Rett syndrome

- A neurodevelopmental disorder seen almost exclusively in females, and found in a variety of racial and ethnic groups worldwide.
- The prevalence rate: 1:10,000 to 1:23,000 live female births.
- An early period of apparently normal or near normal development until 6–18 months of life.
- Followed by a period of temporary stagnation or regression.
- The child loses communication skills and purposeful use of the hands followed by stereotyped hand movements, gait disturbances, and slowing of the rate of head growth.

Prevalence of Rett syndrome

<table>
<thead>
<tr>
<th>Study (publication year)</th>
<th>Prevalence year</th>
<th>Location</th>
<th>Number of cases</th>
<th>Classification</th>
<th>Prevalence per 10,000 females</th>
<th>Prevalence per 10,000 live female births</th>
<th>Age range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hugging (1992)</td>
<td>1992</td>
<td>Sweden</td>
<td>10</td>
<td>Classical only</td>
<td>0.01</td>
<td>1.28</td>
<td>4–17</td>
</tr>
<tr>
<td>Ketel and Steenweg (1993)</td>
<td>1992</td>
<td>The Netherlands</td>
<td>10</td>
<td>Classical only</td>
<td>0.01</td>
<td>1.28</td>
<td>4–17</td>
</tr>
<tr>
<td>Ketel and Steenweg (1994)</td>
<td>1992</td>
<td>Sweden</td>
<td>13</td>
<td>Classical only</td>
<td>0.01</td>
<td>1.28</td>
<td>4–17</td>
</tr>
<tr>
<td>Ketel and Steenweg (1995)</td>
<td>1992</td>
<td>The Netherlands</td>
<td>22</td>
<td>Classical only</td>
<td>0.01</td>
<td>1.28</td>
<td>4–17</td>
</tr>
<tr>
<td>Boher and Kurz (1997)</td>
<td>1997</td>
<td>Switzerland</td>
<td>27</td>
<td>Classical only</td>
<td>0.01</td>
<td>1.28</td>
<td>4–17</td>
</tr>
<tr>
<td>Ong se et al. (1998)</td>
<td>1998</td>
<td>Japan</td>
<td>89</td>
<td>Classical and expressed</td>
<td>0.01</td>
<td>1.28</td>
<td>1–17</td>
</tr>
<tr>
<td>Boed et al. (2001)</td>
<td>2001</td>
<td>Spain</td>
<td>55</td>
<td>Classical only</td>
<td>0.01</td>
<td>1.28</td>
<td>4–17</td>
</tr>
<tr>
<td>Karmens et al. (1989)</td>
<td>1989</td>
<td>Texas, USA</td>
<td>84</td>
<td>Classical and expressed</td>
<td>0.01</td>
<td>1.28</td>
<td>5–10</td>
</tr>
<tr>
<td>Carriers et al. (1993)</td>
<td>1993</td>
<td>Eminence</td>
<td>6</td>
<td>Classical only</td>
<td>0.01</td>
<td>1.28</td>
<td>5–10</td>
</tr>
<tr>
<td>Lavender et al. (1993)</td>
<td>1993</td>
<td>Australia</td>
<td>67</td>
<td>Classical and expressed</td>
<td>0.01</td>
<td>1.28</td>
<td>5–10</td>
</tr>
<tr>
<td>Lass et al. (1993)</td>
<td>1993</td>
<td>Norway</td>
<td>12</td>
<td>Classical and expressed</td>
<td>0.01</td>
<td>1.28</td>
<td>5–10</td>
</tr>
<tr>
<td>Hugging and Hugging (1997)</td>
<td>1997</td>
<td>Sweden</td>
<td>84</td>
<td>Classical and expressed</td>
<td>0.01</td>
<td>1.28</td>
<td>5–10</td>
</tr>
<tr>
<td>Present study</td>
<td>2004</td>
<td>Australia</td>
<td>643</td>
<td>Classical and expressed</td>
<td>0.01</td>
<td>1.28</td>
<td>5–10</td>
</tr>
</tbody>
</table>

