

RETT SYNDROME 101

Clinical Update and Recent Progress

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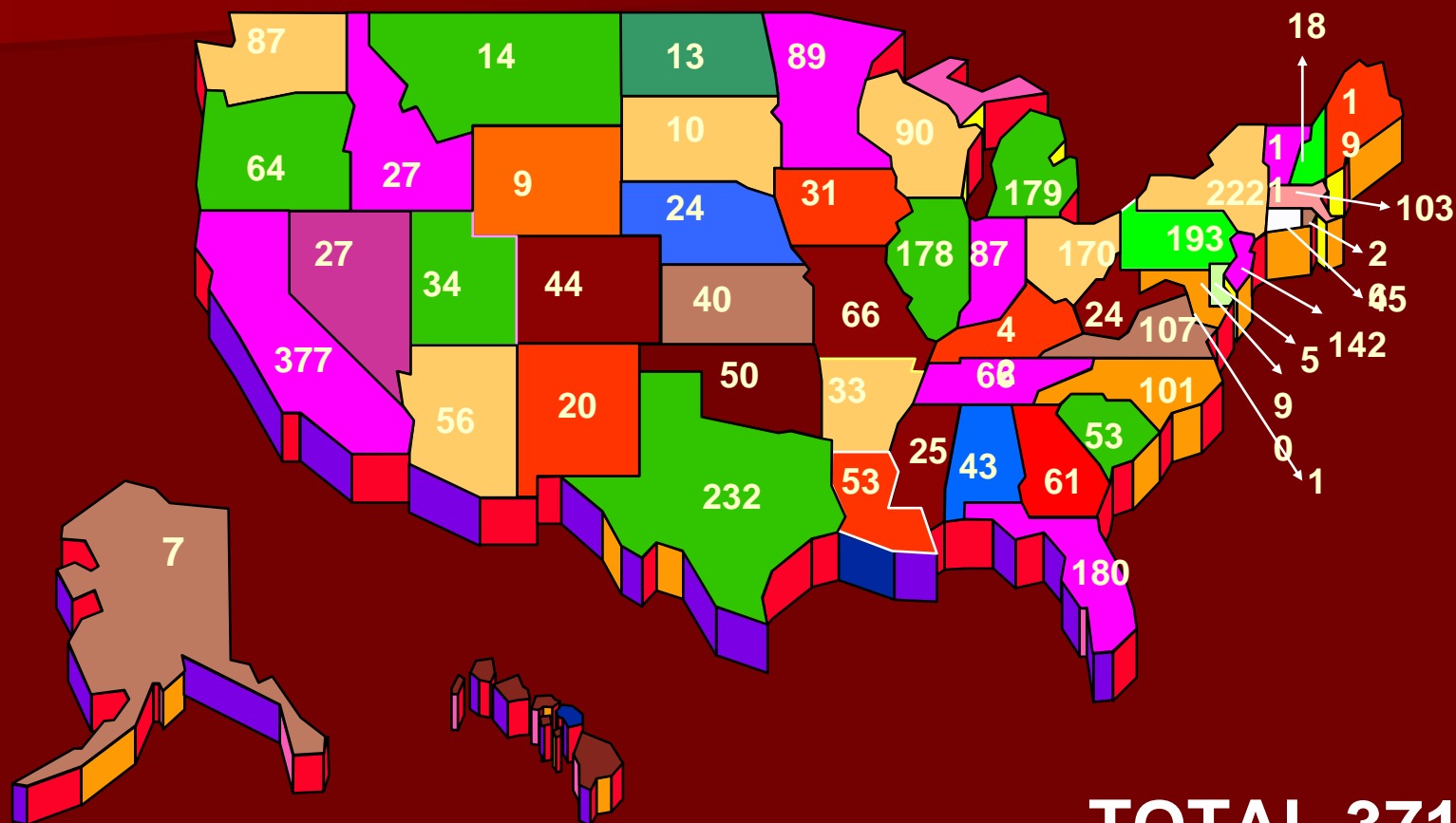
May 24, 2008



RETT SYNDROME: AN UNFINISHED STORY

Rett Syndrome in USA

IRSA Case Registry by State (May 2007)

