

## Newly Revised Criteria for Rett Syndrome

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Rett syndrome (RTT) is defined by unique clinical features, notably regression of hand and spoken language skills, difficulty walking, and the development of specific repetitive hand skills. With the discovery in 1999 of mutations in *Methyl-CpG-binding protein 2* (*MECP2*) in some individuals with RTT, there has been increasing evidence that the majority of those with the disease have mutations in this gene. However, even with the best diagnostic testing, 5% of people who have clearly-defined Rett syndrome do not have mutations in *MECP2*. Additionally, people have been identified who have *MECP2* mutations, but do not have the distinctive clinical features found in Rett syndrome.

Despite this, there has been ongoing confusion about the relationship of a *MECP2* mutation to Rett syndrome. In my clinic, I often see people who, despite clearly having all the clinical features of RTT, have been told by a physician that they do not have Rett syndrome because they do not have a mutation in *MECP2*. Additionally, I also see individuals who do not have the clinical features of RTT, but have been informed that they have Rett syndrome simply because they have a mutation in *MECP2*.

In an effort to clarify this, the [RettSearch Clinical Research Consortium](#) undertook a project to revise the clinical criteria for Rett syndrome and to clarify the relationship to genetic mutations. RettSearch is composed of 51 RTT experts from 13 different countries and is funded by IRSF. The Consortium's mission has been to promote the development of new therapeutic approaches for Rett syndrome by collecting information and pursuing research in areas of relevance to clinical trials in RTT. The revised criteria developed by RettSearch was published in December 2010 in the [Annals of Neurology](#), and information regarding it can be found on [here](#). We tested this new criteria and found that essentially all people who previously had a diagnosis of classic Rett syndrome continue to have the same diagnosis. In general, the revised criteria provides an easier to follow set of criteria for making the diagnosis of Rett syndrome, which we hope will clarify issues regarding the diagnosis.

The previous clinical criteria was developed in 2001 by a group of experts in Rett syndrome. Despite best efforts to develop a clear set of criteria, those criteria led to some degree of confusion amongst doctors. One of the major goals we had in developing new criteria was to make them simple and easy to apply. For the diagnosis of typical, or classic Rett syndrome, there must be a period of regression followed by recovery or stabilization (**See table below**). Additionally, people must have all four of the main criteria, and none of the two exclusion criteria. Specific regression includes loss of hand skills and spoken language. Additionally there is the development of specific problems walking (gait) and the development of specific repetitive hand movements (stereotypies). For this diagnosis, we exclude individuals who have markedly abnormal development in the first six months of life, or those with other brain deficiencies that might cause neurological problems.

One thing different between these new criteria and the old criteria is that in the new criteria there is no mention of small head size. This is because we have found that many people with Rett syndrome have a normal head size. However, because a small head is one reason people with RTT are identified by physicians, we included a statement at the beginning of the criteria mentioning that this feature should raise concern for the diagnosis of the disease.

We also developed revised criteria for atypical, or variant, Rett syndrome. Again to keep this new criteria simple and user friendly, we made it as similar as possible to the criteria for typical RTT. Because regression is a key defining feature of any form of the disease, it is required for atypical RTT. Additionally, to meet the criteria for atypical Rett syndrome, a person must have two of the

four main criteria (**see table below**). Furthermore, a person must have five of the eleven supportive criteria.

The publication emphasizes that Rett syndrome remains a clinical diagnosis and that a mutation in *MECP2* is not required for the diagnosis. Furthermore, a mutation in *MECP2* does not make the diagnosis. The paper also makes recommendations regarding nomenclature and abbreviations, including emphasizing that the correct abbreviation for Rett syndrome is “RTT.”

In a companion paper led by Dr. Alan Percy, the newly revised criteria was validated using information generated by the Rett Syndrome Natural History Study. This work determined that the vast majority of people with the diagnosis of typical Rett syndrome using the previous criteria, continued to be diagnosed with typical RTT using the newly revised criteria. A similar correlation was found for those with atypical Rett syndrome. Thus, the new criteria was shown to be valid and consistent in categorizing individuals with Rett syndrome.

