



RETT SYNDROME 101

Ain't No Mountain High Enough

Alan K. Percy, MD
May 29, 2010




RETT SYNDROME: AN UNFINISHED STORY

Andreas Rett






**Bengt
Hagberg**

A teal decorative graphic consisting of a vertical bar and a triangular shape at the top left corner.

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



CLINICAL DIAGNOSIS



RETT SYNDROME

A NEURODEVELOPMENTAL DISORDER OF
YOUNG FEMALES CHARACTERIZED BY

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



RETT SYNDROME

CONSENSUS CRITERIA - 2010

- Regression followed by recovery or stabilization
- Main and exclusion criteria
 - Supportive criteria often present but not required
- Main criteria
 - Partial or complete loss of acquired purposeful hand skills
 - Partial or complete loss of acquired spoken language
 - Gait abnormalities: Impaired or absent
 - Stereotypic hand movements
- Exclusion criteria
 - Brain injury: trauma, metabolic disease, or infection
 - Abnormal psychomotor development in first 6 months



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



RETT SYNDROME

WHAT DO WE KNOW?

- Genetic disorder predominantly in females
- Incidence is 1:10,000 female births
- Variable clinical expression
- Variant forms account for 15-20%
- Pervasive growth problems
- Longevity may be significant
- Consistent neuropathology



***MECP2* AND RETT SYNDROME ?**

- >95% of classic Rett syndrome caused by *MECP2* mutations; ~70% in variant forms
- 8 mutations account for ~ 65% of those in Rett syndrome
- Deletion or insertions about 15-18%
- Rett syndrome is mainly sporadic: majority appear to be of paternal origin
- Familial Rett syndrome is <<1% of total



RETT SYNDROME AND *MECP2*

- Rett syndrome
 - a clinical diagnosis
 - NOT synonymous with *MECP2* mutations
 - Occurs WITH or WITHOUT *MECP2* mutations
 - *MECP2* mutations occur WITHOUT 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