Clinical Staging of Rett Syndrome

- Stage I: Early Onset
  - Age: 6 months to 1½ years
  - Duration: months
- Stage II: Rapid Destructive
  - Age: 6 to 4 years
  - Duration: weeks to months
- Stage III: Plateau
  - Age: Pre-school to school years (5–10 years)
  - Duration: years
- Stage IV: Late Motor Deterioration
  - Stage IV A (Previously ambulant)
  - Stage IV B (Never ambulant)
  - Age: When stage III ceases, 5½–25½ years
  - Duration: up to decades

Main criteria for Rett

- Partial or complete loss of acquired purposeful hand skills.
- Partial or complete loss of acquired spoken language.
- Gait abnormalities: Impaired (dyspraxic) or absence of ability.
- Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms.
Diagnosis of Rett and variants

• Required for typical or classic RTT
  – A period of regression followed by recovery or stabilization
  – All main criteria and all exclusion criteria
  – Supportive criteria are not required, although often present in typical RTT

• Required for atypical or variant RTT
  – A period of regression followed by recovery or stabilization
  – At least 2 of the 4 main criteria
  – 5 out of 11 supportive criteria

Supportive criteria for atypical RTT

• Breathing disturbances when awake
• Bruxism when awake
• Impaired sleep pattern
• Abnormal muscle tone
• Peripheral vasomotor disturbances
• Scoliosis/kyphosis
• Growth retardation
• Small cold hands and feet
• Inappropriate laughing/screaming spells
• Diminished response to pain
• Intense eye communication - “eye pointing”

臨床表徵

• 第一期：早期
  – 約在六至十八個月發作，持續約一個月到一年
  – 病童的症狀不明顯，輕微的發展遲緩容易被父母及醫生忽略。
  – 坐立或爬行的大運動發展遲緩。
  – 患童喪失一些視覺接觸的能力，或對玩具失去興趣。
  – 父母若回溯嬰兒早期時，會感覺嬰兒很安靜、乖巧，
    也有母親覺得病嬰特別喜歡搓手，另外也注意到頭圍
    成長趨緩。

臨床表徵

• 第二期：發展明顯遲緩及退化期
  – 在一到四歲時發作，持續數週到幾個月不等。
  – 無法運用手部做有意的目的的任務（如抓東西、拿取物品等），以及
    可能喪失繫鞋能力。
  – 有類似自閉症的症狀。
  – 典型刻板的手部動作出現（如搓手、拍手、拍某物體），不自主
    反覆的將手移動到嘴巴附近，或伴隨刻板的手部動作。
  – 清醒時，可能發生呼吸障礙異常問題，像間歇性的暫停呼吸或換
    氣過度。
  – 不正常的睡眠週期，或發怒。
  – 因步伐不稳會影響之後的動作發展（跑、跳等）。
  – 頭圍過小常在這個時期被發現。

臨床表徵

• 第三期：幼稚園至國小年齡之穩定期
  – 在兩歲到十歲間發作
  – 發作後可能持續至一年
  – 病童特徵為失用症，動作發展問題及癲癇。
  – 易怒、哭泣、類自閉症行為獲得改善。
  – 對周遭環境感興趣，溝通技能、注意力廣度有所改善，對環境的
    改變較為敏感。
  – 部分雷特氏症的女孩子症狀停留在此階段，並停止惡化下去。
  – 兩期期可維持相當長的時間。

臨床表徵

• 第四期：運動退化之晚期
  – 5～25歲
  – 活動力降低。
  – 主要特徵為肌肉無力、身體僵硬，易抽搐、肌肉張力異常（四肢
    或顱幹張力過大），以及發性感覺。
  – 少可自主行動的患童可能逐漸喪失行走能力，有些因下肢虛弱受
    壑，需坐輪椅。
  – 異常，溝通或手部功能退化情況減緩。
  – 反覆固著性手部動作頻率減低；眼睛凝視能力改善。
  – 異常，語言溝通及手部動作較穩定，溝通他人能力仍能維持，不
    過有些患兒出現脊椎側彎。
Hand stereotypies