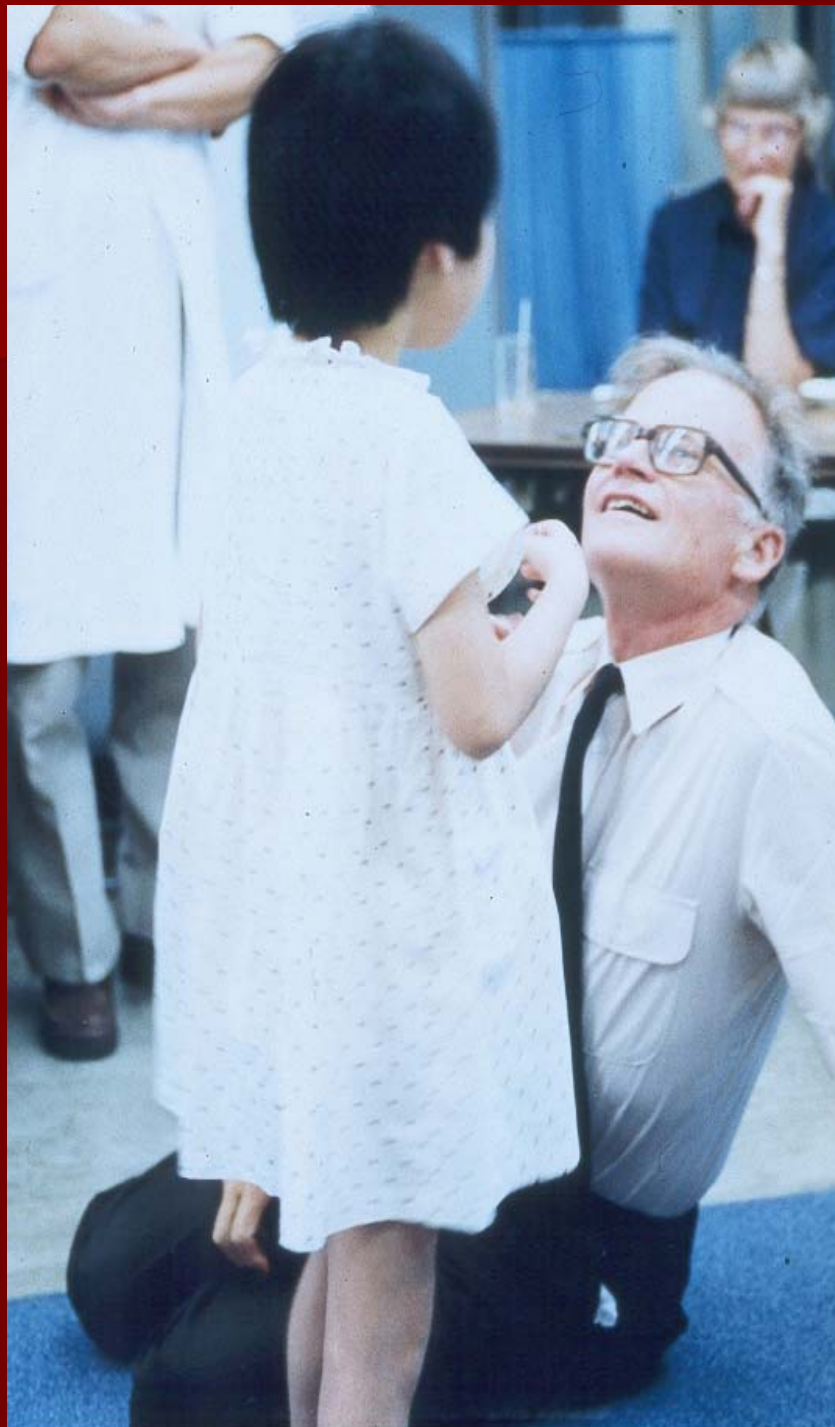


TOTAL 3712

Andreas Rett



Bengt Hagberg



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**

- **PROFOUND COGNITIVE IMPAIRMENT**
- **COMMUNICATION DYSFUNCTION**
- **STEREOTYPIC MOVEMENTS**
- **PERVASIVE GROWTH FAILURE**

RETT SYNDROME

WHAT DO WE KNOW?

- **GENETIC DISORDER AFFECTING FEMALES PREDOMINANTLY**
- **VARIABLE CLINICAL EXPRESSION**
- **PERVASIVE GROWTH FAILURE**
- **SIGNIFICANT LONGEVITY**
- **CONSISTENT NEUROPATHOLOGY**
- **MORE THAN 95% MEETING CONSENSUS CRITERIA HAVE MUTATIONS IN *MECP2***

RETT SYNDROME

CONSENSUS CRITERIA - 2001

- Normal at birth
- Apparently normal early development (may be delayed from birth)
- Postnatal deceleration of head growth in most
- Lack of achieved purposeful hand skills
- Psychomotor regression: Emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment
- Stereotypic movements: Hand washing/wringing/squeezing; Hand clapping/tapping/rubbing; Hand mouthing
- Gait dysfunction: Impaired (dyspraxic) or failing locomotion

VARIANT EXPRESSIONS

- Delayed onset or forme fruste
- Preserved speech
- Early-onset seizures
- Congenital

