Epidemiology
Clinical variability
& Genotype phenotype relationships

Helen Leonard and Crystal Laurvick
Telethon Institute for Child Health Research

Rett Syndrome:
Diagnosis, Genetics, Epidemiology, Clinical Management
and the Parents Perspective
November 2005
Co-investigators & Contributors

APSU

Co-investigators & Contributors

APSU

AUSSIERETT STUDY PARTNERS

Telethon Institute for Child Health Research, Perth
Helen Leonard
Carol Bower
Nick de Klerk
Sven Silburn
Crystal Laurvick
Oria Mclroy
Carol Philippe
Alison Anderson
Anne Pugh
Le Jian
Jenny Downs

Telethon Institute for Child Health Research, Perth
Helen Leonard
Carol Bower
Nick de Klerk
Sven Silburn
Crystal Laurvick
Oria Mclroy
Carol Philippe
Alison Anderson
Anne Pugh
Le Jian
Jenny Downs

Women's & Children's Hospital Adelaide
Clair Pridmore
Elizabeth Thompson

Women's & Children's Hospital Adelaide
Clair Pridmore
Elizabeth Thompson

Princess Margaret Hospital for Children
Lakshmi Nagarajan

Princess Margaret Hospital for Children
Lakshmi Nagarajan

University of Chicago Children's Hospital
Michael Msall

University of Chicago Children's Hospital
Michael Msall

University of Western Australia
Sonj Hall
Delia Hendrie

The University of Western Australia
Sonj Hall
Delia Hendrie

The Royal Children's Hospital, Melbourne
Sheena Reilly
Gordon Baike
Lyndall Mulready
Ruth Nicholls

The Royal Children's Hospital, Melbourne
Sheena Reilly
Gordon Baike
Lyndall Mulready
Ruth Nicholls

University of Glasgow
Bronwen Burford

University of Glasgow
Bronwen Burford

Royal Perth Hospital
David Ravine
Mark Davis

Royal Perth Hospital
David Ravine
Mark Davis

The Children's Hospital at Westmead, Sydney
John
Christodoulou
Carolyn Ellaway
Belinda Todd

The Children's Hospital at Westmead, Sydney
John
Christodoulou
Carolyn Ellaway
Belinda Todd

Sydney Children's Hospital / Campbeltown Hospital
Helen Woodhead

Sydney Children's Hospital / Campbeltown Hospital
Helen Woodhead

Curtin University of Technology Perth
Sue Fyfe

Curtin University of Technology Perth
Sue Fyfe

Australian Paediatricians

Australian Paediatricians

Rett Syndrome Association of Australia

Rett Syndrome Association of Australia

Australian Families

Australian Families
Overview of today's talk

- Provide some historical background to Australian Rett syndrome research
- Provide a current update on epidemiology of Rett syndrome
- Demonstrate the clinical variability in Rett syndrome
- Provide examples of some research outcomes from the Australian Rett Syndrome Database
• 1985 - Dr Athel Hockey - first diagnosis of Rett syndrome in Western Australia
• 1989 - Rett Syndrome Association of Australia-parent support group- set up by Mr Bill Callaghan
• 1993 - Rett syndrome- one of the first projects to use the APSU -
• 1993-1995 - epidemiology, family health tree study
• 1996 - radiology study, clinical studies
• 2000 onwards - molecular studies
• 2000-calendar study
• 2000, 2002, 2004 - follow-up studies
• 2002 - inaugural Annual Report
• 2003-funding received by NIH and NHMRC for five year longitudinal study
Original aims of the study were:

- to estimate the incidence and prevalence of juvenile Rett syndrome in Australia
- establish a database for future research

Aims of the research today include:

- describing and investigating the variability of severity and its determinants, both genetic and environmental
- providing longitudinal data to identify changes in phenotype over time
- describing patterns of health service usage and morbidity and mortality in Rett syndrome
- investigating the impact of Rett syndrome on family life (resources, time, holiday/respite options)
- comparing the burden for families with Rett syndrome with that of families with Down syndrome
New diagnostic criteria
Baden Baden 11/9/2001

Necessary criteria
1. apparently normal prenatal and perinatal history
2. psychomotor development largely normal through the first six months or may be delayed from birth
3. normal head circumference at birth
4. postnatal deceleration of head growth in the majority
5. loss of achieved purposeful hand skill between ages 1½ - 2½ years
6. stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
7. emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment
8. impaired (dyspraxic) or failing locomotion

Supportive criteria
1. awake disturbances of breathing (hyperventilation, breath-holding, forced expulsion of air or saliva, air swallowing
2. bruxism
3. impaired sleep pattern from early infancy
4. abnormal muscle tone successively associated with muscle wasting and dystonia
5. peripheral vasomotor disturbances
6. scoliosis/kyphosis progressing through childhood
7. growth retardation
8. hypotrophic small and cold feet; small, thin hands

Exclusion criteria
1. organomegaly or other signs of storage disease
2. retinopathy, optic atrophy, or cataract
3. evidence of perinatal or postnatal brain damage
4. existence of identifiable metabolic or other progressive neurological disorder

Revised delineation of variant phenotypes

Inclusion criteria
1. meet at least 3 of 6 main criteria
2. meet at least 5 of 11 supportive criteria

Six main criteria
1. absence or reduction of hand skills
2. reduction or loss of babble speech
3. monotonous pattern to hand stereotypies
4. reduction or loss of communication skills
5. deceleration of head growth from first years of life
6. RS disease profile: a regression stage followed by a recovery of interaction contrasting with slow neuromotor regression

