa Sahin received research support from Roche, Pfizer, Novartis, Neuren. He is also on the Scientific Advisory Board of Sage Therapeutics.

Walter E. Kaufmann is a consultant to Neuren, Edison, Newron, EryDel, Marinus, GW Pharmaceuticals and Echo Pharmaceuticals. He has received funding to his institution from Novartis, Ipsen and Eloxx.

Marisela E. Dy, Alissa M. D'Gama, Nutan Sharma, Jeff L. Waugh, Heather O'Leary, Kush Kapur, and David K. Urion have no additional financial disclosures to report.

References

1. Hagberg B, Aicardi J, Dias K, Ramos O. A Progressive Syndrome of Autism, Dementia, Ataxia, and Loss of Purposeful Hand Use in Girls: Rett's Syndrome: Report of 35 Cases. *Ann Neurol*. 1983; 14:471–479. DOI: 10.1002/ana.410140412 [PubMed: 6638958]
2. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: Revised Diagnostic Criteria and Nomenclature. *Ann Neurol*. 2010; 68(6):944–950. DOI: 10.1002/ana.22124 [PubMed: 21154482]

3. Temudo T, Maciel P, Sequeiros J. Abnormal movements in Rett syndrome are present before the regression period: a case study. *Mov Disord.* 2007; 22(15):2284–2287. DOI: 10.1002/mds.21744 [PubMed: 17914728]
4. Carter P, Downs J, Bebbington A, et al. Stereotypical hand movements in 144 subjects with Rett syndrome from the population-based Australian database. *Mov Disord.* 2010; 25(3):282–288. DOI: 10.1002/mds.22851 [PubMed: 19908321]
5. Goldman S, Temudo T. Hand stereotypies distinguish Rett syndrome from autism disorder. *Mov Disord.* 2012; 27(8):1060–1062. DOI: 10.1002/mds.25057 [PubMed: 22711266]
6. Nomura Y, Segawa M, Hasegawa M. Rett syndrome—Clinical studies and pathophysiological consideration. *Brain Dev.* 1984 Jan; 6(5):475–486. [PubMed: 6517222]
7. Kerr AM, Montague J, Stephenson JB. The hands, and the mind, pre- and post-regression, in Rett syndrome. *Brain Dev.* 1987; 9(5):487–490. [PubMed: 3434724]
8. FitzGerald PM, Jankovic J, Percy AK. Rett syndrome and associated movement disorders. *Mov Disord.* 1990; 5(3):195–202. DOI: 10.1002/mds.870050303 [PubMed: 2388636]
9. Nomura Y, Segawa M. Characteristics of motor disturbances of the Rett syndrome. *Brain Dev.* 1990; 12(1):27–30. [PubMed: 2344020]
10. Fitzgerald PM, Jankovic J, Glaze DG, Schultz R, Percy AK. Extrapyramidal involvement in Rett's syndrome. *Neurol.* 1990; 40:293–295.
11. Temudo T, Oliveira P, Santos M, et al. Stereotypies in Rett syndrome: analysis of 83 patients with and without detected MECP2 mutations. *Neurol.* 2007; 68(15):1183–1187. DOI: 10.1212/01.wnl.0000259086.34769.78
12. Temudo T, Ramos E, Dias K, et al. Movement disorders in Rett syndrome: an analysis of 60 patients with detected MECP2 mutation and correlation with mutation type. *Mov Disord.* 2008; 23(10):1384–1390. DOI: 10.1002/mds.22115 [PubMed: 18512755]
13. Marschik PB, Kaufmann WE, Einspieler C, et al. Profiling early socio-communicative development in five young girls with the preserved speech variant of Rett syndrome. *Res Dev Disabil.* 2012; 33(6):1749–1756. DOI: 10.1016/j.ridd.2012.04.012 [PubMed: 22699249]
14. Quest KM, Byiers BJ, Payen A, Symons FJ. Rett syndrome: A preliminary analysis of stereotypy, stress, and negative affect. *Res Dev Disabil.* 2014; 35(5):1191–1197. DOI: 10.1016/j.ridd.2014.01.011 [PubMed: 24582142]
15. Jankovic, J. Stereotypies in autistic and other childhood disorders. In: Fernandez-Alvarez, E., Arzimanoglou, A., Tolosa, E., editors. *Paediatr Mov Disord Prog Underst.* Esher, Surrey: John Libbey Eurotext; 2005. p. 247–260.
16. Fernandez-Alvarez, E., Aicardi, J. Movement disorders in cerebral palsy; Miscellaneous movement disorders in childhood. In: Fernandez-Alvarez, E., Aicardi, J., editors. *Mov Disord Child First edit.* Mac Keith Press for the International Child Neurology Association; 2001. p. 216–227.
17. Kaufmann WE, Tierney E, Rohde CA, et al. Social impairments in Rett syndrome: characteristics and relationship with clinical severity. *J Intellect Disabil Res.* 2012; 56(3):233–247. DOI: 10.1111/j.1365-2788.2011.01404.x [PubMed: 21385260]
18. Fyfe S, Downs J, McIlroy O, et al. Development of a video-based evaluation tool in Rett syndrome. *J Autism Dev Disord.* 2007; 37(9):1636–1646. [PubMed: 17180458]
19. Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev.* 2002; 8(2):61–65. DOI: 10.1007/s10803-006-0293-9 [PubMed: 12112728]
20. Mahone EM, Bridges D, Prahme C, Singer HS. Repetitive arm and hand movements (complex motor stereotypies) in children. *J Pediatr.* 2004; 145(3):391–395. DOI: 10.1016/j.jpeds.2004.06.014 [PubMed: 15343197]
21. Singer HS. Stereotypic movement disorders. *Handb Clin Neurol.* 2011:631–639. [PubMed: 21496612]
22. Elian M, de M Rudolf N. Observations on hand movements in Rett syndrome: a pilot study. *Acta Neurol Scand.* 1996; 94(3):212–214. [PubMed: 8899055]
23. Einspieler C, Freilinger M, Marschik PB. Behavioural biomarkers of typical Rett syndrome: moving towards early identification. *Wien Med Wochenschr.* 2016; 166:333–337. DOI: 10.1007/s10354-016-0498-2 [PubMed: 27514944]

