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
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Co-investigators & Contributors

APSU

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

Rett Syndrome Association of Australia

Princess Margaret Hospital for Children
Lakshmi Nagarajan

The University of Western Australia
Sonj Hall
Delia Hendrie

WomenÕs& ChildrenÕs Hospital Adelaide
Clair Pridmore
Elizabeth Thompson

The Royal ChildrenÕs Hospital, Melbourne
Sheena Reilly
Gordon Baike
Lyndall Mulready
Ruth Nicholls

University of Chicago ChildrenÕs Hospital
Michael Msall

AUSSIERETT STUDY PARTNERS

Sydney ChildrenÕs Hospital /Campbeltown Hospital
Helen Woodhead

University of Glasgow
Bronwen Burford

Curtin University of Technology Perth
Sue Fyfe

Royal Perth Hospital
David Ravine
Mark Davis

The ChildrenÕs Hospital at Westmead, Sydney
John Christodoulou
Carolyn Ellaway
Belinda Todd

Australian Paediatricians

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

Rett syndrome Research in Australia: Timeline & involvement with APSU

- 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**

The Australian Paediatric Surveillance Unit
A Unit of the Royal Australasian College of Physicians, Paediatrics Division

Aims of Australian Rett syndrome research

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 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

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. deceleraton of head growth from first years of life
6. RS disease profile: a regression stage followed by a recovery of interaction c ontrasting with slow neuromotor regression

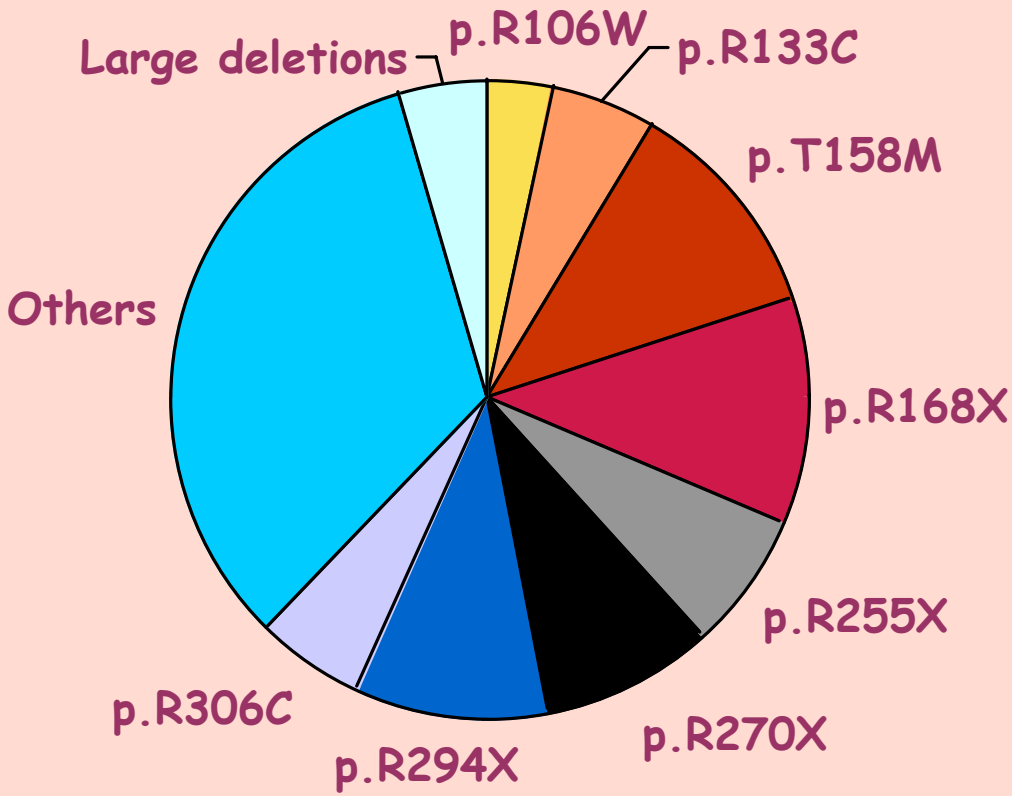
Eleven supportive criteria

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

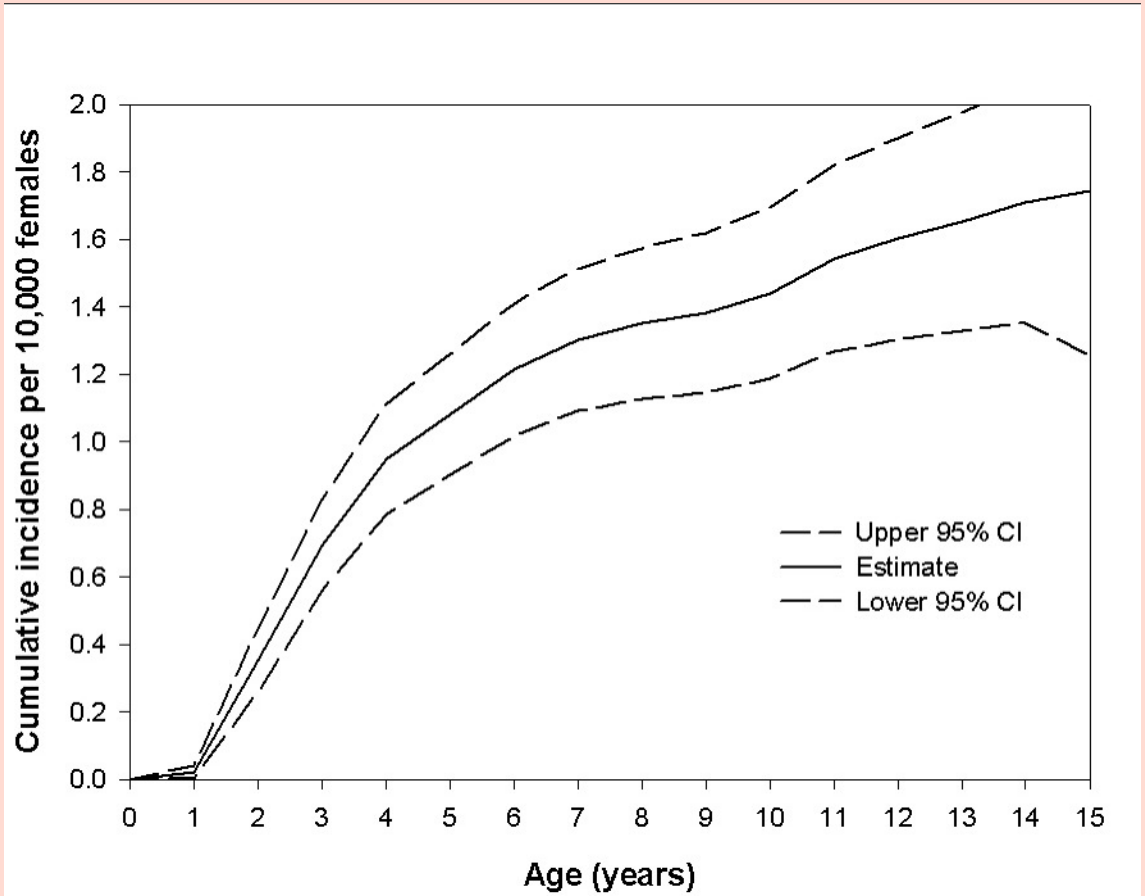
Status of Australian cohort December 2004