Eleven supportive criteria
1. breathing irregularities
2. bloating/air swallowing
3. teeth grinding, harsh sounding type
4. abnormal locomotion
5. scoliosis/kyphosis
6. lower limb amyotrophy
7. cold, purplish feet, usually growth impaired
8. sleep disturbances including night screaming outbursts
9. laughing/screaming spells
10. diminished response to pain
11. intense eye contact/eye pointing
• As at 31st December 2004, 276 verified cases (2 males excluded from the analysis)
  • 5. acquired neurological disorder resulting from severe infections or head trauma

• Mean age at diagnosis 5.3 years

• Genetic testing undertaken in 244/274 (88%)

• 179 (73%) mutation positive
Distribution of mutations

- p.R106W
- p.R133C
- p.R168X
- p.R255X
- p.R270X
- p.R294X
- p.R133C
- Large deletions
- Others

Cumulative incidence of Rett syndrome diagnosis by year of age 1990-1999

Cumulative incidence of Rett syndrome diagnosis by five year birth cohort
Cases by residential state and age group

State: ACT, NSW, NT, QLD, SA, TAS, VIC, WA

Age groups:
- <5 yrs
- 5 -<10 yrs
- 10 -<15 yrs
- 15 -<20 yrs
- >20 yrs
Survival according to RTT classification

The graph illustrates the survival probability over time for two categories: Atypical RTT and Classical RTT. The survival probability decreases over time, indicating a lower survival rate as time progresses.
MECP2 Gene

- R133C
- P152R
- T158M
- R168X
- R255X
- R270X
- R294X
- R306H
- R306C

Inter-Domain
Methyl-binding domain
Transcription repression domain

NLS region

Courtesy of Lyn Colvin
Walking

Age: 14  
**Mutation:** Large Deletion

Age: 4  
**Mutation:** R306C
Running/Jumping

Age: 7

Mutation: R306C
Grasping

Age: 12
Mutation: T158M

QuickTime™ and a Sorenson Video decompressor are needed to see this picture.
Grasping

Age: 5
**Mutation:** R255X

Age: 9
**Mutation:** C Terminal
Age: 3
Mutation: R133C

Age: 9
Mutation: R306C
Age: 3  
**Mutation:** R133C

Age: 5  
**Mutation:** R255X
Age: 5
Mutation: R255X

Age: 5
Mutation: R168X
Age: 7
Mutation: R306C

Age: 11
Mutation: R133C
• Discovery of gene and multiple mutations led to the need for a phenotypic scoring system.

• Several systems derived:
  – Kerr (2001) - Glasgow
  – Percy (2001) - USA
  – Pineda (2001) - Spain
  – WeeFIM (1994)-Msall

**Clinical Severity Score**

*from Percy et al. (2000)*

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age at onset of regression</td>
</tr>
<tr>
<td>2</td>
<td>Head growth</td>
</tr>
<tr>
<td>3</td>
<td>Motor function</td>
</tr>
<tr>
<td>4</td>
<td>Crawling and creeping</td>
</tr>
<tr>
<td>5</td>
<td>Ambulation</td>
</tr>
<tr>
<td>6</td>
<td>Nonverbal communication</td>
</tr>
<tr>
<td>7</td>
<td>Language</td>
</tr>
<tr>
<td>8</td>
<td>Respiratory dysfunction</td>
</tr>
<tr>
<td>9</td>
<td>Epilepsy and seizures</td>
</tr>
<tr>
<td>10</td>
<td>Hand use</td>
</tr>
<tr>
<td>11</td>
<td>Feeding</td>
</tr>
<tr>
<td>12</td>
<td>Onset of stereotypies</td>
</tr>
<tr>
<td>13</td>
<td>Somatic growth</td>
</tr>
<tr>
<td>14</td>
<td>Autonomic dysfunction</td>
</tr>
<tr>
<td>15</td>
<td>Scoliosis</td>
</tr>
</tbody>
</table>
Clinical Scores

Individual phenotype items - variation with different mutations

Common Mutations

- Onset of epilepsy
- Sitting alone
- Onset of hand stereotypies
- Onset of regression
- Loss of social interaction

Mean Age (mths)

- MBD R133C (9)
- MBD T158M (14)
- I-D R168X (13)
- TRD-NLS R255X (8)
- TRD-NLS R270X (11)
- TRD-aft NLS R294X (9)
- TRD-aft NLS R306C (7)

L. Colvin 2003
AussieRett results

significant more severe region

milder

R133C
P152R
T158M
R168X
R106W
R255X
R294X
R270X
R306H
R306C

Inter-Domain
Methyl-binding domain
Transcription repression domain

NLS region

most severe mutation

Courtesy of Lyn Colvin
Genotype and Early Development in Rett Syndrome: the Value of International Data.
Leonard et al Brain & Development in press
Risk of onset of scoliosis for common major mutations compared with T158M.

Survival with p.R270X mutation compared with other mutations

Hospital admission and medical appointments by X inactivation status

Thanks go to...

- Financial Markets Foundation for Children
- Rett Syndrome Association Research Fund
- International Rett Syndrome Association
- APSU
- National Institutes of Health
- NHMRC

- Janelle Lillis and family
- Bill Callaghan and the Rett Syndrome Association of Australia
- The families and clinicians who support the research so well

Current funding NIH 1 R01 HD043100-01A1 & NHMRC #303189