Bengt Hagberg Memorial Lecture

Rett Syndrome: From Recognition to Gene Discovery to Clinical Trials

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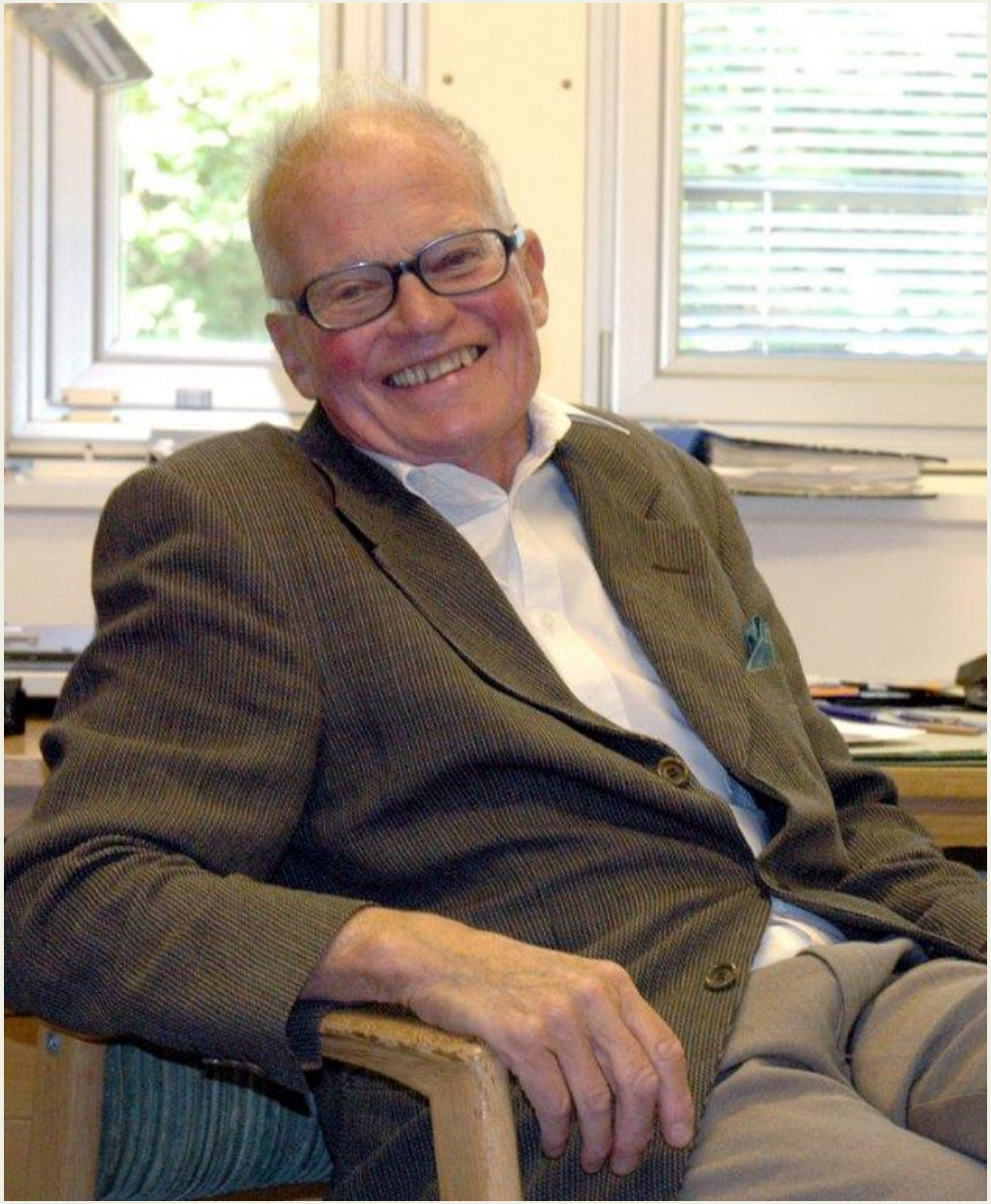
January 21, 2016



Acta Pediatrica Scandinavica 55: l-9. Jan. 1966

From the Institute of Medical Biochemistry, University of Gothenburg, Gothenburg, Sweden

Kidney Glycolipids in Late Infantile Metachromatic Leucodystrophy

by Erik Mårtennson, Alan Percy, and Lars Svennerholm

…one important point….

…mapping the way ahead…

…a celebration…

…a scholarly moment....

...special day....