- **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

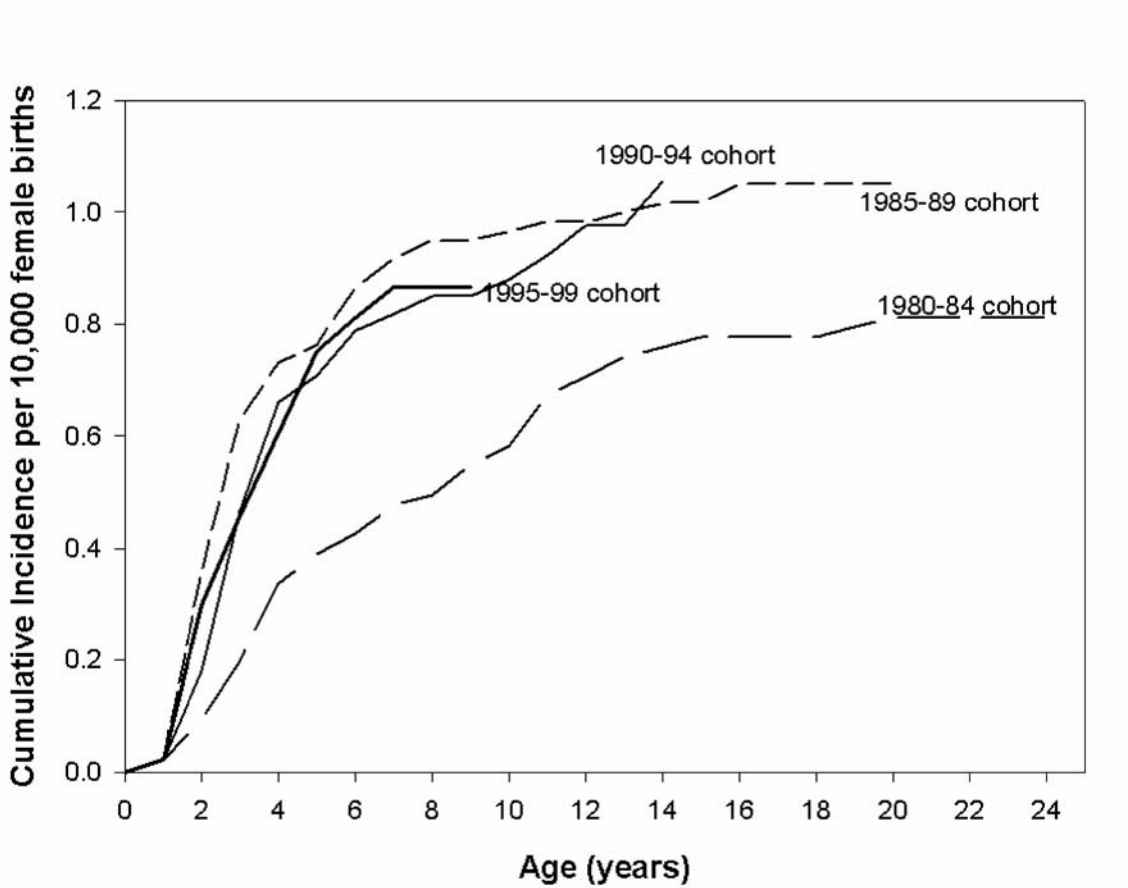


Cumulative incidence of Rett syndrome diagnosis by year of age 1990-1999

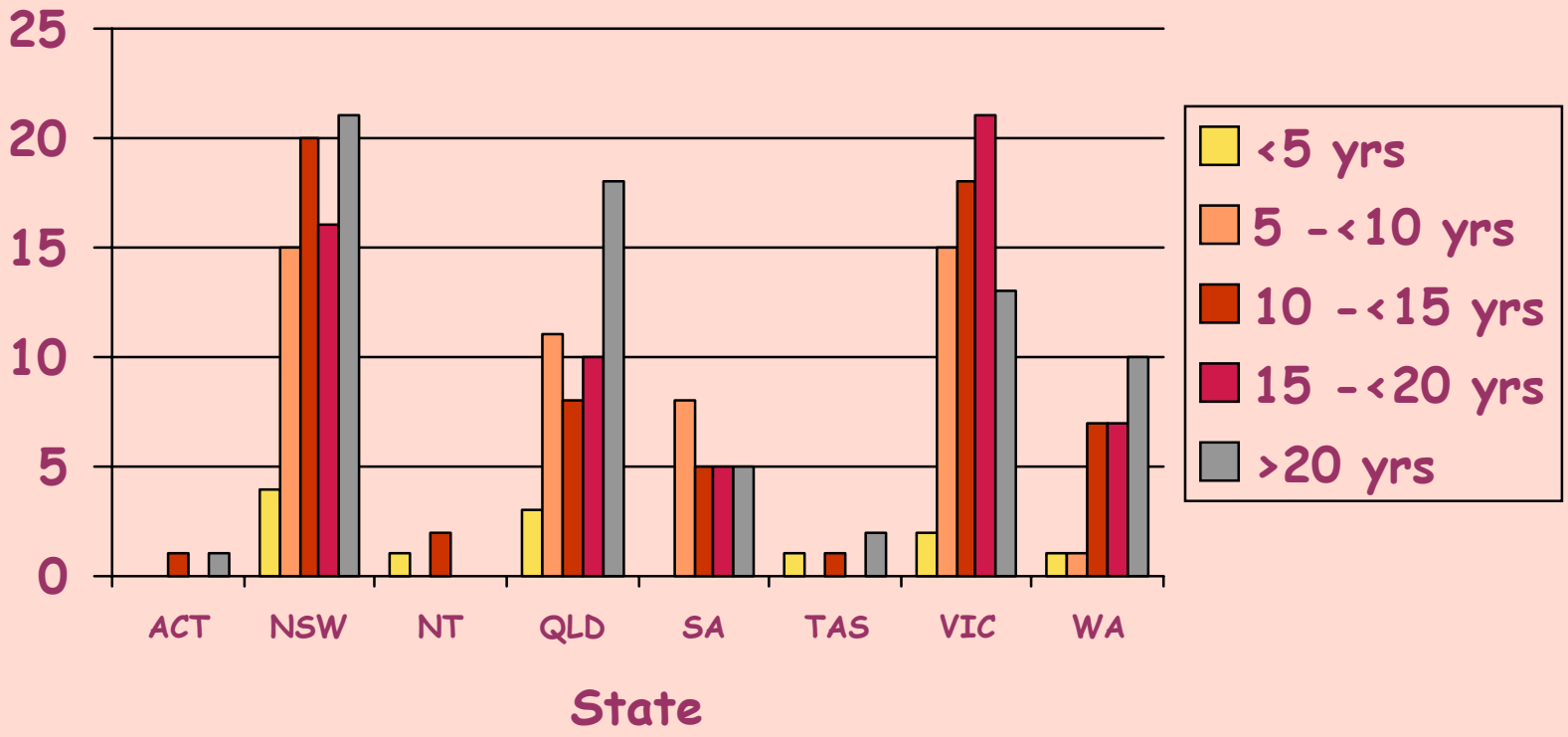