- Hand stereotypies in RTT children are localized predominantly in front of and at a close distance to the midline of the chest.
  - In 60%, they were accompanied by mouthing, and hands were joined or close to each other in 70%.
- In autism, the repetitive patterned movements occurred in 75% away from the body with hands apart.
- Unilateral hand stereotypy was 2.5-fold more frequent in RTT than in AD children.
- Hand gaze is never observed in this RTT group, but in 20% of autism children.

Hand stereotypies distinguish Rett syndrome from autism disorder

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RETT syndrome</th>
<th>Autism disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Continuous</td>
<td>Intermittent</td>
</tr>
<tr>
<td>Position</td>
<td>Midline predom.</td>
<td>Varied, more distal</td>
</tr>
<tr>
<td>Object</td>
<td>Does not involve object</td>
<td>Involves objects and their properties</td>
</tr>
<tr>
<td>Visual behavior</td>
<td>No hand gaze</td>
<td>Visual inspection and peripheral fingers flickering</td>
</tr>
</tbody>
</table>

Clinical severity score

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting</td>
<td>Normal situation</td>
<td>Impaired</td>
<td>Lost</td>
<td>Never acquired</td>
</tr>
<tr>
<td>Walking</td>
<td>Impaired</td>
<td>Lost</td>
<td>Never acquired</td>
<td></td>
</tr>
<tr>
<td>Hand use</td>
<td>Reduced</td>
<td>Lost</td>
<td>Never acquired</td>
<td></td>
</tr>
<tr>
<td>Speech</td>
<td>Some words</td>
<td>Lost</td>
<td>Never acquired</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Controlled</td>
<td>Uncontrolled</td>
<td>Status epilepticus</td>
<td></td>
</tr>
<tr>
<td>Spine deformation</td>
<td>Mild</td>
<td>Severe</td>
<td>Operated</td>
<td></td>
</tr>
</tbody>
</table>
**Epilepsy**

- Age of onset of epilepsy was 4.68±3.5 years (range of 3 months to 21 years of age).
- Epilepsy appeared slightly later than the other core symptoms of Rett syndrome.
- Epilepsy onset was most prevalent between 3 and 5 years of age.
- It appeared before the age of 8 years in >80% of the patients.
- hand stereotypies (2.43±1.67)
- speech regression (2.09±1.1)
- loss of hand use (2.28±1.4)

**Prevalence of epilepsy**

-约只有三分之一家长所描述的抽搐行为是真的癫痫.
-洗手、捻手、搓手等刻板动作
- 呼吸中止
-不规律的呼吸包括过度换气
- 眼睛的异常动作 (oculogyric movements, blinking episodes)
- Orofacial dyskinesias
- 其他动作障碍(tremor, dystonia, jerking, spasticity, and episodic atonia)
Longitudinal bone mineral content and density in Rett syndrome and their contributing factors

Bone outcome exam annual change in z-score and conditions by mobility level

- Walk
- Walk aided
- Unable to walk

- The bone mineral content (BMC), bone mineral density, bone area and lean tissue mass z-scores for all outcome measures declined, with the total body BMC showing significant decreases.
- Weight, height and muscle mass appear to have impacts on bone formation.
- We recommend that nutritional intake should be closely monitored and a physical activity plan developed to optimise bone health.
- Pubertal progression should also be assessed in conjunction with serial densitometry assessments to track bone mass and density changes over time.