Diagnosis by variant consensus criteria

Variant forms may account for 15-20%

MECP2 mutations in approximately 55%

RETT SYNDROME

TEMPORAL PROFILE

- APPARENTLY NORMAL DEVELOPMENT
- ARREST OF DEVELOPMENTAL PROGRESS
- FRANK REGRESSION WITH POOR SOCIAL CONTACT AND FINGER SKILLS
- STABILIZATION: BETTER SOCIAL CONTACT AND EYE GAZE, BUT GRADUAL SLOWING OF MOTOR FUNCTIONS

RETT SYNDROME AND *MECP2*

- RETT SYNDROME: CLINICAL DIAGNOSIS
- RETT SYNDROME: NOT SYNONYMOUS WITH *MECP2* MUTATIONS
- RETT SYNDROME: SEEN WITH OR WITHOUT *MECP2* MUTATIONS
- *MECP2* MUTATIONS: SEEN WITHOUT RETT SYNDROME

Female Phenotypes With *MECP2* Mutations

- Rett Syndrome
- Preserved Speech Variant
- Delayed Onset Variant
- Congenital Onset Variant
- Early Onset Seizure Variant
- Autistic-like Variant
- Angelman Syndrome
- Mild Learning Disability
- Normal Carriers

Male Phenotypes With *MECP2* Mutations

- Severe Encephalopathy
- Rett/Klinefelter Syndrome
- X-Linked MR/Progressive Spasticity
- Somatic Mosaicism/NDD
- *MECP2* Duplications and X-linked MR

WHAT DO WE KNOW ABOUT *MECP2* AND RETT SYNDROME ?

- >95% OF CLASSIC RETT SYNDROME CAUSED BY MUTATIONS IN *MECP2*
- 8 MUTATIONS ACCOUNT FOR ~ 65% OF THOSE IN RETT SYNDROME
- SPORADIC RS: MAJORITY APPEAR TO BE OF PATERNAL ORIGIN
- FAMILIAL RS (<<1% of total): MAJORITY DUE TO LARGE DELETION

MEDICAL ISSUES

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

EPILEPSY

- Occurrence variable; from 20 to 80% in different reports
- From our experience with video-EEG monitoring as few as 25% of clinical behaviors require medication
- Seizure types: focal, generalized, or atypical absence
- Video-EEG monitoring may be required to differentiate from non-epileptic behaviors

SLEEP

- Often disrupted; frequent awakenings
- Sleep stages abnormal; REM sleep reduced
- Consider infection (otitis media), hunger, constipation, GE reflux
- Need sleep study if noisy breathing while asleep; rule out airway obstruction
- Need good sleep hygiene
- Consider medication when family quality of life adversely affected

SLEEP AIDS

- Antihistamines: limited effectiveness
- Melatonin may induce sleep, but not prevent arousals
- Trazodone and zolpidem may promote full night of sleep
- Chloral hydrate effective but unpalatable
 - Private pharmacy may formulate as suppository or capsule

BREATHING IRREGULARITIES

- Hyperventilation, breathholding, or both are common; may notice forced air expulsion
- Occur while awake
- Modified by hunger, agitation, other stress
- Typically reach maximum in school years
- Significant air swallowing may occur
- Effective treatment may be elusive

GASTROINTESTINAL ISSUES

- Chewing and swallowing often poor
- May choke on thin liquids
 - May require swallow study
- GE reflux typical; it may **Hurt ... a lot**
 - Often require anti-reflux medication
- Untreated may result in esophagitis
- Constipation also common; may require laxative; we recommend Miralax[®]
- Gall bladder dysfunction also possible

NUTRITION

- Assuring adequate nutrition critical
- Daily calorie-protein needs above average
- Enriched supplements may be required
- Daily vitamin good; supplements suffice
- In some instances, gastrostomy feeding necessary
- Use BMI (body mass index) to assess adequacy of nutrition

OSTEOPENIA

- Occurs in almost all girls or women
- Worse with poor calorie-protein intake
- Fractures much more common; may be unrecognized
 - Unexplained immobility of limb a red flag
- Regardless of age, use of oral calcium supplementation should be considered

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°
- ~10% will require surgery
 - 84% of parents felt quality of life improved

AMBULATION

- 80% learn to walk
- About 25% lose this ability with regression
- Overall, ~ 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

SEXUAL MATURATION

- Puberty acquired at ages similar to peers
 - Appropriate consideration essential to prevent unwarranted contact
- Menstrual cycles usually predictably regular after puberty well-established
- Menstrual management strategies

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, other family members should be checked