Laurvick C, De Klerk N, Bower C, Christodoulou J, Ravine D, Ellaway C, et al.
Rett syndrome in Australia: A review of the epidemiology.Journal of Pediatrics in press.

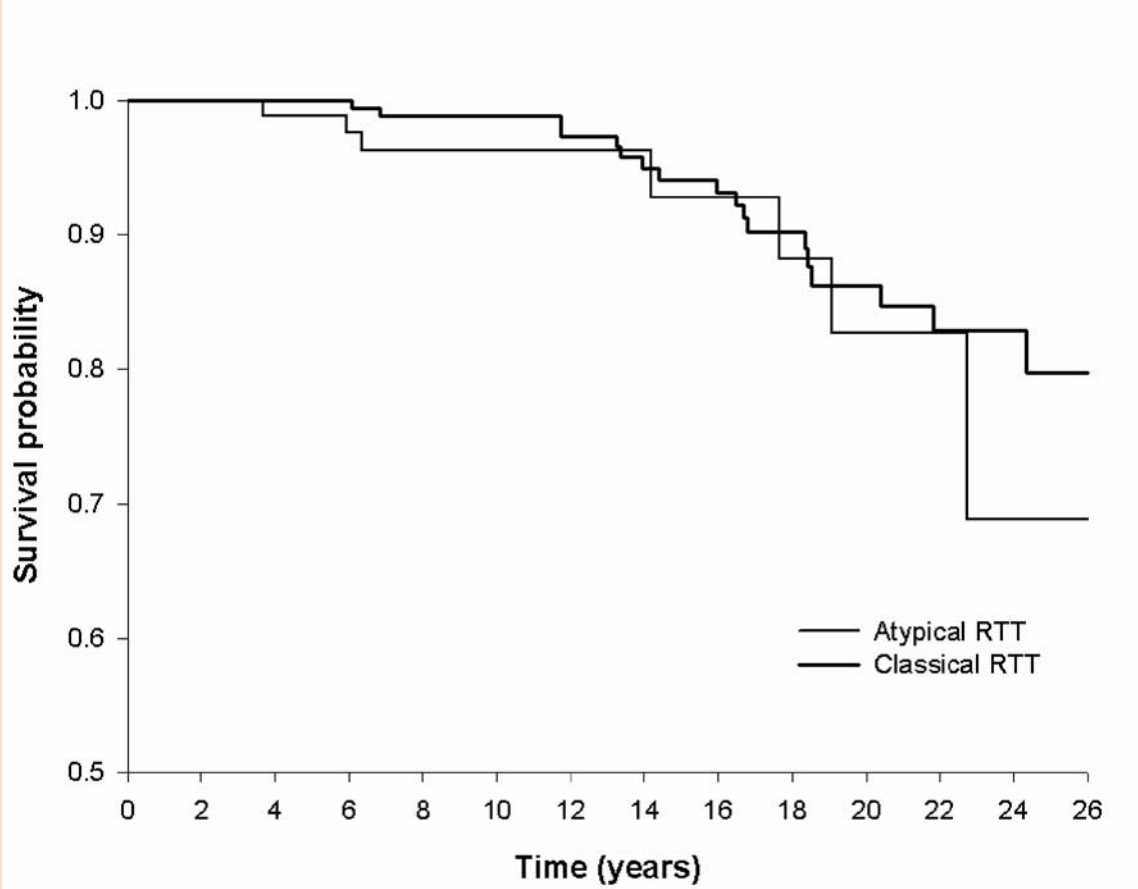
Cumulative incidence of Rett syndrome diagnosis by five year birth cohort



