RETT SYNDROME: AN UPDATE

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Described in 1966 by Andreas Rett


1999 – mutations in MECP2 gene (Xq28) reported

1 in 10,000 females

Rett variants

Diagnostic criteria (revised)
RETT SYNDROME

- Developmental disorder of the central nervous system with a highly characteristic time course and evolution
- Almost exclusively affects girls
- X-linked dominant disorder
- Is a clinical diagnosis!

Typical Rett Syndrome: clinical features & criteria
Variant forms of Rett Syndrome
Management
TYPICAL RETT SYNDROME

STAGE I: Early stagnation

Age: 6 to 18 months
Duration: months

Slight delay in development, tonus
Reduced interest in toys
“Good and calm baby”

Bottom shuffler
TYPICAL RETT SYNDROME

STAGE II: Rapid regression

Age: 1 to 4 years
Duration: weeks to months (sometimes acute onset)

Purposeful hand skills and spoken language are lost. Stereotyped hand movements begin to emerge, hand-to-mouth movements, midline hand wringing or hand washing. Autistic-like behavior with loss of social interaction and communication. General irritability and sleep irregularity. Slowing of head growth. Breathing irregularities and epileptic discharges may already occur.
**TYPICAL RETT SYNDROME**

**STAGE III: Stationary phase**

Age: pre-school to school  
Duration: years

Apraxia, motor problems (ataxia) and seizures are more prominent. Improvement in behavior with less irritability and less autistic features. More interest, alertness, attention span and communication skills improve. Many girls with RS remain in Stage III for most of their lifetime.
STAGE IV: Late motor deterioration stage

Age: after stage III
Duration: up to decades

Reduced mobility, loss of ambulation:
- stage IV A (previously ambulant)
- stage IV B (never ambulant)

Secondary deformations (scoliosis, low muscle tone, foot deformities)

No decline in cognition, communication or hand skills
Figure 1  Staging system for classical Rett syndrome. Derived from Hagberg and Witt-Engerstrom.\textsuperscript{10}
Think Rett!

- Listen to the parents
- All girls with autistic-like behaviour
- All girls with history of developmental stagnation or loss of skills around one year of age
- Boys with neonatal encephalopathy
Typical characteristics

Deformities

Autistic-like behavior, communication

Autonomic dysfunction

Epilepsy

Growth
Deformities

<< low muscle tone, dystonia, muscle wasting

Scoliosis

C or S deformity
Keep them mobile
10 to 30 % surgical correction
Multidisciplinary approach

Foot deformities

Equinus position
Tiptoeing
Claw toes
**Hands**

Young children: intense hand wringing

Adults: Repetitive hand movements may decrease, almost no development of contractures
Communication

Loss of speech, lack of interest, stereotypic movements might suggest autism,
But Rett syndrome ≠ autism!
Communication

Most girls with RS show an intense desire to communicate through their eyes, gestures and body language. This should be stimulated. There is often a delay in response to stimuli, they need sufficient time to react. Very much interested in people. Receptive language is better than expected.
Autonomic dysfunction

- Delayed reaction to pain, high pain threshold
- Disturbed sleeping pattern
- **Breathing dysfunction when awake**
- Non-epileptic “seizures”
- Abnormal Spontaneous Brainstem Activation – ASBA – Abnormal Sensitivity for Brainstem Activity “Brainstem epilepsy” “Brainstem storm”
- Gastro-oesophageal reflux, obstipation, air swallowing
- Abnormal sweating
- Cold extremities
Epilepsy

- Seizures are reported in a high number of girls, but the incidence of true clinical seizures is felt to be overestimated.
- Video-EEG monitoring may be necessary to determine appropriate treatment.
- Drugs to control seizures are very effective in most cases.
Growth and feeding problems

- Growth usually slows, with most girls and women quite small for their age.
- Head circumference often -2 to -3 SD
- No hormonal problem
- Studies have shown that despite what appears to be voracious appetite, many girls meet the criteria for moderate to severe malnutrition.
- Swallowing difficulties, inadequate intake of food, energy expenditure imbalance, or inadequate utilization of nutrients.
- Supplemental feeding (oral feeding with high-calorie/high-fat diet, NG tube or gastrostomy button) has been shown to bring about significant weight and height gains, which may improve alertness and interaction.

**Required for typical or classic RTT**
1. A period of regression followed by recovery or stabilization
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
2. At least 2 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
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
2. Grossly abnormal psychomotor development in first 6 months of life

**Supportive criteria for atypical RTT**
1. Breathing disturbances when awake
2. Bruxism when awake
3. Impaired sleep pattern
4. Abnormal muscle tone
5. Peripheral vasomotor disturbances
6. Scoliosis/kypnosis
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”
## MOLECULAR DIAGNOSIS OF TYPICAL RETT SYNDROME

<table>
<thead>
<tr>
<th>MECP2</th>
<th>Test Method</th>
<th>Mutations Detected</th>
<th>Mutation Detection Frequency by Test Method and Phenotype</th>
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<tr>
<td></td>
<td>Sequence analysis/</td>
<td>Sequence variants</td>
<td>Classic Rett Syndrome</td>
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<tr>
<td></td>
<td>mutation scanning</td>
<td></td>
<td>80%</td>
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<tr>
<td></td>
<td>Deletion/ duplication analysis</td>
<td>Partial- and whole-gene deletions</td>
<td>8%</td>
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</tbody>
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The image below illustrates the genetic structure of MECP2, showing various exons and the positions of different mutations, including splice site changes and frameshift mutations, which are crucial for understanding the molecular basis of Rett Syndrome.