24. Marschik PB, Kaufmann WE, Sigafoos J, et al. Changing the perspective on early development of Rett syndrome. *Res Dev Disabil.* 2013; 34(4):1236–1239. DOI: 10.1016/j.ridd.2013.01.014 [PubMed: 23400005]
25. Goodwin MS, Intille SS, Albinali F, Velicer WF. Automated detection of stereotypical motor movements. *J Autism Dev Disord.* 2011; 41(6):770–782. DOI: 10.1007/s10803-010-1102-z [PubMed: 20839042]
26. Wright M, Van der Linden ML, Kerr AM, et al. Motion analysis of stereotyped hand movements in Rett syndrome. *J Intellect Disabil Res.* 2003; 47(Pt 2):85–90. [PubMed: 12542573]
27. Barth J, Sünkel M, Bergner K, et al. Combined analysis of sensor data from hand and gait motor function improves automatic recognition of Parkinson's disease. *Conf Proc IEEE Eng Med Biol Soc.* 2012; 2012:5122–5125. DOI: 10.1109/EMBC.2012.6347146 [PubMed: 23367081]
28. Huisinga JM, Mancini M, St George RJ, Horak FB. Accelerometry reveals differences in gait variability between patients with multiple sclerosis and healthy controls. *Ann Biomed Eng.* 2013; 41(8):1670–1679. DOI: 10.1007/s10439-012-0697-y [PubMed: 23161166]

Figure 1.

A. Final Simplified Protocol: Hands were rated separately as “Central” or “Peripheral.” Hand movements were then stratified as “Simple” or “Complex.” “Simple” was defined as a single type of hand movement. “Complex” was defined as having more than one type of hand movement. **Figure 1B. Operational Definitions: Central vs. Peripheral:** “Central” was defined as hand movements performed within a rhomboid bounded by the nose, the bilateral acromioclavicular joints, and the navel. “Mouthing” was incorporated into “Central.” “Peripheral” was defined as hand movements located outside the region defined as “Central.”

Table 1**Operational Definitions of Hand Stereotypies**

Clapping	Any instance where palms of hands come together like someone is applauding. Fingers cannot interlace.
Wringing/Washing/Clasping	Proposal for spectrum: Requires that both hands are involved in the movement.
	A) Wringing/Washing: Any instance where hands/fingers are interlaced with wrist rotation.
	B) Clasping: Any instance in which fingers are interlaced.
Squeezing/Clenching	Proposal for spectrum: Can be unilateral or bilateral.
	A) Squeezing: Any instance where the hands open and close repetitively to make a fist.
	B) Clenching: Any instance where the hands make a fist.
Flapping	Any instance where arms/wrists make a back and forth movement. Can be unilateral or bilateral.
Mouthing	Any instance where any part of fingers or hands are in the mouth.
	This can include nail biting/finger licking. Can be unilateral or bilateral.
Tapping	Any instance where there is repetitive contact made with fingers or palm on a surface or on chest.
Mixed midline hand movements	Any instance where each hand is involved in different hand stereotypy (within seconds) e.g., mouth/tap, clasp/clap.
Mixed asymmetric hand movements	Any instance where the hands are midline with a repetitive, non-purposeful movement, but one hand is less active with wrist flexed or extended and/or fingers flexed.
Repetitive finger movements	Any instance where there is a piano-like movement of fingers.
Other	Any other hand stereotypy that does not fit the above categories (includes arm extension, posturing).

Table 2
Kappa Statistics for Initial Protocol and Final Simplified Protocol

Videos were initially reviewed to identify a five-minute window with the two most common hand stereotypies observed. HS1 is the most common hand stereotypy observed in the five-minute window. HS is the second most commonly observed hand stereotypy in the five-minute window.

	Agreement between raters	S.E	p-value	95% LCL	95% UCL
Initial Protocol HS1	0.207	0.0512	<0.0001	0.107	0.307
Initial Protocol HS2	0.282	0.0001	<0.0001	0.282	0.282
Final Protocol					
HS1 Left	0.508	0.1183	<0.0001	0.276	0.740
Final Protocol					
HS1 Right	0.422	0.1155	<0.001	0.196	0.648
Final Protocol HS2 Left	0.212	0.1160	0.0351	0.000	0.439
Final Protocol HS2 Right	0.295	0.1212	0.0077	0.057	0.533