Why rare diseases are important

- True burden difficult to estimate:
  - ~7,000 rare diseases; affect ~7-10% population
- Little general information
- Absence of reliable or consistent data
- Difficult research funding

- **Inadequate health service coverage**
- **Little effective treatment**
- **Scarce biochemical/ molecular testing**

The path forward

- Recognize clinical disorder
- Clinical-pathological correlation
- Determine causation:
  - If genetic, molecular diagnosis
- Basic science: understand molecular signal and develop lines of investigation
- Translation approaches to treatment
- Initiate clinical trials
- Requires sound natural history data

Rett Syndrome

Where we have traveled

Bengt Hagberg

Andreas Rett

A Progressive Syndrome of Autism, Dementia, Ataxia, and Loss of Purposeful Hand Use in Girls: Rett's Syndrome: Report of 35 Cases

Bengt Hagberg, MD,* Jean Aicardi, MD,† Karin Dias, MD,‡ and Ovidio Ramos, MD†

Rett syndrome is caused by mutations in X-linked *MECP2*, encoding methyl-CpG-binding protein 2

Ruthie E. Amir, Ignatia B. van den Veyver, Mimi Wan, Charles Q. Tran, Uta Francke & Huda Y. Zoghbi

Nature Genet 1999;23:185

Basic Science Insights

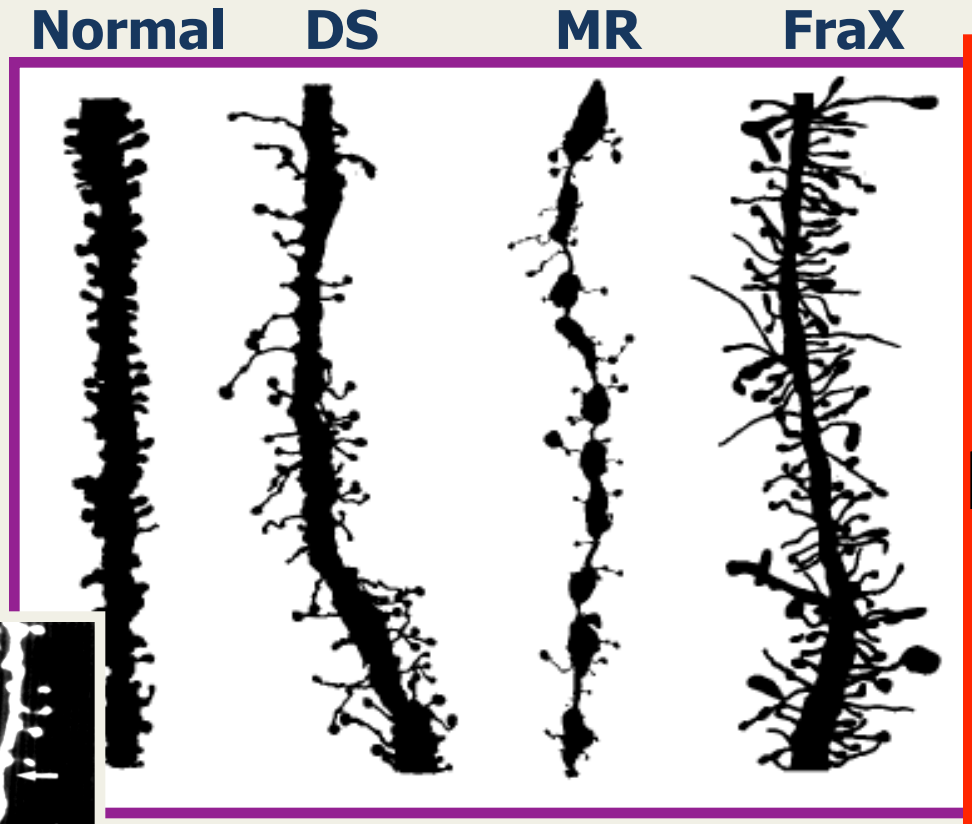
METHYL-CpG-BINDING PROTEIN 2

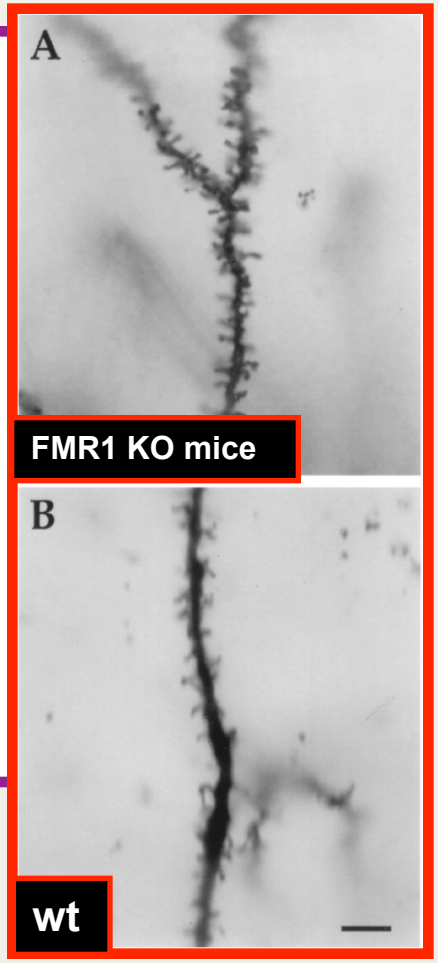
- Member of family of methyl-binding proteins
- Capable of transcriptional regulation
- Ubiquitous in mammalian tissues
- Highly expressed in brain
- Specific gene targets not defined totally
- Function in maintenance of developing and mature neurons

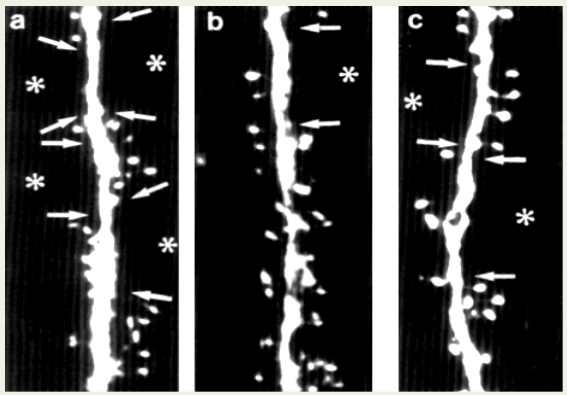
RETT SYNDROME
BRAIN MORPHOLOGY

- Reduced brain weight
- Reduced volume of specific regions
- Reduced melanin pigmentation
- Small neurons, simplified dendrites, and reduced dendritic spines
- No recognizable disease progression