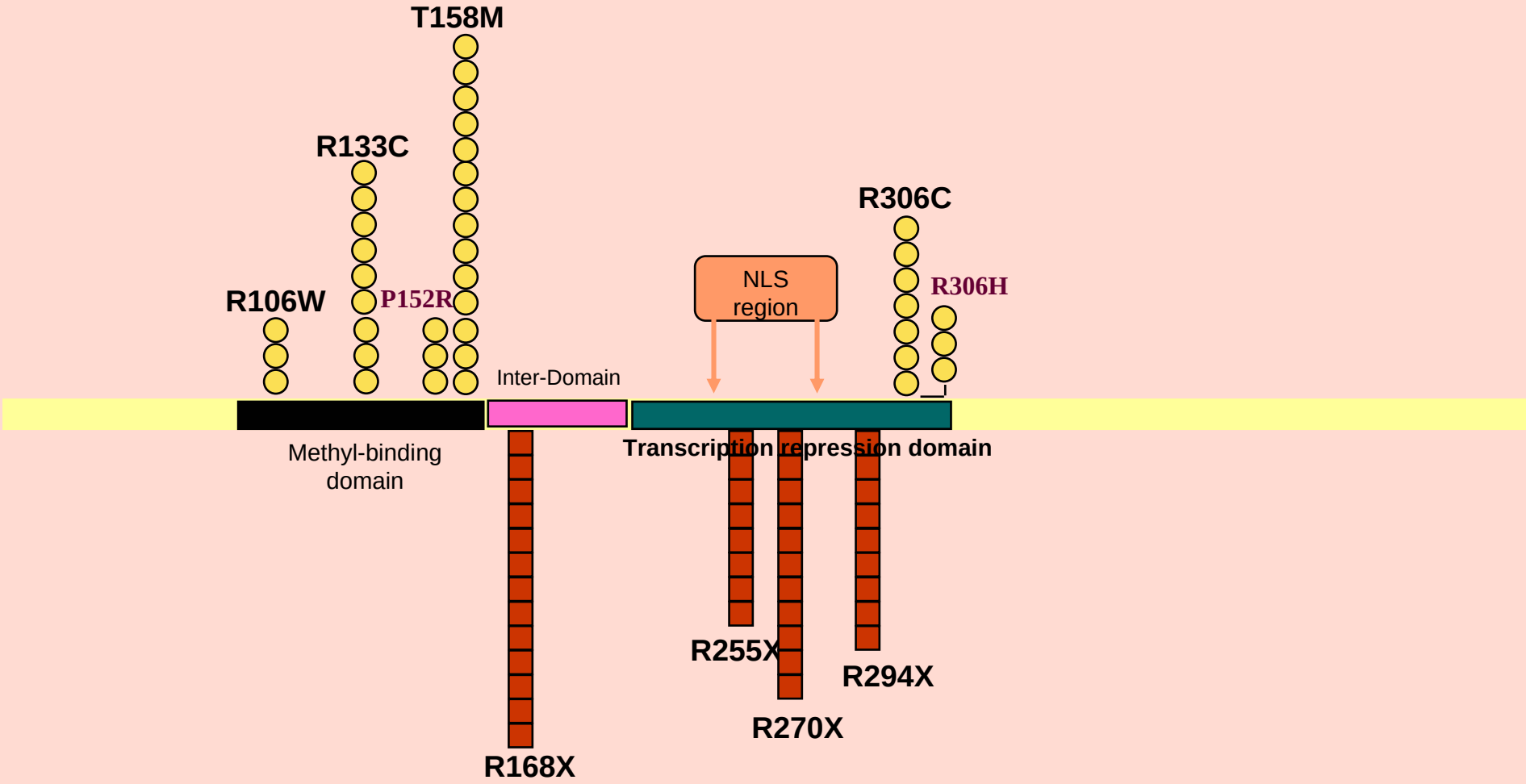
Cases by residential state and age group



Survival according to RTT classification



MECP2 Gene



Courtesy of Lyn Colvin

Walking

QuickTime™ and a
DVCPRO - PAL decompressor
are needed to see this picture.

Age: 14
Mutation: Large Deletion

Age: 4
Mutation: R306C

QuickTime™ and a
DVCPRO - PAL decompressor
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Running/Jumping

QuickTime™ and a
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are needed to see this picture.

Age: 7
Mutation: R306C

Grasping

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are needed to see this picture.

Age:12

Mutation: T158M

Grasping

QuickTime™ and a
DVCPRO - PAL decompressor
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Age:5
Mutation: R255X

Age: 9
Mutation: C Terminal

QuickTime™ and a
DVCPRO - PAL decompressor
are needed to see this picture.

Using a Fork

QuickTime™ and a
DVCPRO - PAL decompressor
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Age: 3
Mutation: R133C

Age: 9
Mutation:R306C

QuickTime™ and a
DVCPRO - PAL decompressor
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Pick-up & Hold

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DVCPRO - PAL decompressor
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Age: 5
Mutation: R255X

Age: 3
Mutation: R133C

QuickTime™ and a
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Stereotypies

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Age: 5
Mutation: R255X

Age:5
Mutation: R168X

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Stereotypies

QuickTime™ and a
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Age: 7
Mutation: R306C

Age: 11
Mutation: R133C

QuickTime™ and a
DVCPRO - PAL decompressor
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Genotype phenotype correlations

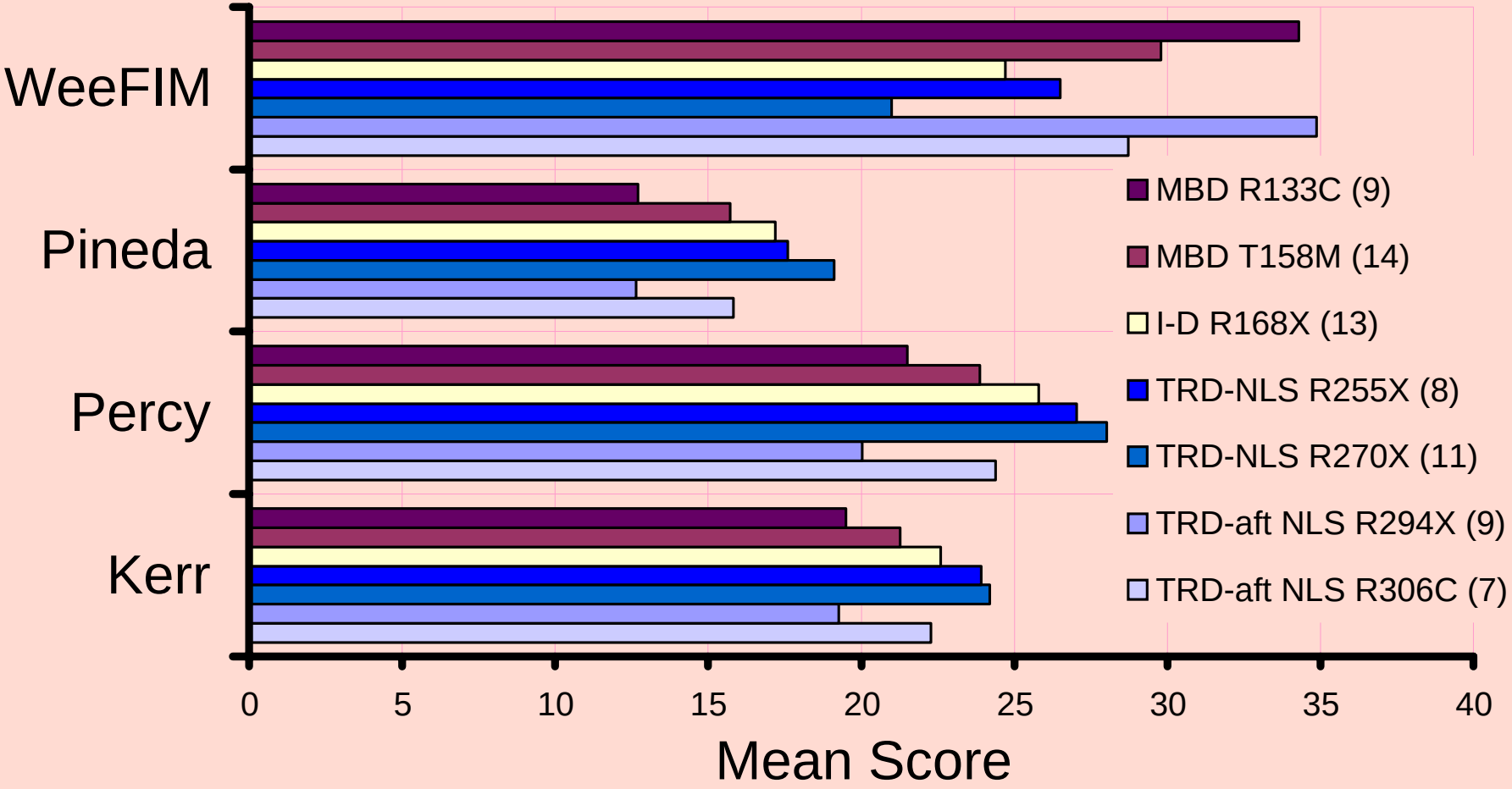
- Discovery of gene and multiple mutations led to the need for a phenotypic scoring system.
- Several systems derived:
  - Kerr (2001) - Glasgow
  - Percy (2001) - USA
  - Pineda (2001) - Spain
  - WeeFIM (1994)-Msall