The table above provides a summary of the mutation detection frequency for both typical and atypical Rett Syndrome, with the most common mutations identified through MECP2 sequence analysis and deletion/duplication analysis.

Legend:
- MBD: Methyl-binding domain
- TRD: Transcriptional repression domain
- MBS: MBD site
- WW: WW domain
VARIANT FORMS OF RETT SYNDROME

- Preserved Speech Variant (Zappella Variant)
- Early Seizure Variant (Hanefeld Variant)
- Congenital Variant (Rolando Variant)
Preserved Speech Variant (Zappella Variant)

- regression at 1-3 yrs
- better retained hand use
- recovery of language after regression (single words – phrases)
- milder intellectual disability
- often autistic behaviour
- other Rett features are less common (normal head size, growth)
VARIANT FORMS OF RETT SYNDROME

Early Seizure Variant (Hanefeld Variant)

- early onset of seizures (< 5 months of age)
- infantile spasms
- first seizures, than regression
- other Rett features are less common (normal head size)
CDKL5 gene

cyclin-dependent kinase-like 5
also X-linked dominant disorder
Congenital Variant (Rolando Variant)

- Severe psychomotor delay from beginning (no speech; no ambulation)
- Severe postnatal microcephaly (< 4 months)
- Lack of typical intense eye contact
- Rett autonomic abnormalities present
- Specific movement abnormalities (jerks; tongue)
**FOXG1 gene**

Transcription factor
Chromosome 14

**Deletions of the whole FOXG1 gene**

**Premature stop codons**

- p.Trp255X
- p.Trp308X
- p.Ser323fsX325
- p.Tyr400X
Variant forms of RTT
- Meets criteria for atypical RTT
- Assess for presence of clinical features of defined variant forms

**Preserved Speech Variant (Zappella Variant)**

**Clinical features**
- Regression at 1-3 yrs, prolonged plateau phase
- Milder reduction of hand skills
  - better retained hand use
- Recovery of language after regression
  - Mean age of recovery is 5 yrs
  - Single words or phrases
- Milder intellectual disability (IQ up to 50)
- Autistic behaviors common
- Decreased frequency of typical RTT features
  - Rare epilepsy
  - Rare autonomic dysfunction
  - Milder scoliosis and kyphosis
  - Normal head circumference
  - Normal height and weight in most

**Molecular Genetics**
Mutations in MECP2 found in the majority of cases

**Early Seizure Variant (Hanefeld Variant)**

**Clinical features**
- Early onset of seizures
  - Before 5 months of life
  - Infantile spasms
  - Refractory myoclonic epilepsy
  - Seizure onset before regression
- Decreased frequency of typical RTT features

**Molecular Genetics**
Mutations in MECP2 rarely found
Analysis for mutations in CDKL5 should be performed

**Congenital Variant (Rolando Variant)**

**Clinical features**
- Grossly abnormal initial development
  - Severe psychomotor delay
  - Inability to walk
- Severe postnatal microcephaly before 4 months
- Regression in first 5 months
- Lack of typical intense "RTT" eye gaze
- Typical RTT autonomic abnormalities present
  - Small cold hands and feet
  - Peripheral vasomotor disturbances
  - Breathing abnormalities while awake
- Specific movement abnormalities
  - Tongue stereotypies
  - Jerky movements of the limbs

**Molecular Genetics**
Mutations in MECP2 rarely found
Analysis for mutations in FOXG1 should be performed

**FIGURE 1: Specific variant forms of RTT flow diagram.**
Rett syndrome in boys?

Rett Syndrome and Beyond: Recurrent Spontaneous and Familial MECP2 Mutations at CpG Hotspots

Mimi Wan,1 Stephen Sung Jae Lee,2 Xianyu Zhang,2 Isa Houwink-Manville,3 Hae-Ri Song,3 Ruthie E. Amir,9 Sarojini Budden,4 Sakkubai Naidu,5 Jose Luiz P. Pereira,6,7 Ivan F. M. Lo,8 Huda Y. Zoghbi,9,10,11 N. Carolyn Schanen,3 and Uta Francke1,2

MECP2 mutation in male patients with non-specific X-linked mental retardation

Alfredo Orricoa,1, Ching-Wan Lamb,1, Lucia Gallia, Maria Teresa Dottic, Giuseppe Hayekd, Sui-Fan Tongb, Priscilla M.K. Poona, Michele Zappella, Antonio Federico, Vincenzo Sorrentinoa,c,f,*

A Mutation in the Rett Syndrome Gene, MECP2, Causes X-Linked Mental Retardation and Progressive Spasticity in Males

Ilaria Meloni,1 Mirella Bruttini,1 Ilaria Longo,1 Francesca Mari,1 Flavio Rizzolio,3 Patrizia D'Adamo,3 Koenraad Denvriendt,2 Jean-Pierre Fryns,2 Daniela Toniolo,3 and Alessandra Renieri1
Rett syndrome in boys?

- Mutations that lead to RTT in girls: severe phenotype in boys

- 47,XXY males – mosaicism: RTT phenotype

- Mutations not present in RTT girls: milder phenotype in boys
Rett syndrome: management

- Intervention programmes
- Nutrition
- Sleep problems
- Epilepsy
- Breathing dysfunction
- Scoliosis
- Osteoporosis