Clinical variability and relationship with genotype in Rett syndrome: insights from AussieRett and InterRett

Telethon Institute for Child Health Research

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Atypical or "Variant" Cases

Case categorisation

Six main criteria of Variant Delineation Model
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

Case categorisation

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 1 2 - 21 2 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
5. acquired neurological disorder resulting from severe infections or head trauma

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
Aims of Australian Rett syndrome research

Aims

• Estimate incidence & prevalence in Australia
• Establish a database for ongoing research
• Provide longitudinal data to identify changes in phenotype over time
• Describe & investigate the variability of severity & its genetic and environmental determinants
• Describe patterns of health service usage & morbidity & mortality
• Investigate the impact on family life

Methods of Data Collection:

• Clinician & Parent Questionnaires
• Follow-up studies (F2000, F2002)
• Video Analysis
Cumulative number of cases by calendar year in Australia
MECP2 gene & distribution of mutations in Australia

R133C
P152R
T158M
R106W
R168X
R255X
R270X
R294X
R306H
R306C
NLS region
Early Truncating mutations up to here

Methyl-binding domain
Inter-Domain
Transcription repression domain
C-terminal Deletions

Early truncating
c Large deletions
C Terminal
R106W
R133C
R168X
R255X
R294X
R270X

Courtesy of Lyn Colvin
Clinical Severity Score
from Percy et al. (2000)

1: Age at onset of regression
2: Head growth
3: Motor function
4: Crawling and creeping
5: Ambulation
6: Nonverbal communication
7: Language
8: Respiratory dysfunction
9: Epilepsy and seizures
10: Hand use
11: Feeding
12: Onset of stereotypies
13: Somatic growth
14: Autonomic dysfunction
15: Scoliosis
### Clinical Features Score

*from Kerr et al. (2001)*

<table>
<thead>
<tr>
<th>A</th>
<th>Head circumference during first year</th>
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<tbody>
<tr>
<td>B</td>
<td>Early developmental progress 0-6 months</td>
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<tr>
<td>C</td>
<td>Present head circumference</td>
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<tr>
<td>D</td>
<td>Weight</td>
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<tr>
<td>E</td>
<td>Height</td>
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<tr>
<td>F</td>
<td>Muscle tone</td>
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<tr>
<td>G</td>
<td>Spine posture</td>
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<tr>
<td>H</td>
<td>Joint contractures (not used)</td>
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<tr>
<td>I</td>
<td>Gross motor function</td>
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<tr>
<td>J</td>
<td>Hand stereotypies (wringing squeezing, patting, mouthing)</td>
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<tr>
<td>K</td>
<td>Other involuntary movements</td>
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<tr>
<td>L</td>
<td>Voluntary hand use</td>
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<tr>
<td>M</td>
<td>Oro-motor function</td>
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<td>N</td>
<td>Intellectual disability</td>
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<td>O</td>
<td>Speech</td>
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<td>P</td>
<td>Epilepsy</td>
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<tr>
<td>Q</td>
<td>Disturbed awake breathing rhythm (hyperventilation, panting, breath holding)</td>
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<td>R</td>
<td>Peripheral circulation of extremities</td>
</tr>
<tr>
<td>S</td>
<td>Mood disturbance</td>
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<tr>
<td>T</td>
<td>Sleep disturbance</td>
</tr>
</tbody>
</table>
Clinical Severity Score
from Pineda et al. (2001)

1: Age at loss of social interaction
2: Head growth
3: Sitting alone
4: Ambulation
5: Language
6: Respiratory function
7: Epilepsy
8: Hand use
9: Air swallowing / bloating
10: Onset of stereotypies
Other = countries with 10 or less participants:

Argentina, Austria, Belgium, Bolivia, Brazil, Chilie, Columbia, Denmark, Germany, Honduras, Hungary, India, Iran, Ireland, Italy, Japan, Malta, Mexico, Netherlands, New Zealand, Norway, Peru, Portugal, South Africa, Sweden, Switzerland, Taiwan, Turkey, United Arab Emirates, Uruguay
Age at regression by mutation

Language development by mutation


Pineda Score: Language
Ambulation history by mutation

Pineda Score: Ambulation

Hand use by mutation


Pineda Score: Hand Use
Kerr severity by common mutations

Pineda severity by common mutations

InterRett data 2008 (n= 836) including 178 ARSD cases
Percy severity by common mutations

InterRett data 2008 (n=660) including 176 ARSD cases
Individual and composite scores relating to early development by six common mutations.

Summary of results

- **R133C**
- **P152R**
- **T158M**
- **R168X**
- **R255X**
- **R270X**
- **R294X**
- **R106W**
- **NLS region**
- **R306H**
- **Inter-Domain**
- **Transcription repression domain**

**Significantly more severe region**

**Early Truncating mutations up to here**

**Also milder**

**C-terminal Deletions**

**milder**

Courtesy of Lyn Colvin
Skewed X-Inactivation

• Mechanism by which mammals achieve gene-dosage compensation i.e. males have one X-chromosome and females have two X-chromosomes
• Females are mosaic - comprising mixtures of cell lines in which the paternal X is inactivated and cell lines where the maternally inherited X is inactivated
• Preferential silencing of one allele, leading to skewed X-inactivation
• Could either be favourable or detrimental
Modulation of severity by X inactivation status

Risk of onset of scoliosis for common major mutations compared with T158M.

Median age at onset of seizures

Association of seizure rate with mutation type in Rett syndrome cases with epilepsy

84 (ex 236) fractured at least once

32 had more than one fracture (maximum 9)

151 fracture episodes

Fracture Incidence Rates
43.3/1000 py - Rett
11.4/1000 py - General Population
(females <20yrs – Cooley & Jones)

Association of fracture rate with mutation type in Rett syndrome

Survival with p.R270X mutation compared with other mutations

Genetic presentation
- Type of MECP2 mutation
- X inactivation status
- Other genetic factors
- Sporadic presentation

Developmental course prior to diagnosis
eg, duration of period prior to developmental regression, learning to walk

Environmental factors
- early therapy interventions,
- ongoing therapy,
- medical management (eg monitoring, medications, orthoses)
- surgical management (eg monitoring, gastrostomy, spinal surgery)
- respite, home modifications, supportive community, financial resources

Individual function factors
- bone health
- control of scoliosis
- growth and maintenance of weight
- control of epilepsy
- manageable behaviour

Activity
- mobility
- hand function
- ability to communicate
- adequacy of sleep

Participation
- school and/or day placement
- minimal hospital admissions

Family functioning
- Function, eg physical and mental health of parents and siblings
- Activity, eg recreation, family holidays
- Participation, eg parental employment, smooth transitions between life stages
- Personal factors, eg resilience

Optimal well-being, quality and duration of life
Thanks go to...

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