Describing the phenotype in Rett syndrome using a population database. Colvin et al. Arch Dis Child 2003;88:38-43

Clinical Severity Score
from Percy et al. (2000)

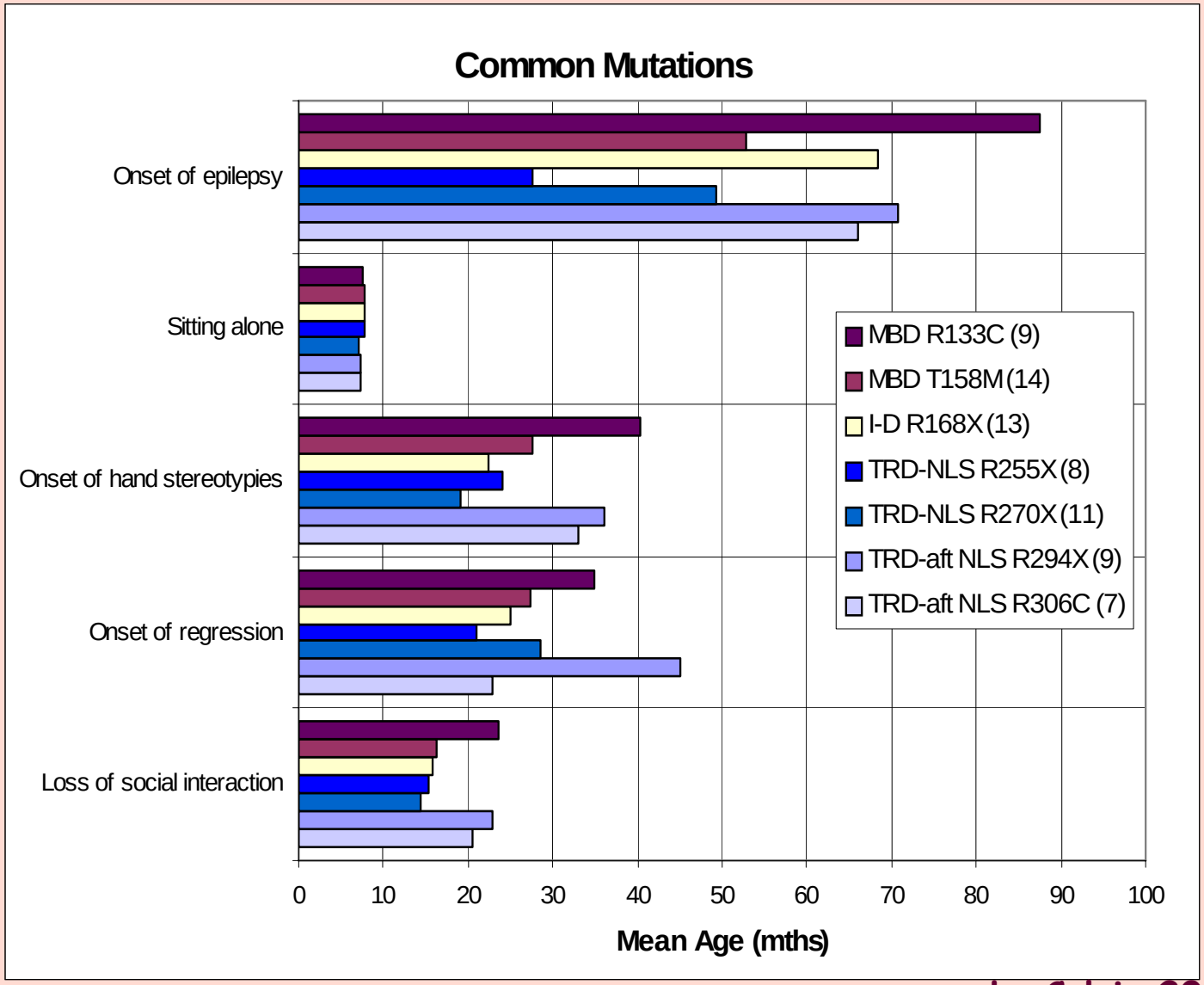
1: Age at onset of regression
2: Head growth
3: Motor function
4: Crawling and creeping
5: Ambulation
6: Nonverbal communication
7: Language
8: Respiratory dysfunction
9: Epilepsy and seizures
10: Hand use
11: Feeding
12: Onset of stereotypies
13: Somatic growth
14: Autonomic dysfunction
15: Scoliosis