Spine Dysgenesis in Mental Retardation







Rett Syndrome

Down Syndrome (Huttenlocher '70, '74; Marin-Padilla '72, '76; Purpura '74, '75); Fragile X Syndrome - and FMR1 KO mice (Wisniewski '85; Greenough '97); Rett Syndrome (Belichenko '94)

Knock-out Mutant

- **Is Mecp2 knock-out reversible?**
- Using estrogen receptor controlled *Mecp2* promoter:
  - *Mecp2* knock-out phenotype reversed in both immature male and mature male and female mice
  - Rapid re-expression in immature males resulted in death in 50%
    - » Guy et al. *Science* 2007;315:1143-1147

Research in Other Tissues

- Single cell culture: neurons or glia
- Tissue slices: specific brain regions
- Lymphoblasts: derived from white cells
- Stem cells: derived from skin fibroblasts
  - Reprogrammed to stem cells; differentiated to neurons or glia or cell type of interest
- Cells represent testbeds for research and drug discovery; no viable direct therapy…

YET

Clinical Diagnosis

Rett Syndrome

Neurodevelopmental Disorder of Young Females Characterized by

- Cognitive Impairment
- Communication Dysfunction
- Stereotypic Movements
- Pervasive Growth Problems

Rett Syndrome
Development of Consensus Criteria

- Initial criteria in 1985 after major conference
  - Hagberg et al. Brain Dev 1985;7:372-373.
- Refined criteria in 2002 following *MECP2* discovery
  - Hagberg et al. Eur J Paediatr Neurol 2002;6:293-297
- Further refined in 2010
  - Neul et al., Ann Neurol 2010;68:944-950.
- All based on clinical consensus of international representatives

Rett Syndrome

Temporal Profile

- Apparently normal early development
- Arrest of developmental progress
- Regression including poor social contact and finger skills
- Stabilization: Better social contact and eye gaze; gradual slowing of motor functions

What we know about *MECP2* and Rett syndrome!