We hope that this revised criteria will be widely adopted and that they will dispel some of the confusion that exists in the field. Furthermore, we feel it will be critical for this criteria to be uniformly applied and reported for future clinical scientific studies.

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**Table 1.** Revised Diagnostic Criteria for Rett Syndrome (RTT) 2010.**Requirements****Consider diagnosis when postnatal deceleration of head growth observed.*****Required for typical or classic RTT***

1. A period of regression followed by recovery or stabilization <sup>a</sup>
2. All main criteria and all exclusion criteria
3. Supportive criteria are not required, although often present in typical RTT

***Required for atypical or variant RTT***

1. A period of regression followed by recovery or stabilization <sup>a</sup>
2. At least 2 of the 4 main criteria
3. 5 out of 11 supportive criteria

**Criteria**

<b>Main criteria</b>	<ol style="list-style-type: none"> <li>1. Partial or complete loss of acquired purposeful hand skills</li> <li>2. Partial or complete loss of acquired spoken language <sup>b</sup></li> <li>3. Gait abnormalities: Impaired (dyspraxic) or absence of ability</li> <li>4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms</li> </ol>	
<b>Exclusion criteria for typical RTT</b>	<ol style="list-style-type: none"> <li>1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems <sup>c</sup></li> <li>2. Grossly abnormal psychomotor development in first 6 months of life <sup>d</sup></li> </ol>	
<b>Supportive criteria for atypical RTT <sup>e</sup></b>	<ol style="list-style-type: none"> <li>1. Breathing disturbances when awake</li> <li>2. Bruxism when awake</li> <li>3. Impaired sleep pattern</li> <li>4. Abnormal muscle tone</li> <li>5. Peripheral vasomotor disturbances</li> <li>6. Scoliosis/kyphosis</li> </ol>	<ol style="list-style-type: none"> <li>7. Growth retardation</li> <li>8. Small cold hands and feet</li> <li>9. Inappropriate laughing/screaming spells</li> <li>10. Diminished response to pain</li> <li>11. Intense eye communication—"eye pointing"</li> </ol>

<sup>a</sup> Because MECP2 mutations are now identified in some individuals prior to any clear evidence of regression, the diagnosis of "possible" RTT should be given to those individuals under 3 years old who have not lost any skills but otherwise have clinical features suggestive of RTT. These individuals should be reassessed every 6-12 months for evidence of regression. If regression manifests, the diagnosis should then be changed to definite RTT. However, if the child does not show any evidence of regression by 5 years, the diagnosis of RTT should be questioned. <sup>b</sup> Loss of acquired language is based on best acquired spoken language skill, not strictly on the acquisition of distinct words or higher language skills. Thus, an individual who had learned to babble but then loses this ability is considered to have a loss of acquired language. <sup>c</sup> There should be clear evidence (neurological or ophthalmological examination and MRI/CT) that the presumed insult directly resulted in neurological dysfunction. <sup>d</sup> Grossly abnormal to the point that normal milestones (acquiring head control, swallowing, developing social smile) are not met. Mild generalized hypotonia or other previously reported subtle developmental alterations during the first 6 months of life is common in RTT and do not constitute an exclusionary criterion. <sup>e</sup> If an individual has or ever had a clinical feature listed it is counted as a supportive criterion. Many of these features have an age dependency, manifesting and becoming more predominant at certain ages. Therefore, the diagnosis of atypical RTT may be easier for older individuals than for younger. In the case of a younger individual (under 5 years old) who has a period of regression and >2 main criteria but does not fulfill the requirement of 5/11 supportive criteria, the diagnosis of "probably atypical RTT" may be given. Individuals who fall into this category should be reassured as they age and the diagnosis revised according.

Adapted from Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, Leonard H, Bailey MES, Schanen NC, Zappella M, Renieri A, Huppke P, Percy AK, for the RettSearch Consortium. 2010. Rett Syndrome: Revised Diagnostic Criteria and Nomenclature. Ann Neurol 68:944-950. Courtesy of Wiley-Blackwell Publishing.