The Infant

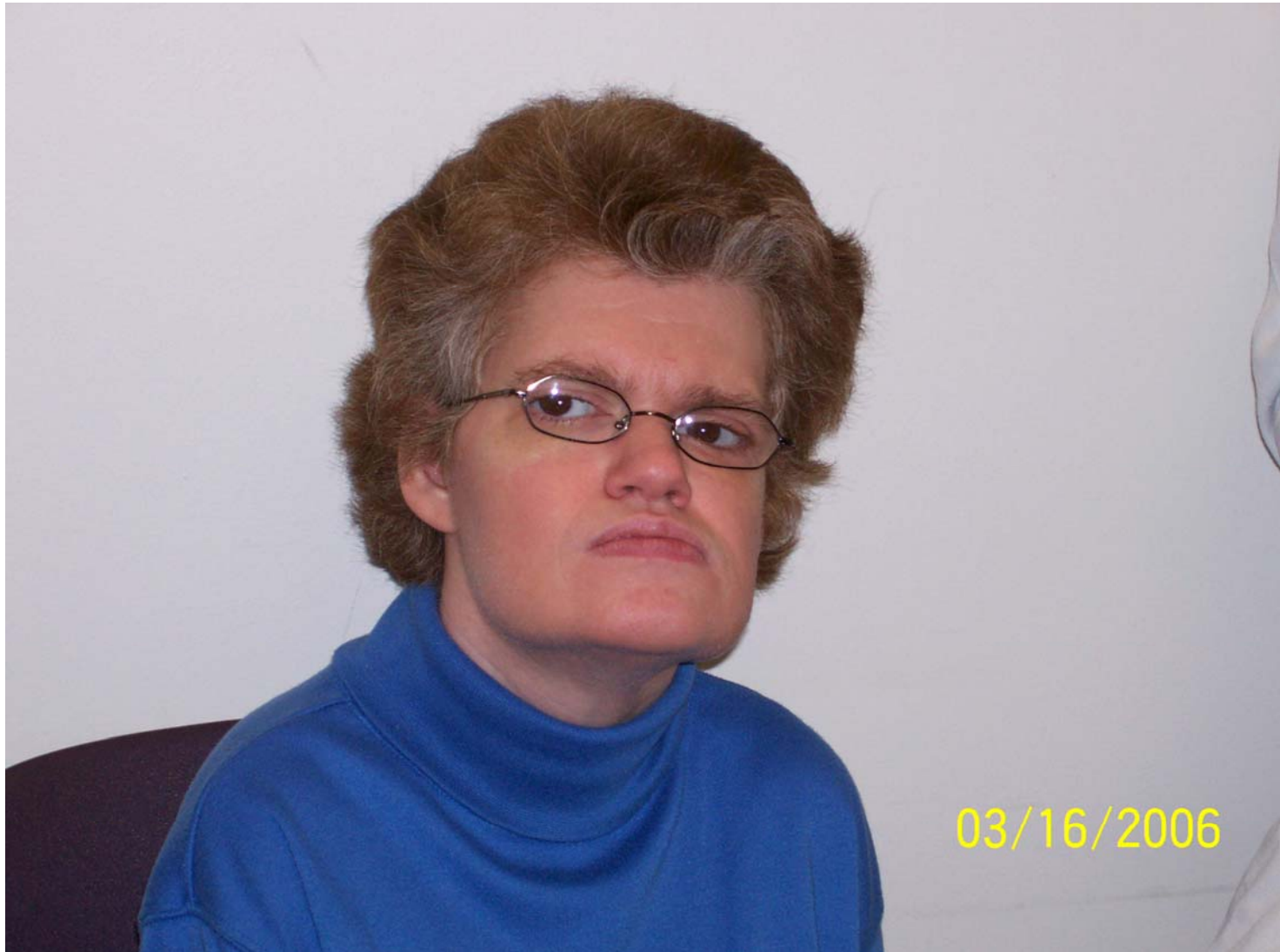
Non Rett, *MECP2*+



The Toddler



The Older Adult





Male Phenotypes With *MECP2* Mutations

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



Non Rett *MECP2*+ Males

X-Linked MR/Progressive Spasticity/NDD



Non Rett *MECP2*+ Males

Duplication



Family: *MECP2*+ Non-Rett Males and Rett Female





DOES MUTATION PREDICT OUTCOME?

- Some mutations are associated with “better outcome” but many factors involved
 - Type and position of mutation
 - X chromosome inactivation
 - Other genetic factors