- Diagnosis based on consensus clinical criteria
- Classic RTT: >95% have *MECP2* mutations
- 8 point mutations represent ~ 60%
- Deletions and insertions ~ 15-18%)
- Incidence: ~1:10,000 female births
- Mainly sporadic: majority of paternal origin
- Familial Rett syndrome is <<1% of total
- Variant forms account for about 15% of total
  - *MECP2* mutations in approximately 75%

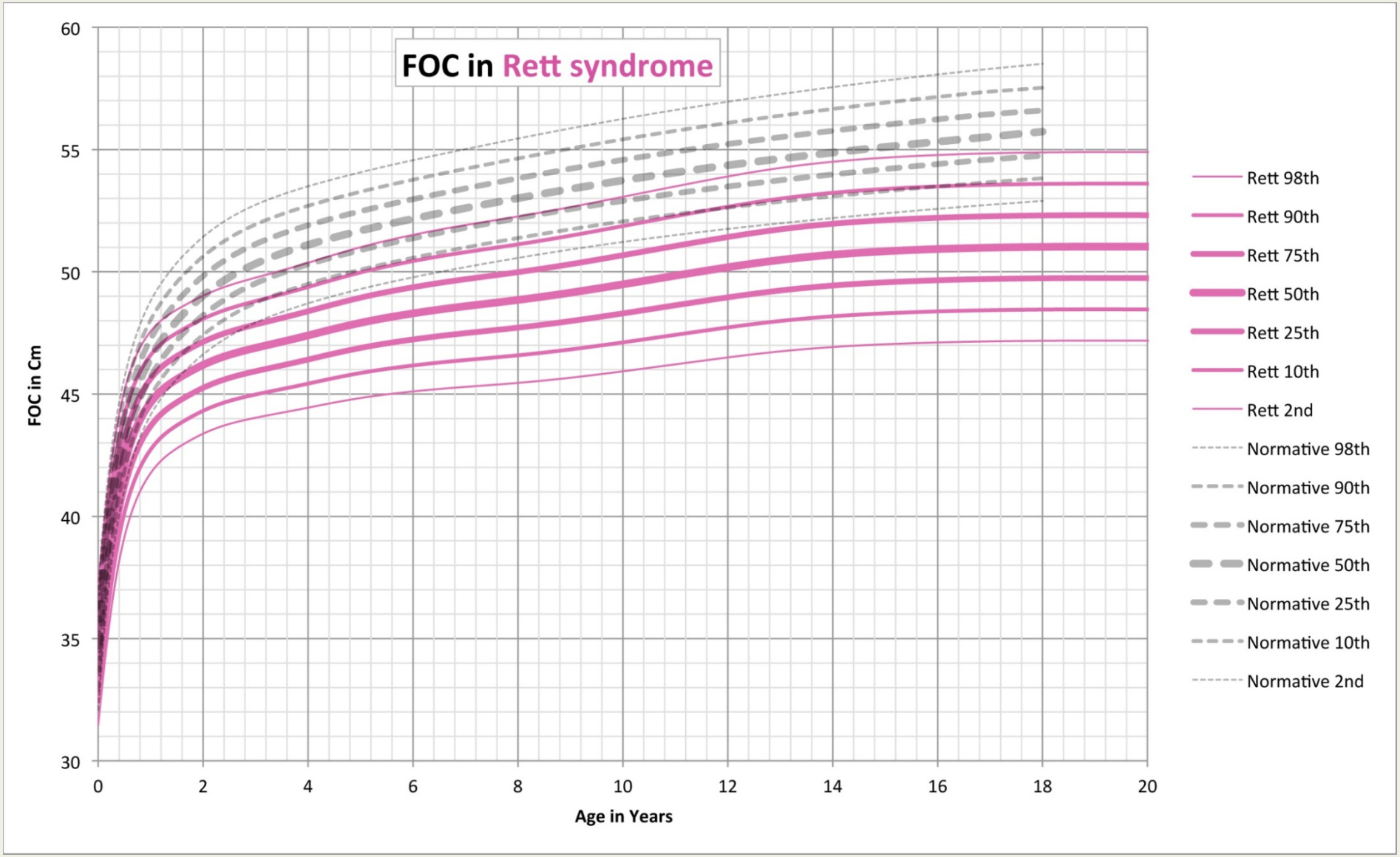
Medical Issues

A multisystem problem

- Growth and Nutrition
- Epilepsy
- Breathing
- Gastrointestinal tract
- Scoliosis and bone health
- Ambulation
- Sleep
- Sexual maturity
- Longevity

Growth

- Small stature is typical
- Deceleration of growth
  - Head circumference as early as 1.5 months; median value at 2nd percentile by age 2
  - Weight as early as 6 months; 2nd % by 12
  - Length as early as 17 months; 2nd % by 12
    - Tarquinio et al., 2012;79:1653-1661.
- Hands and feet small; feet relatively moreso