Clinical Scores



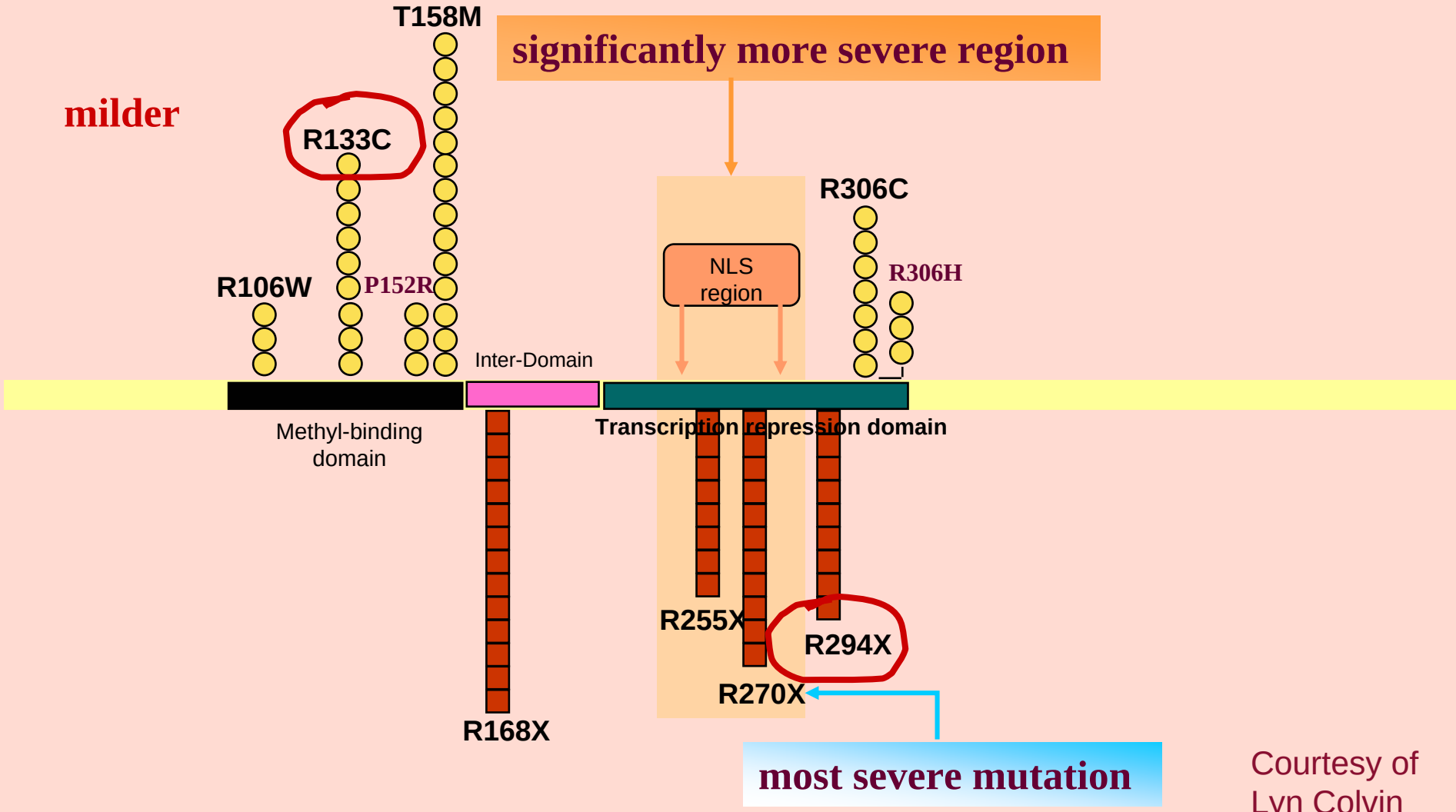
Colvin L, Leonard H, de Klerk N, et al. Refining the phenotype of common mutations in Rett syndrome. *J Med Genet.* 2003;41(1):25-30.