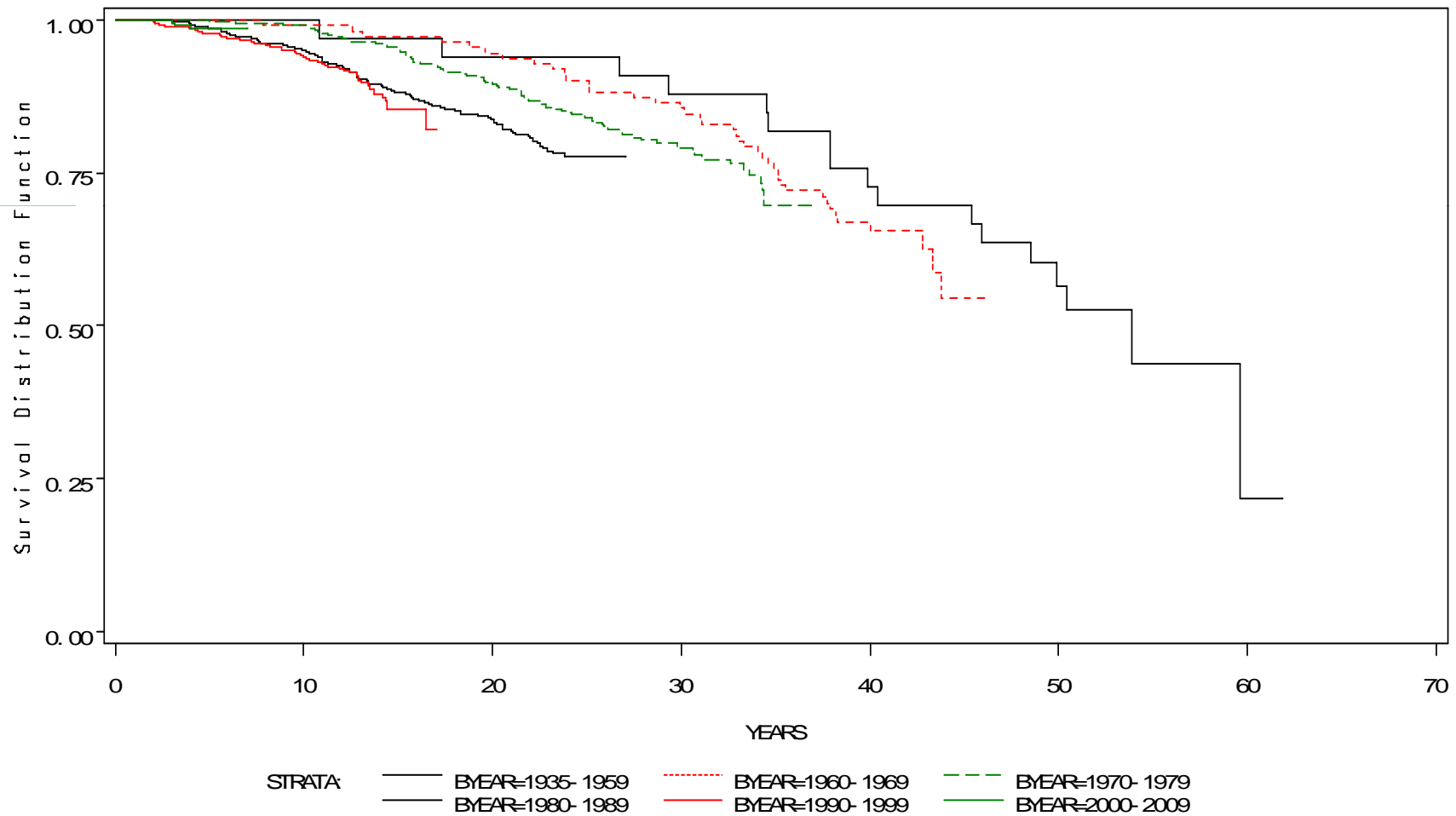


Medical Issues in Rett syndrome

- Longevity
- Growth and nutrition
- Epilepsy
- GI dysfunction
- Anxiety
- Scoliosis
- Breathing irregularities
- Sleep
- Cardiac conduction
- Sexual Maturation

RETT SYNDROME – SURVIVAL BY DATE OF BIRTH

RETT SYNDROME STUDY – DISTRIBUTION OF ALL CASES BY DECADE OF BIRTH AND SURVIVAL —





GROWTH

- Small stature is typical
- Deceleration of growth
 - Head circumference as early as 3 months
 - Median value at 2nd percentile by age 2 years
 - Weight as early as 8 months
 - Length as early as 12-14 months
- Hands and feet small
 - Feet relatively smaller than hands



AMBULATION

- 80% learn to walk
- About 25% lose this ability with regression
- Overall, ~ 55-60% remain ambulatory
 - Orthotic devices may be needed
- Great effort should be exerted to maintain ambulation
- Standing frames, walkers, or parallel bars should be used at home and school for those who do not walk



CARDIAC CONDUCTION SYSTEM

- Cardiac conduction may be immature
- Prolonged QT interval may be observed
- At diagnosis, an electrocardiogram (EKG) should be obtained; likely to be normal
- If abnormal, a cardiologist should be seen; medical treatment should be effective
- If abnormal, check other family members



AUTONOMIC NERVOUS SYSTEM

- Hands and feet tend to be cool to cold
- More likely in lower extremities; not only cold but red or purple discoloration involving much of lower extremity
- Thought to be due to increased threshold of sympathetic nervous system
- Does not appear to cause discomfort
- No specific treatment available



BRUXISM or TEETH GRINDING

- Occurs in almost all girls or women
- Described by Bengt Hagberg as the sound of slowly uncorking a bottle of wine
- Varies in frequency and intensity
- May increase with anxiety or excitement
- Efforts to reduce generally unrewarding
- Tend to diminish or disappear after school age



OTHER MOTOR SYSTEMS

- Hypotonia the rule during infancy
- Strength typically normal
- After puberty, motor activities may slow and muscle tone is often increased
- In addition to hand stereotypies, other movements may be seen
 - Tremor, myoclonus, or choreiform
- Dystonia may be prominent with age



RESEARCH PROGRESS



MOUSE MODELS

- Knock-out mouse: *Mecp2* deleted
- Knock-in mouse: Insertion of human *Mecp2* mutation; R168X, R255X, R270X, and A140V
 - Test bed for promising therapies



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 with estrogen analog, tamoxifen
 - Guy et al. *Science* 2007;315:1143-1147



OTHER ACTIVITIES AND RESOURCES



NATURAL HISTORY STUDY

- Goal: Enroll 1000 girls or women with RS
- 900 typical and 100 atypical
- Must meet consensus criteria or have *MECP2* mutation
- Purpose: expand phenotype-genotype studies and set stage for clinical trials
- Principal sites: Baylor, Children's Hospital Boston, Greenwood Genetic Center, and UAB



NATURAL HISTORY STUDY

- Current enrollment = 882 participants
- Rett syndrome = 684
- Variant forms = 117
- Awaiting data curation = 34
- *MECP2* positive, non-Rett = 56
 - Females = 30 (4 with *MECP2* duplications)
 - Males = 26 (13 with *MECP2* duplications)

Jane Lane

Rare
Disease
Project
Manager





IRSF Clinics

- Natural History Clinics
 - Chicago - Marie Kral
 - Oakland - Paige Nues
 - New Jersey - Leslie Greenfield
 - Florida - Henry Perez
- Emerging Clinics
 - St. Paul; Los Angeles; New York



DATABASE RESOURCES

- Rare Disease Network
 - Rarediseasesnetwork.epi.usf.edu
- RettBase: Dr. John Christodoulou
 - *MECP2* Mutation Repository
 - mecp2.chw.edu.au
- InterRett: Dr. Helen Leonard
 - Clinical information repository from parents and physicians
 - www.ichr.uwa.edu.au



That's all folks!!!