FOC in Rett syndrome
FOC in Cm
60
55
50
45
40
35
30
0
2
4
6
8
10
12
14
16
18
20
Age in Years
Rett 98th
Rett 90th
Rett 75th
Rett 50th
Rett 25th
Rett 10th
Rett 2nd
Normative 98th
Normative 90th
Normative 75th
Normative 50th
Normative 25th
Normative 10th
Normative 2nd

Epilepsy

- Occurrence variable; from 20 to 80% in different reports
- Seizure types: focal, generalized, or atypical absence
- Video-EEG monitoring often required to differentiate from non-epileptic behaviors
- At any point in time, 25-30% have seizures that require medication

» Glaze et al., Neurology 2010;74:909-912.

Scoliosis

- Present in ~8% of preschoolers; ~80% by age 16 years; and 87% by age 25 years
  - Progression should stop at maturity
- Usually apparent by age 8 years
- Curvature often greater if non-ambulatory
- Consider bracing above 25° curve
  - No systematic evidence that it works
- Consider surgery if curvature exceeds 40°
- ~13% will require surgery; most parents feel surgery improved quality of life

» Percy et al., Pediatr Res 2010;67:435-439.

Sexual Maturation

- Puberty acquired at ages similar to peers
  - Precocious in ~25%; delayed in 19%
  - Varies in part with body mass index
  - Appropriate consideration essential to prevent unwarranted contact
- Menstrual cycles usually predictably regular after puberty well-established
- Many menstrual management strategies
  - Killian et al. Pediatr Neurol 2014;51:769-775.