Individual phenotype items - variation with different mutations



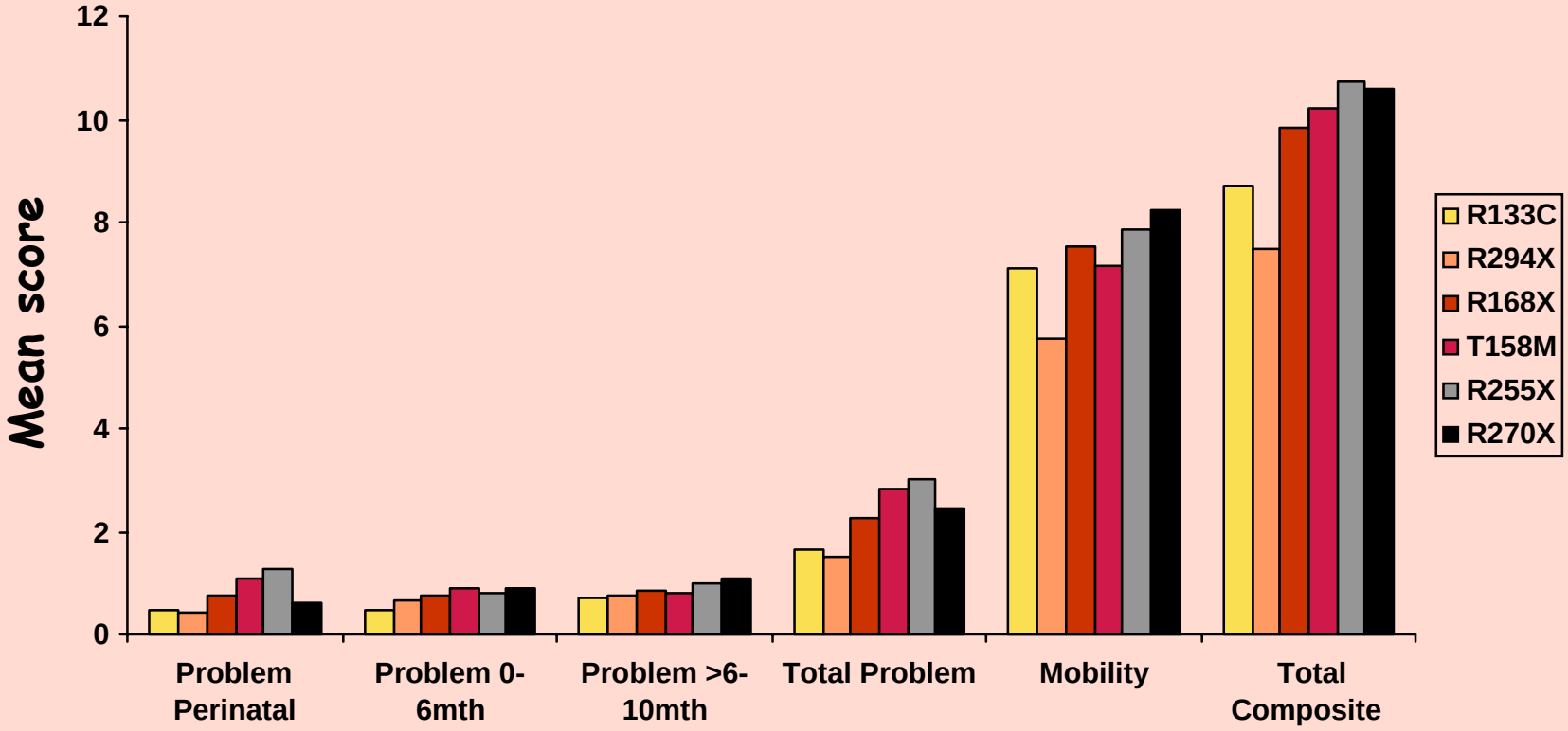
L. Colvin 2003

AussieRett results



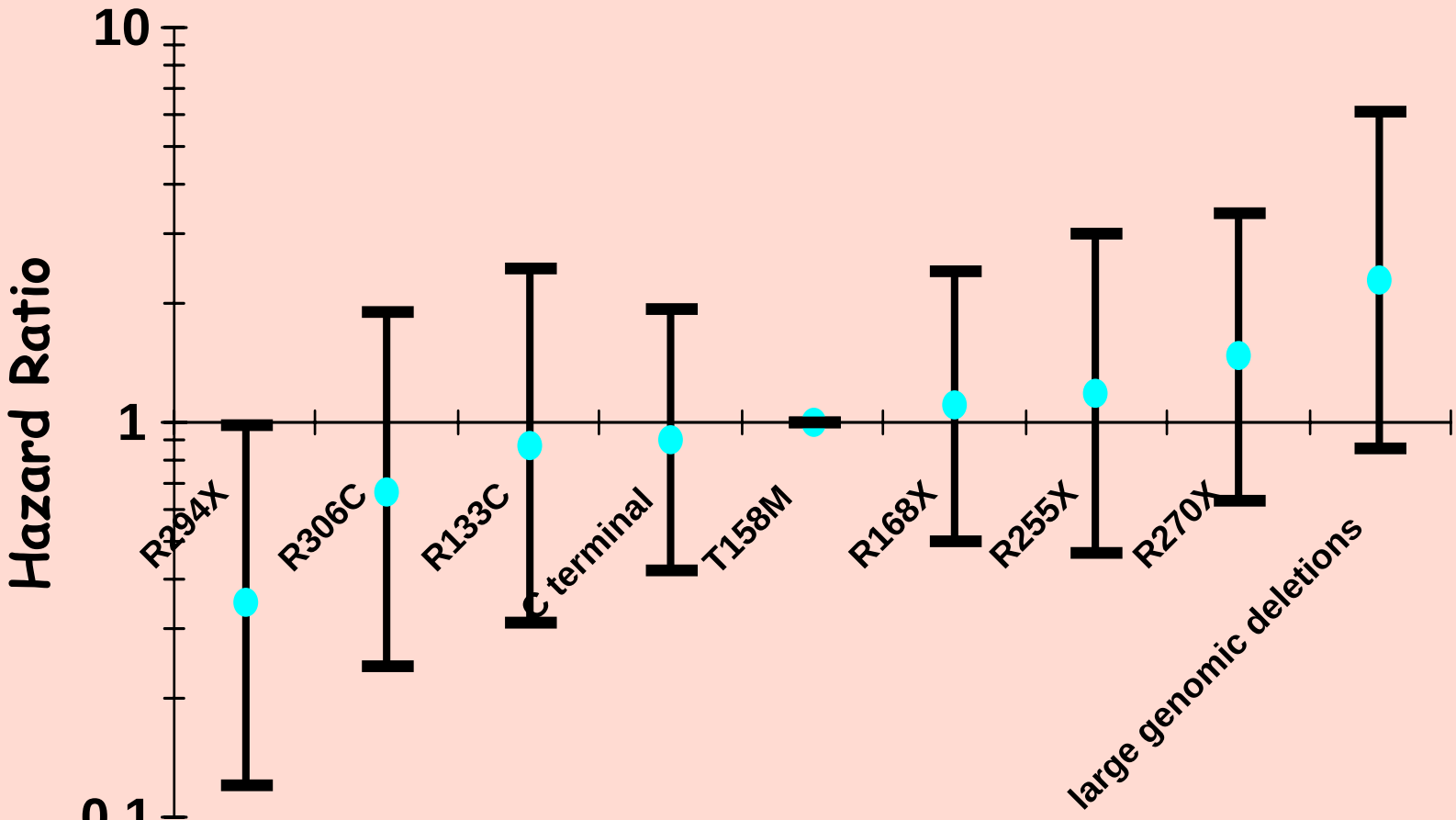
Courtesy of Lyn Colvin

Individual and composite scores relating to early development by six common mutations



