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Rett syndrome diagnostic criteria: Lessons from the Natural History Study

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Introduction

The diagnosis of Rett syndrome, described by Andreas Rett in 1965¹ as a neurodevelopmental disorder predominantly affecting females, is based on clearly defined clinical criteria, modified periodically with improved understanding of its core features. In 1985, Hagberg and colleagues developed consensus criteria exclusively for females², modified in 1988 to include males³. Following identification of mutations in the gene, *Methyl-CpG-binding-protein 2 (MECP2)*, in individuals with RTT⁴, an international consensus meeting further modified those criteria to affirm the importance of carefully applied diagnostic criteria⁵ and to clarify possible ambiguities in interpretation of these criteria. This included recognition that 1) abnormal deceleration in the rate of head growth was not always present, 2) early development could be delayed, and 3) apraxia of gait should include the possibility of failure to develop gait. Further, it was important to provide consensus criteria for variant forms of RTT⁶. More recently, RettSearch, an international group of clinicians, completed a systematic review of these criteria to provide further clarifications including those core features that are essential for considering the diagnosis of RTT or its variants and to refine definitions of other previous criteria not included in this core group (see accompanying paper, Neul et al.). This revision follows on refinements in molecular diagnosis including identification of previously unrecognized *MECP2* mutations in exon 1⁷, large deletions encompassing one or more exons^{8,9}, and duplication of the *MECP2* Xq28 region in males with severe neurodevelopmental disorders¹⁰⁻¹², as well as confirmation of mutations in 95% of females with classic RTT¹³. Further, an increasing number of females and males, not meeting RTT criteria, have been identified with *MECP2* mutations.

The RTT Rare Disease Clinical Research Center (RDCRC) natural history study began enrolling participants in 2006 with the goal of 1000 individuals with classic or variant RTT based on the 2002 criteria⁵. The present analysis was conducted on 819 participants enrolled as of February 28, 2010, to assess the recently modified clinical criteria. The results validate the revised diagnostic format and emphasize the importance of having clearly defined criteria based on clinical features including clear regression of previously acquired skills in both classic and variant RTT and the necessity of supportive criteria only for variant forms.

Methods

Participants were enrolled into the RDCRC natural history if they met diagnostic criteria for RTT or had a mutation in *MECP2*. All participants had complete mutation testing including *MECP2* sequencing and, if negative, deletion/duplication testing. Clinical diagnosis utilized the 2002 consensus criteria⁵. Classic RTT was based on meeting all necessary criteria, although supportive criteria from the 2002 criteria were also assessed (periodic breathing, bruxism, sleep disruption, abnormal muscle tone, vasomotor disturbances, scoliosis, growth failure, and small hands and feet). For variant RTT, diagnosis was based on the 2002 variant criteria, namely, meeting 3 of 6 main criteria (loss of hand skills, communication skills, and babble speech, hand stereotypies, deceleration of head growth, and a disease profile of regression followed by recovery of interaction) and 5 of 11 supportive criteria (periodic breathing, aerophagia, bruxism, apraxia of or no gait, scoliosis, lower limb muscle atrophy, cold feet, sleep disruption, inappropriate screaming/ laughing, diminished nociception, and intense eye contact).

The following analyses were conducted on 819 participants enrolled through February 28, 2010: 1) diagnostic category (classic RTT, variant RTT or non-RTT using the 2002 criteria) and distribution of *MECP2* mutations within each category and 2) number of participants in each category meeting the diagnostic and supportive criteria. This cross-sectional analysis is based on assessment at initial enrollment and does not reflect longitudinal follow-up. The clinical diagnostic categories determined using the 2002 criteria for these individuals was compared with the diagnostic categories that would be assigned to these individuals using the revised 2010 criteria (see accompanying paper).

Results and Discussion

The distribution of *MECP2* mutations for 819 participants enrolled as of February 28, 2010, is displayed in Table 1. Data include frequency of the eight most common mutations, large deletions, C-terminal truncations, all other mutations, and no mutations as well as occurrence of more than one mutation in participants with classic and variant RTT. Of 765 females fulfilling criteria for classic or variant RTT, 653 (85.4%) were diagnosed as classic and 112 (14.6%) were classified as variant. A mutation was identified in 95% of 653 females with classic and 73.2% of 112 females with variant RTT and in all 31 females (identified either as carriers in multiplex families, based on a single feature such as hand stereotypies or deceleration of head growth, or in some cases the presence of developmental delay and autistic features in a girl) and 23 males that did not meet criteria for classic or variant RTT. In classic RTT, frequency of the eight most common mutations was similar to that in the North American database¹⁴. The greater frequency of large deletions in the natural history study likely reflects the requirement for complete testing in the present study as large deletion testing was not completed uniformly in North American database registrants. For variant RTT and females with non-RTT, the greater frequency of C-terminal truncations, R133C, and R306C (non-RTT females only) confirms earlier reports of milder clinical severity for these mutations^{13,15}. Males with non-RTT tend to have mutations not commonly identified in classic RTT. Although we have evaluated several potential