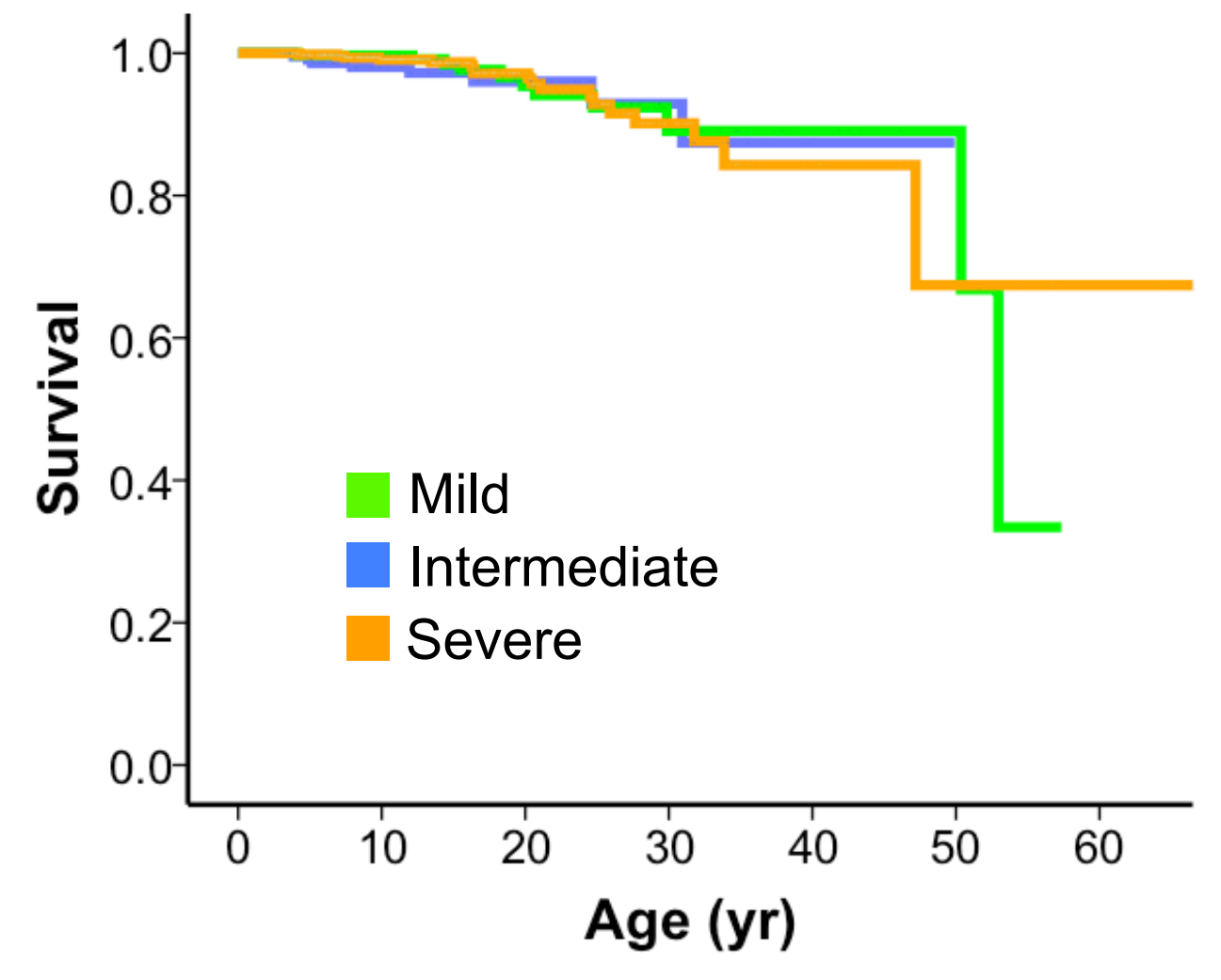
Longevity by Age

- Overall longevity double Andy Rett's original group

Age in years	% survival
0-10	normal
20	90
30	>75
40	>65
50	>50

Kirby et al., J Pediatr 2010;156:135-138.

Clinical Severity Correlation



Recent Report on Survival

- Confirmed survival beyond age 50
- Cardiorespiratory issues lead to difficulties
- Ambulation, adequate weight, and effective seizure control promote survival
- Extreme frailty reported in the 1990's rarely seen in current study
- Emphasizes results of good diet and effective therapies
  - Tarquinio et al. Pediatr Neurol 2015;53:402-411.