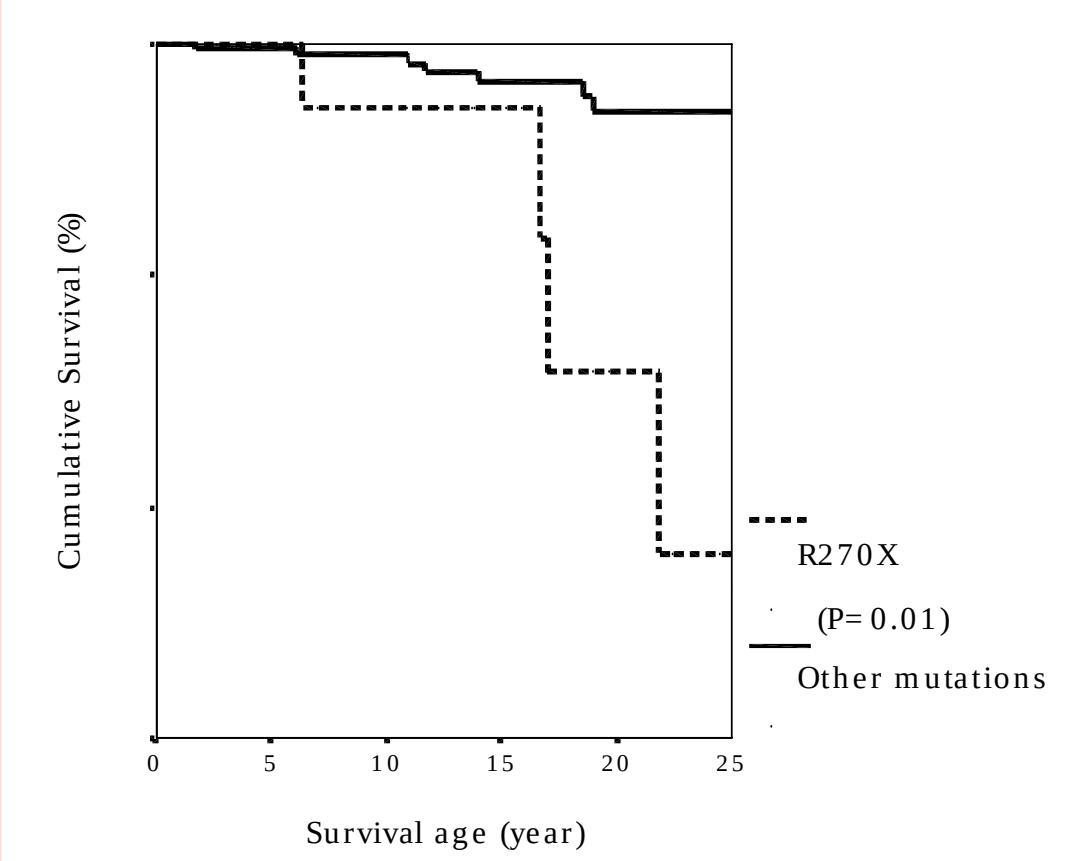
Genotype and Early Development in Rett Syndrome: the Value of International Data.
Leonard *et al* Brain & Development in press

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



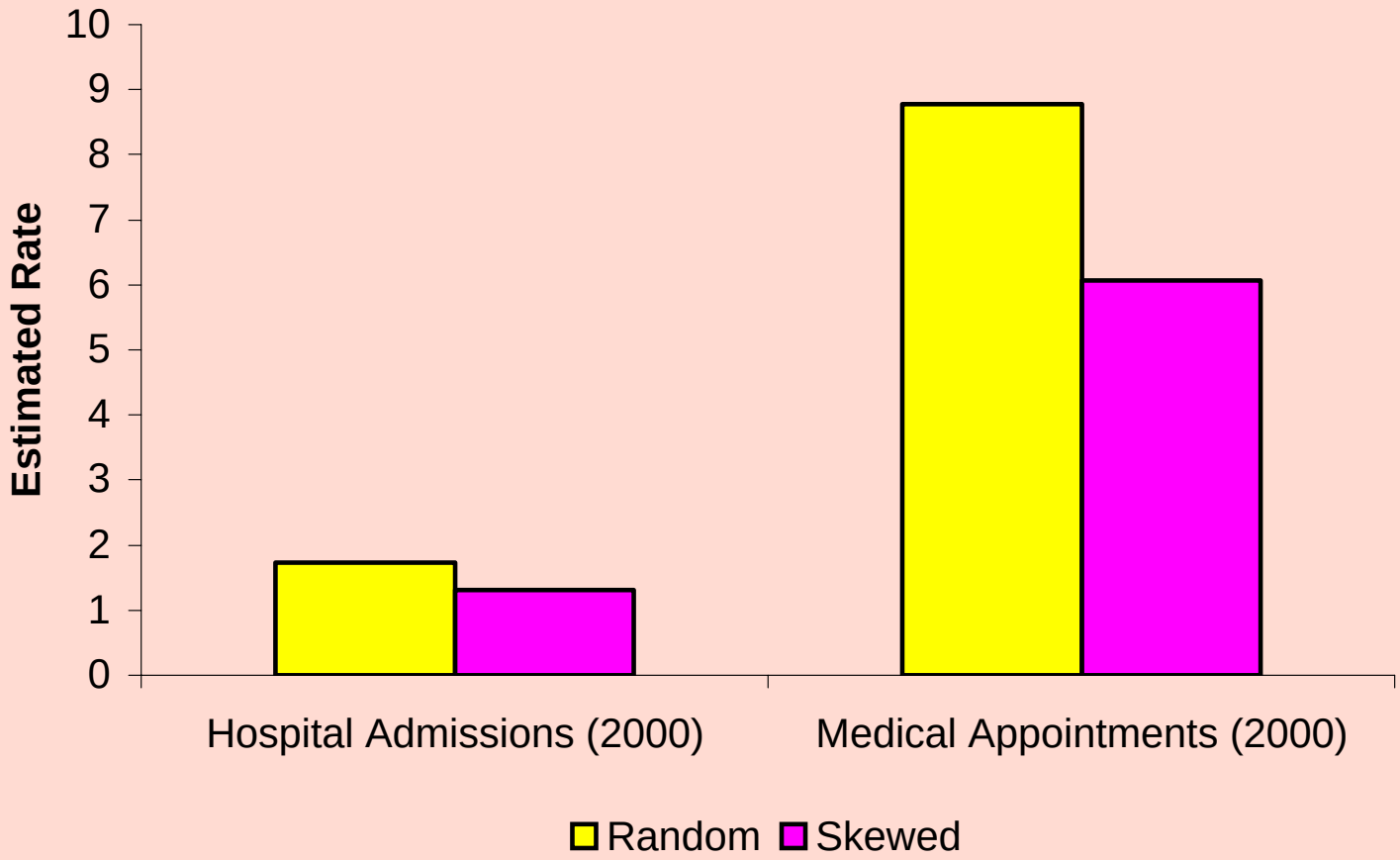
Ager S, Fyfe S, Christodoulou J, Jacoby P, Schmitt L, Leonard H. Predictors of scoliosis in Rett syndrome. Journal of Child Neurology in press.

Survival with p.R270X mutation compared with other mutations



Jian L, Archer HL, Ravine D, Kerr A, de Klerk N, Christodoulou J, et al. p.R270X MECP2 mutation and mortality in Rett syndrome. Eur J Hum Genet 2005;13(11):1235-8.

Hospital admission and medical appointments by X inactivation status



Moore H, Leonard H, de Klerk N, Robertson I, Fyfe S, Christodoulou J, et al. Health service use in Rett syndrome. J Child Neurol 2005;20(1):42-50.

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