Spine operation for scoliosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Complications</th>
<th>Inpatient stay (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Superficial wound infection, persistent diarrhoea</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Haemothorax, extended intubation, superficial wound infection, UTI sepsis, aspiration pneumonia</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Deepwound infection requiring washout and prolonged antibiotics</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>Severe hypokalaemia</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>Pneumothorax, hospital-acquired pneumonia</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>Superficial wound infection</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>UTI, aspiration pneumonia</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>Hospital-acquired pneumonia</td>
<td>20</td>
</tr>
</tbody>
</table>

Bone marrow density in Rett

- Improved when getting older

<table>
<thead>
<tr>
<th>Prevalence of GI problems in Rett</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diarrhoea</td>
</tr>
<tr>
<td>2. Vomiting</td>
</tr>
<tr>
<td>3. Abdominal pain</td>
</tr>
<tr>
<td>4. Anorexia</td>
</tr>
<tr>
<td>5. Constipation</td>
</tr>
<tr>
<td>6. Flatulent stools</td>
</tr>
<tr>
<td>7. Abdominal distention</td>
</tr>
<tr>
<td>8. Reflux</td>
</tr>
<tr>
<td>9. Blood in stool</td>
</tr>
<tr>
<td>10. Haematochezia</td>
</tr>
</tbody>
</table>

Eur Spine J. 2014


CV problems in Rett syndrome

Table 1  Summary of studies investigating QTC-interval prolongation in Rett syndrome

<table>
<thead>
<tr>
<th>First author</th>
<th>Total</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>Pw with QTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takahashi*</td>
<td>430</td>
<td>430</td>
<td>440</td>
<td>440</td>
<td>440</td>
<td>0.20</td>
</tr>
<tr>
<td>Johnson**</td>
<td>461</td>
<td>461</td>
<td>461</td>
<td>461</td>
<td>461</td>
<td>0.20</td>
</tr>
<tr>
<td>Gardner***</td>
<td>441</td>
<td>441</td>
<td>441</td>
<td>441</td>
<td>441</td>
<td>0.20</td>
</tr>
<tr>
<td>Elloy**</td>
<td>438</td>
<td>438</td>
<td>438</td>
<td>438</td>
<td>438</td>
<td>0.20</td>
</tr>
<tr>
<td>Gardner***</td>
<td>440</td>
<td>440</td>
<td>440</td>
<td>440</td>
<td>440</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Other health problems in Rett

- Nutritional assessment
- Clinical severity score
- EKG every year
- Abdominal echo every year
- BMD assessment every year
- Spine x-ray for scoliosis every year
- EEG every year if there is seizure
The Role of MECP2 in Rett Syndrome

- Amir and others (1999)
- 80% of patients with RS have mutations in MECP2
- Two forms of MECP2: 2A and 2B
- X-linked

**Mutation Frequency in Rett Syndrome**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

**Rett Syndrome Phenotypes With MECP2 Mutations**

- **Females**
  - Rett Syndrome
  - Preserved Speech Variant
  - Delayed Onset Variant
  - Mild Learning Disability
  - Angelman Syndrome
  - Normal Carriers

- **Males**
  - Fatal Encephalopathy
  - Rett/Klinefelter Syndrome
  - Angelman Syndrome
  - X-Linked Mental Retardation/Progressive Spasticity
  - Somatic Mosaicism/Neurodevelopmental Delay

Rett syndrome and its variants

- **RTT variants**
  - Zappella variant (preserved speech variant), characterized by the recovery of some degree of speech
  - the congenital variant (recognized since birth and often caused by FOXG1 mutation)
  - the “early onset seizure variant” or Hanefeld variant.
- **MECP2**: Methyl-CpG-binding protein 2 (MeCP2)
- **CDKL5**: Cyclin-dependent kinase-like 5
- **FOXG1**: forkhead box G1
- **NTNG1**: Netrin-G1 precursor
Early-onset seizure variant of Rett

- CDKL5 is a putative serine/threonine kinase of unknown function.
- The clinical features are mostly of atypical RTT, myoclonic encephalopathy, or epilepsy and mental retardation or autism.
  - infantile spasms
  - myoclonic jerks
  - generalized tonic-clonic seizures
  - tonic seizures
  - less common: absences and complex partial seizures.