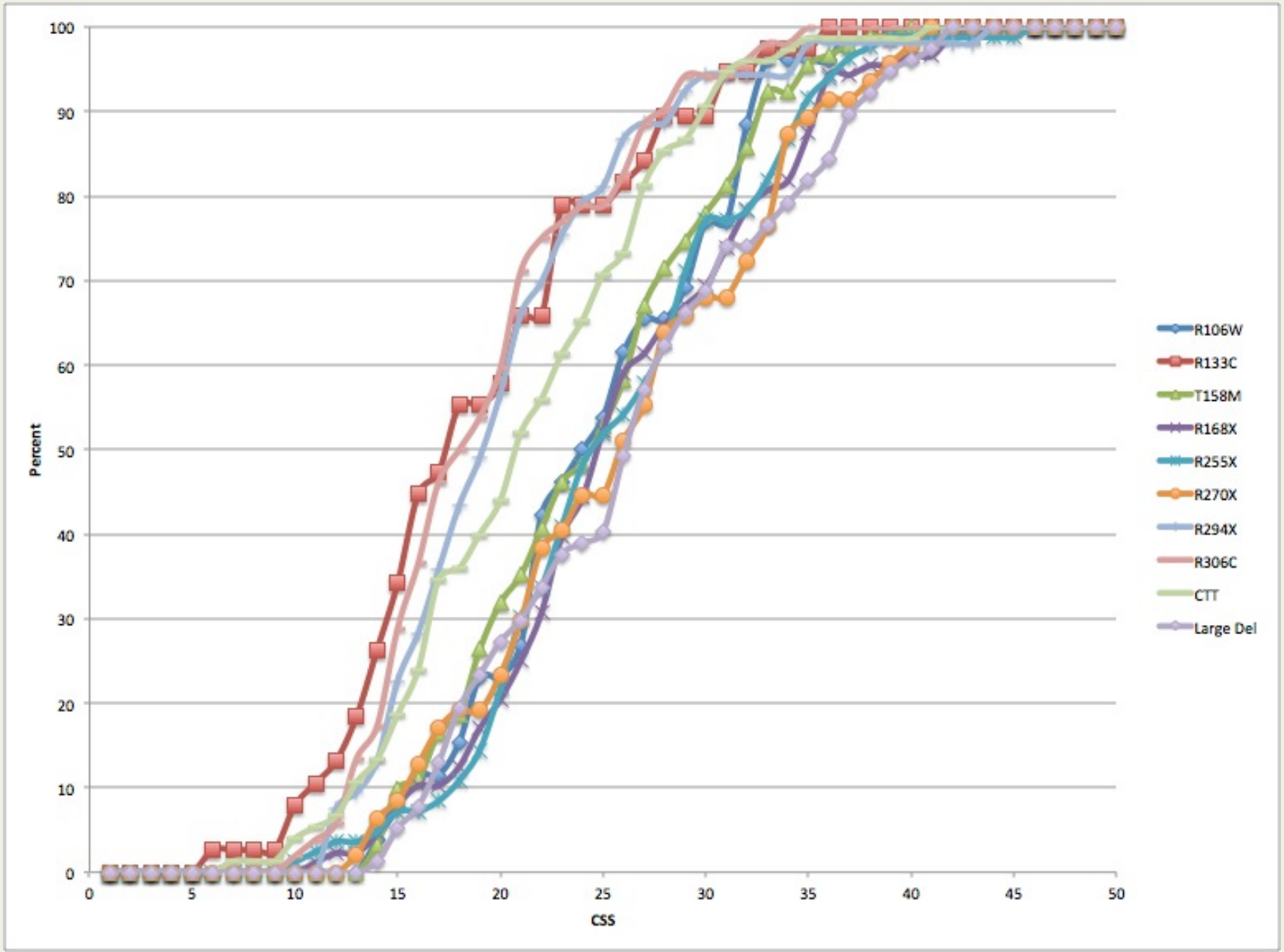
Quality of Life

- CHQ: Poor motor function yields fewer behavioral problems; better motor function results in more behavioral issues
  - Could modest improvement in motor function adversely affect behavior?
- SF-36: Parent quality of life: Over time, physical QOL declines whereas mental QOL improves; similar to other disorders
  - Lane et al. Neurol 2011;77:1812-1818.
  - Killian et al. Pediatr Neurol 2016 in press.

Phenotype-Genotype Correlation

- Classic and atypical RTT: R133C, R294X, R306C, and 3’ truncations relatively less severe than R106W, R168X, R255X, and R270X, splice site, and deletion/insertions
- Clinical severity generally increases with age
- Ambulation, hand use, and age at onset strongly linked to overall severity

MECP2 Mutations and CSS



Phenotype-Genotype Caveats

- Same genotype may yield *different* outcome
- X chromosome inactivation may differ
  - XCI (blood from 183) revealed 11% highly skewed, 26% moderately skewed, 51% random, and 12% uninformative
- Genetic background may differ
- Clonal distribution of normal and mutant X chromosomes in brain is different
- Environmental influences affect outcome

Age at Diagnosis

- Diagnosis often delayed: mean = 2.7 years from US NHS Tarquinio et al. Pediatr Neurol 2015;52:585-591.
- To begin treatment, early diagnosis required
- Clues to earlier diagnosis:
  - Declining head circumference in infancy
  - Declining for weight and height
  - Slowing of development or frank regression
  - Inattentiveness or lack of response to parents
  - Is the infant passive or too good?

Pharmacologic Approaches

Prior Clinical Trials

- Lamotrigine for seizures
- Bromocriptine for motor performance
- Naltrexone for periodic breathing
- Folate-betaine to increase methyl-binding

- Little benefit aside from improved seizure management with lamotrigine

Gene Therapy

- Gene correction
  - Problem: Correcting only abnormal allele
- Stem cell transplant
  - No effect in symptomatic male mice; some improvement in asymptomatic females
  - Noted positive response in microglia
  - Recent studies unable to confirm results
- X chromosome activation of normal allele
  - Critical: activate normal allele in all cells

Symptomatic Therapy

- Serotonin reuptake inhibitors
  - ameliorate anxiety
- NMDA receptor blocker: Memantine
  - reverse glutamate hyperexcitability
- IGF-1: full length and tri-peptide
  - downstream effect in BDNF cascade
- BDNF-mimetics: TrkB agonists
  - restore BDNF levels
- Read-through compounds: Stop mutations
  - produce full length MeCP2

Summation

- Remarkable progress from first recognition more than 50 years ago, the first widely read publication in 1983, and identifying the genetic basis in 1999.
- Basic and clinical research has flourished.
- Translational results suggest several line of potentially effective treatments.
- A number of clinical trials on-going with disease-modifying agents.
- Role of a ‘cure’ is being explored.