participants with CDKL5 mutations, only one participant is included in this study because most fail to meet RTT clinical criteria.

Table 2 indicates the number of participants in each group fulfilling the 2002 Necessary and Exclusion criteria. For classic RTT, the pre-, perinatal, and early development periods appeared normal in most participants. The small group (1-2%) with minor prenatal, perinatal, or early development abnormalities did not include any significant problem leading to neurological dysfunction. Similarly, among the exclusion criteria, the infrequent occurrence of IUGR (<1%) was also not associated with a pervasive systemic or neurological disorder. All participants with classic RTT fulfilled the main criteria in the 2010 revised version (see accompanying paper, Neul et al.), namely, regression including loss of communication and fine motor hand skills, apraxia or absence of gait, and hand stereotypies. Abnormal deceleration in the rate of head growth was noted in 82%, supporting the 2002 criteria revision expecting this finding 'in the majority'. None of the supportive criteria from the 2002 criteria was present in every classic RTT participant and only bruxism was noted in more than 80% (Table 3). As such, supportive criteria are not crucial for diagnosis in classic RTT.

Among the variant RTT participants, all met the 2002 consensus criteria and the recently revised criteria for at least 2 of 4 main and 5 of 11 supportive criteria. Loss of hand use and communication and abnormal head growth deceleration was noted in 54-60%, while hand stereotypies appeared in 98% (Table 2). For supportive criteria in variant RTT (Table 3), seven were present in more than 50% [abnormal gait (93%), bruxism (83%), sleep disruption (72%), reduced nociception (71%), intense eye contact (66%), inappropriate laughing/screaming (63%), and periodic breathing (61%)]. Scoliosis, lower limb muscle atrophy, cold feet, and aerophagia were much less common. As such, in combination with the main criteria, supportive criteria appear essential for the diagnosis of variant RTT.

For non-RTT females, only one lost hand use and other main criteria of the 2010 revision did not exceed 30%. Abnormal gait was noted in 42%. In contrast, a majority of non-RTT males had hand stereotypies, particularly repetitive rubbing of the nose, and early development was normal in only 57%. Among the non-RTT group, preserved eye contact and reduced nociception were present nearly uniformly whereas the remaining variant supportive criteria were observed less frequently with only bruxism and sleep disruption (52%) and abnormal gait (59%) in a majority of these participants. As the non-RTT participants do not fulfill the main criteria, application of the supportive criteria does not appear to be critical.

Conclusion

Analysis of diagnostic features for 819 participants enrolled in the RDCRC natural history study, based on the 2002 diagnostic criteria, underscores the critical role of the main criteria, namely, regression of fine motor and communication skills, abnormal or no gait, and hand stereotypies for the diagnosis of classic and variant RTT. For classic RTT, these core criteria are sufficient for diagnosis as none of the eight 2002 supportive criteria is noted uniformly. For variant RTT, diagnosis requires application of both main (2 of 4) and supportive (5 of 11) criteria. They should be considered in partnership.

In their summation of the 2002 consensus criteria⁵, the authors commented that 'In order for the accurate conduct of phenotype-genotype studies, these criteria must be applied consistently. This seems self-evident. However, such is not always the case.' As we approach treatment trials in RTT, the importance of consistent application of diagnostic criteria is even more crucial. The present analyses validate the conceptual framework

incorporated within the most recent revision of RTT diagnostic criteria, demonstrate that utilization of the revised criteria does not alter pre-existing diagnostic categorization, and underscore the importance of clearly defined criteria based on clinical features of RTT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Natural History Study *MECP2* Status