- Most CDKL5 patients are in polytherapy, unlike classic RTT where seizures are usually treated in monotherapy with good results.
- Seizures are not always intractable and cognitive levels are highly variable.
- Eye gaze and repetitive head movements were common in addition to the typical RTT signs.
- A possible relationship with the Forceful and Apneustic cardiorespiratory phenotype.

In cases of negativity in both MECP2 and CDKL5, a further investigation of FOXG1 gene could be useful.
- Epilepsy may begin even earlier in the congenital variant.

The core FOXG1 syndrome phenotype: postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis.

**Table: Rett Syndrome vs. MECP2:**

<table>
<thead>
<tr>
<th>Rett Syndrome</th>
<th>MECP2 Mutation</th>
<th>CDKL5 Mutation</th>
<th>FOXG1 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development</td>
<td>Regression at 1-3 yrs.</td>
<td>Sudden early delay</td>
<td>Sudden early delay</td>
</tr>
<tr>
<td>Social interaction</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Facial appearance</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td>Speech</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td>Abnormal movements</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td>Motor impairment</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td>Other features</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
</tr>
</tbody>
</table>

**Figure: Early-onset seizure variant of Rett**

- Early-onset seizure variant of Rett
- Congenital Rett Variant

**Diagram: Variants of Rett**

- Presumed Sporadic Variant (Sporadic Variant)
  - Clinical features: Early onset of seizures, infantile spasms, hypotonia, nystagmus, hypotonia
  - Molecular Genetics: Mutations in MECP2

- Early Seizure Variant (Rett-variant)
  - Clinical features: Early onset of seizures, infantile spasms, hypotonia, nystagmus, hypotonia
  - Molecular Genetics: Mutations in MECP2

- Congenital Variant (Rett-variant)
  - Clinical features: Usually normal fetal development, survival beyond 4 months
  - Molecular Genetics: Mutations in MECP2

**Diagram: Congenital Rett Variant**

- In cases of negativity in both MECP2 and CDKL5, a further investigation of FOXG1 gene could be useful.
- Epilepsy may begin even earlier in the congenital variant.

**Figure: The core FOXG1 syndrome phenotype**

- Seizures are not always intractable and cognitive levels are highly variable.
- Eye gaze and repetitive head movements were common in addition to the typical RTT signs.
- A possible relationship with the Forceful and Apneustic cardiorespiratory phenotype.

**Figure: Early-onset seizure variant of Rett**

- Infantile spasms
- Myoclonic jerks
- Generalized tonic-clonic seizures
- Tonic seizures
- Less common: absences and complex partial seizures.

**Table: Rett Syndrome vs. MECP2 vs. CDKL5 vs. FOXG1**

<table>
<thead>
<tr>
<th>Rett Syndrome</th>
<th>MECP2 Mutation</th>
<th>CDKL5 Mutation</th>
<th>FOXG1 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development</td>
<td>Regression at 1-3 yrs.</td>
<td>Sudden early delay</td>
<td>Sudden early delay</td>
</tr>
<tr>
<td>Social interaction</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Facial appearance</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td>Speech</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td>Abnormal movements</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td>Motor impairment</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td>Other features</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
<td>Absent or reduced</td>
</tr>
</tbody>
</table>

**Figure: Early-onset seizure variant of Rett**

- CDKL5 is a putative serine/threonine kinase of unknown function.
- The clinical features are mostly of atypical RTT, myoclonic encephalopathy, or epilepsy and mental retardation or autism.
  - infantile spasms
  - myoclonic jerks
  - generalized tonic-clonic seizures
  - tonic seizures
  - less common: absences and complex partial seizures.
De novo \textit{SHANK3} mutation causes Rett syndrome-like phenotype in a female patient

- **Brief history**
  - Motor milestones were delayed.
  - Both her speech development and nonverbal communication were also delayed.
  - She began to regress in verbal communication, gross and fine motor skills after 4 years and 6 months old, and became unable to walk after 5 years old.

