Revised diagnostic criteria for Rett syndrome (RTT), typical and variant forms

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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[1]
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[1]
2. At least 2 out of the 4 main criteria
3. 5 out of 11 supportive criteria

Main criteria

1. Partial or complete loss of acquired purposeful hand skills
2. Partial or complete loss of acquired spoken language[2]
3. Gait abnormalities: impaired (dyspraxic) or absence of ability
4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms

Exclusion criteria for typical RTT

1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems[3]
2. Grossly abnormal psychomotor development in first 6 months of life[4]

Supportive criteria for atypical RTT[5]

1. Breathing disturbances when awake
2. Bruxism when awake
3. Impaired sleep pattern
4. Abnormal muscle tone
5. Peripheral vasomotor disturbances
6. Scoliosis/kyphosis
7. Growth retardation
8. Small cold hands and feet
9. Inappropriate laughing/screaming spells
10. Diminished response to pain
11. Intense eye communication - “eye pointing”

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[1]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.
[2]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.

[3]There should be clear evidence (neurological or ophthalmological examination and MRI/CT) that the presumed insult directly resulted in neurological dysfunction.

[4]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 six months of life is common in RTT and do not constitute an exclusionary criterion.

[5]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 reassessed as they age and the diagnosis revised accordingly.

The clinical features and the genetic loci associated with **the specific variant forms of atypical RTT (Zapella, Hanefeld and Rolando variants)** are described in Figure 1 of the original article, that can be accessed in PMC: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058521/.