Mutation	Classic N (%)	Variant N (%)	Non-RTT [N (%)]		NA Database (%)
			Female	Male	
T158M	72 (11.0)	4 (3.6)	1 (3.2)	0	11.9
R255X	71 (11.0)	10 (8.9)	1 (3.2)	0	9.0
R168X	68 (10.4)	4 (3.6)	0	0	9.4
R306C	45 (6.9)	7 (6.3)	4 (12.9)	0	6.9
R294X	41 (6.3)	4 (3.6)	1 (3.2)	0	6.2
R270X	36 (5.5)	4 (3.6)	0	0	7.2
R133C	25 (3.8)	10 (8.9)	4 (12.9)	0	6.4
R106W	20 (3.1)	2 (1.8)	1 (3.2)	1 (4.4)	4.4
Large deletion	57 (8.7)	4 (3.6)	2 (6.5)	0	6.4
C-terminal truncation	45 (6.9)	14 (12.5)	12 (38.7)	3 (13.0)	8.8
Other mutations	130 (19.9)	17 (15.2)	5 (16.2)	19 (82.6)	23.4
>1 mutation	10 (1.5)	2 (1.8)	0	0	NR
No mutation	33 (5.0)	30 (26.8)	0	0	NR
Total	653	112	31	23	1059

Table 2

Natural History Study: Diagnostic Criteria

2002 Criteria	2010 Revised Main Criteria	Classic [N (%)]		Variant [N (%)]		Non-RTT Female [N (%)]		Non-RTT Male [N (%)]	
		Yes	No	Yes	No	Yes	No	Yes	No
Normal Prenatal		644 (99)	9 (1)	97 (87)	15 (13)	28 (90)	3 (10)	22 (96)	1 (4)
Normal Perinatal		643 (98)	10 (2)	99 (88)	13 (12)	30 (97)	1 (3)	22 (96)	1 (4)
Normal Initial Development		645 (99)	8 (1)	65 (58)	47 (42)	27 (87)	4 (13)	13 (57)	10 (43)
Loss of Hand Use	✓	653 (100)	0	60 (54)	52 (46)	1 (3)	30 (97)	10 (43)	13 (57)
Loss of Communication	✓	653 (100)	0	63 (56)	49 (44)	6 (19)	25 (81)	11 (48)	12 (52)
Hand Stereotypies	✓	653 (100)	0	110 (98)	2 (2)	9 (29)	22 (71)	16 (70)	7 (30)
Head Growth Deceleration		535 (82)	118 (18)	67 (60)	45 (40)	8 (26)	23 (74)	11 (48)	12 (52)
Gait Apraxia/No Gait	✓	653 (100)	0	104 (93)	8 (7)	13 (42)	18 (58)	19 (83)	4 (17)
No IUGR		650 (99)	3 (1)	105 (94)	7 (6)	28 (90)	3 (10)	22 (96)	1 (4)
No Organomegaly		653 (100)	0	109 (97)	3 (3)	25 (81)	6 (19)	22 (96)	1 (4)
No Retinopathy		653 (100)	0	108 (96)	4 (4)	27 (87)	4 (13)	22 (96)	1 (4)
No Peri-Postnatal Injury		653 (100)	0	108 (96)	4 (4)	26 (84)	5 (16)	21 (91)	2 (9)
Total		Classic RTT = 653		Variant RTT = 112		Non-RTT female = 31		Non-RTT male = 23	

Table 3

Natural History Study: Supportive Criteria

Criteria	Classic [N (%)]		Criteria	Variant [N (%)]	
	Yes	No		Yes	No
Periodic Breathing	500 (77)	153 (23)	Periodic Breathing	68 (61)	44 (39)
Bruxism	595 (91)	58 (9)	Bruxism	93 (83)	19 (17)
Sleep Disruption	458 (70)	195 (30)	Sleep Disruption	81 (72)	31 (28)
Abnormal muscle tone	505 (77)	148 (23)	Abnormal Gait	104 (93)	8 (7)
Cold hands/feet	273 (42)	380 (58)	Cold feet	21 (19)	91 (81)
Scoliosis	321 (49)	332 (51)	Scoliosis	40 (36)	72 (64)
Growth Failure	454 (70)	199 (30)	Aerophagia	43 (38)	69 (62)
Small hands	152 (23)	501 (77)	Lower limb muscle atrophy	23 (21)	89 (79)
Small feet*	425/642 (66)	217/642 (34)	Laughing/screaming spells	70 (63)	42 (37)
			Reduced nociception	80 (71)	32 (29)
			Intense eye contact	74 (66)	38 (34)
Total	653		Total	112	

* Values for foot length were available for 642 of 653 (98%) classic RTT participants.