My First Friend with Rett Syndrome

Female Phenotypes With *MECP2* Mutations

- Rett syndrome
- Preserved speech variant
- Delayed onset variant
- Congenital or early onset seizure variant
- Autistic-like variant
- Angelman syndrome
- Mild learning disability
- Normal carriers

Male Phenotypes With *MECP2* Mutations

- Severe encephalopathy
- RTT with Klinefelter syndrome or somatic mosaicism
- X-Linked MR and progressive spasticity
- *MECP2* duplications

NHS Today

- Current enrollment = 1220 participants
  - ~40% enrolled at travel clinics
- Rett syndrome = 952
- Variant forms = 167

- *MECP2* positive, non-Rett = 101
  - Females = 52 (9 with *MECP2* duplications)
  - Males = 49 (29 with *MECP2* duplications)


Weight in Rett syndrome
Weight in Cm
0
10
20
30
40
50
60
70
80
0
2
4
6
8
10
12
14
16
18
20
Age in Years
Rett 98th
Rett 90th
Rett 75th
Rett 50th
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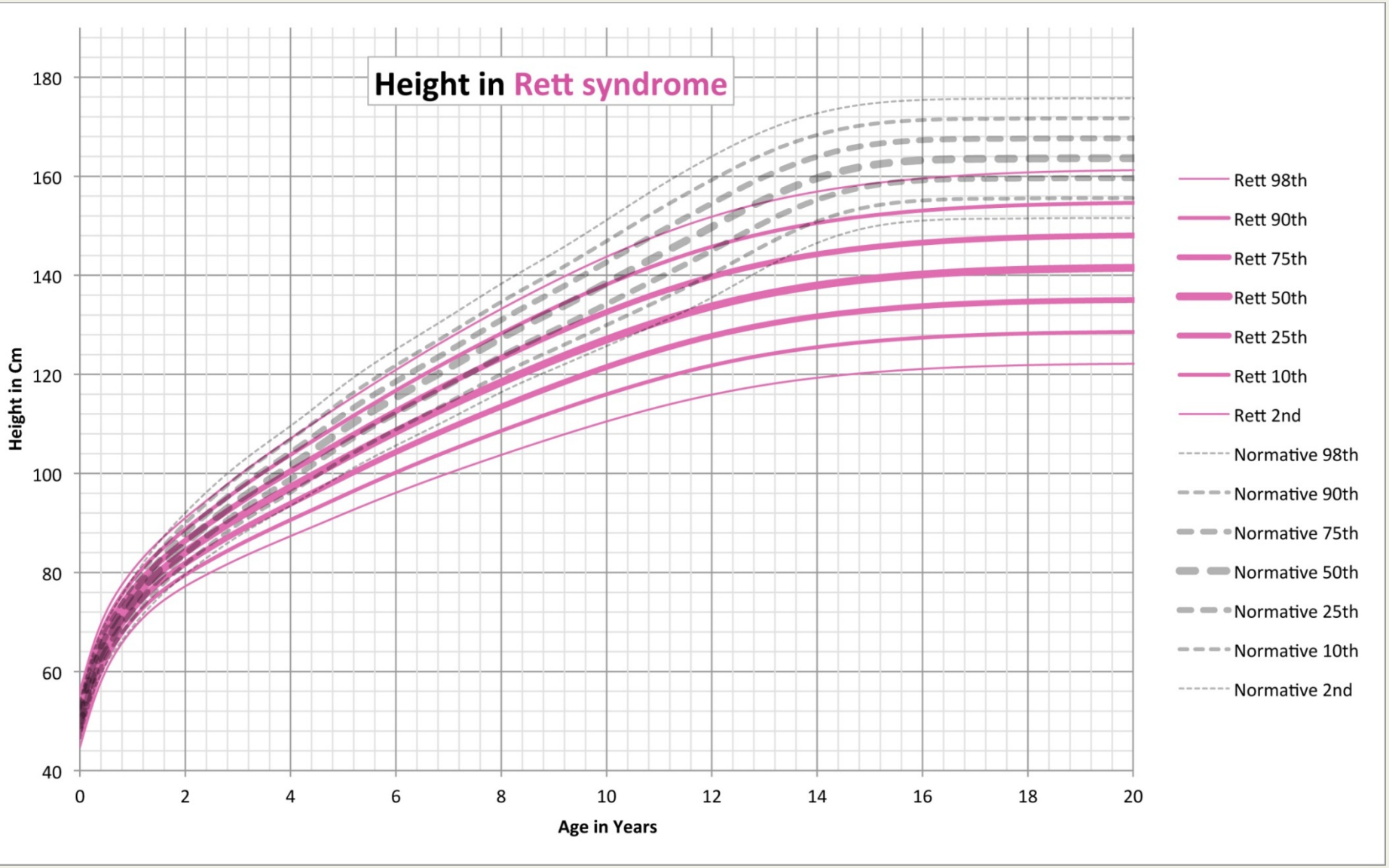
Height in Rett syndrome
Height in Cm
180
160
140
120
100
80
60
40
0
2
4
6
8
10
12
14
16
18
20
Age in Years
Rett 98th
Rett 90th
Rett 75th
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