- **Whole Exome Sequencing**
- \textit{SHANK3} (SH3 and multiple ankyrin repeat domain 3) mutations were found in developmental delay, severe delay or absence of expressive speech, autistic behaviors, schizophrenia, and intellectual disability.

In MECP2-positive cases, survival at 25 years was 87.2\% (95\% CI 76.1-93.3), compared with 46.5\% (95\% CI 17.3-83.0) in those in whom no mutation was detected.
### Treatment

- **Autonomic nervous system abnormalities**:
  - Respiratory and cardiac abnormalities
  - Increased GABA synthesis through GABA reuptake inhibitors (fluoxetine, buspirone)
  - Serotonin reuptake inhibitors (desipramine)

- **Rigid behavior**:
  - Increased GABA synthesis (vigabatrin)

### BDNF's Role

#### Reducing BDNF gene expression

- Morphological and synaptic phenotypes observed in the brains of RTT patients:
  - Reduced brain weight
  - Decreased dendritic arbors and impaired hippocampal long-term potentiation
  - Irregular breathing and impaired locomotion similar to RTT mice

### Enhancing BDNF/TrkB Signaling in RTT

- **Ampakines**:
  - Promote the activity of glutamatergic AMPA receptors
  - Enhance BDNF expression
  - Increase BDNF-related functions
  - Repeated administration of ampakines in rats and mice increase BDNF mRNA and protein expression

- **Sphingosine-1-phosphate receptor modulator** (fingolimod): Enhances BDNF/TrkB signaling

- **Glatiramer acetate** (GA, Copolymer 1, Copaxone): Used in multiple sclerosis

- **Environmental enrichment and exercise**: Particularly at early stages of postnatal development

- **Cysteamine**:
  - Increases vesicular trafficking of BDNF
  - Used in the treatment of cystinosis (cystine storage disease)
Targeting the BDNF Receptor, TrkB

- LM22A-4, which functions as a direct and specific partial agonist of TrkB
  - reduces synaptic hyperexcitability in the brainstem respiratory network in brain slice preparations (Kron et al. 2012b).
  - Reverses deficits in TrkB activation in the brainstem (Schmid et al. 2012).
  - Improves respiratory function.
  - LM22A-4 can delay Huntington's disease.

IGF-1

- IGF-1 and its tri-peptide form [(1–3)IGF-1]
  - Crosses the blood–brain barrier.
  - Stimulates neural stem cell proliferation, survival, and synaptogenesis.
  - In a mouse model, IGF-1 improves neuronal function and behavior in Rett syndrome (Kron et al. 2012b).

NNZ-2566

- NNZ-2566 is a synthetic analogue of a naturally occurring neuropeptide derived from IGF-1, a growth factor produced by brain cells.
  - NNZ-2566 is a neuropeptide that reduces neuroinflammation and improves neurological function in Rett syndrome.
  - NNZ-2566 is a Phase II trial in Rett Syndrome.

Dextromethorphan

- Young Rett syndrome patients (≤10 years) show increased brain glutamate receptors, particularly NMDA receptors.
  - Dextromethorphan can improve language and social function in Rett Syndrome.

Other Therapies

- VPA improves neurofunctional recovery in a mouse model of Rett syndrome.
  - VPA improves neurofunctional recovery in Rett mouse brains.
  - Anaplerotic Triheptanoin Diet Enhances Mitochondrial Substrate Use to Remodel the Metabolome and Improve Lifespan, Motor Function, and Sociability in MeCP2-Null Mice.
Absence of MECP2 in RTT causes excessive Sqc1 transcription and accumulation of cholesterol.

- L-carnitine (肉鹼), 可改善粒線體功能
  - 睡眠維持，溝通能力的改善
- 骨髓移植 (2012, 小鼠)
Thank you for your attention

特別感謝