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

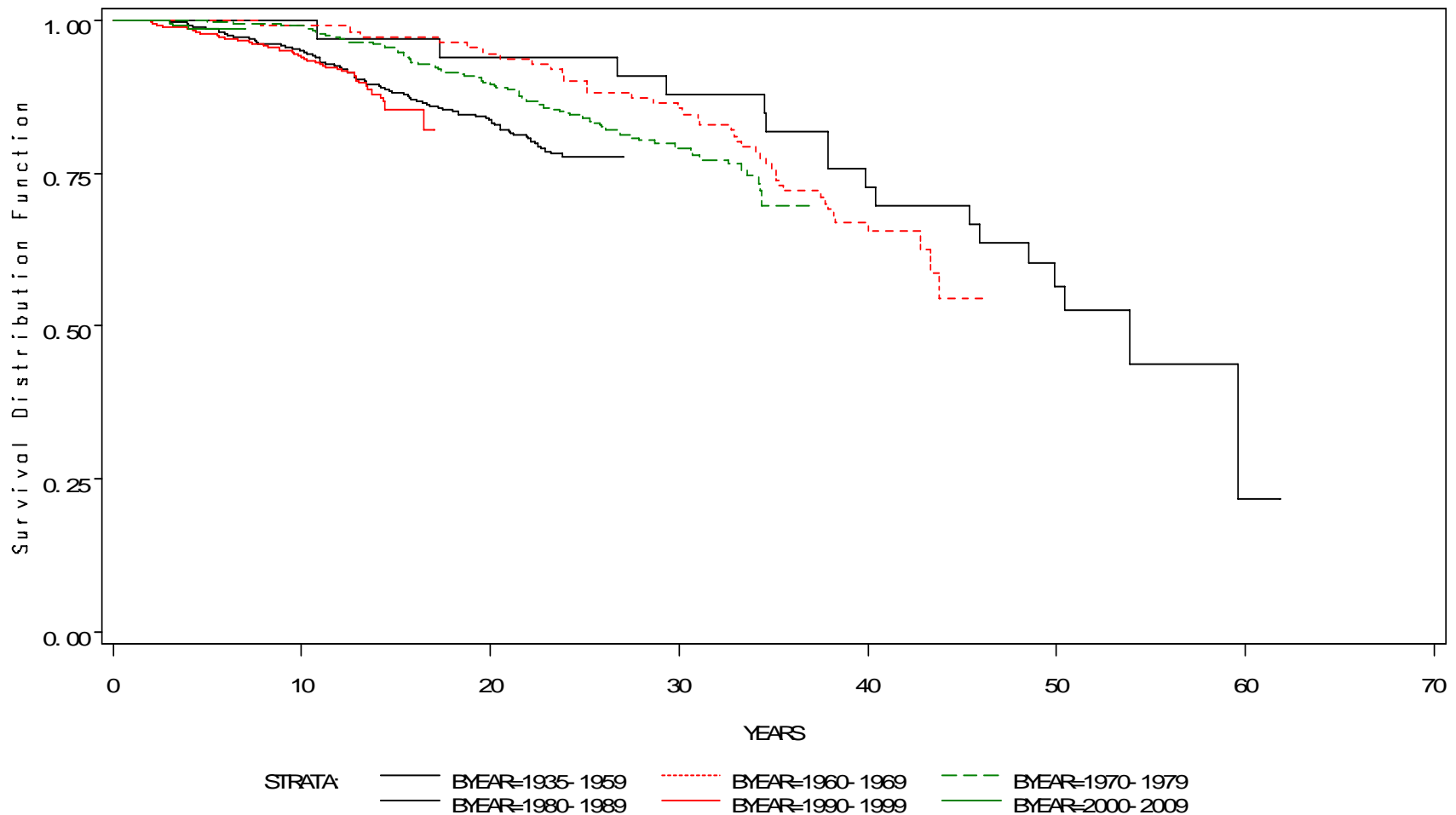
- Hypotonia the rule during infancy
- Strength typically normal
- After puberty, motor activities may slow and muscle tone is often increased
- In addition to hand stereotypies, other movements may be seen
 - Tremor, myoclonus, or choreiform
- Dystonia may be prominent with age

LONGEVITY IN RETT SYNDROME

- Normal survival until age 10
- > 50% survival to age 50 versus > 95% in all females and 27% in persons with profound motor and cognitive impairments

RETT SYNDROME – SURVIVAL BY DATE OF BIRTH

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



GENETICS AND *MECP2*

METHYL-CpG-BINDING PROTEIN 2

- One of family of methyl-binding proteins
- Highly expressed in brain
- Function in transcriptional silencing or regulation (control gene expression)
- Critical for developing and mature neurons

ABC's of DNA CODE

- DNA made of four molecules called nucleotides; each denoted in DNA code by its first letter
Adenosine Thymidine Guanosine Cytosine
- Proteins composed of amino acids
- Each amino acid's code is a combination of three nucleotides; most have > one code
 - Arginine code is CGA, CGC, CGG, or CGT;
 - TAA, TAG, and TGA are nonsense codes leading to no amino acid

MUTATION TYPES

- Missense – Code changed to different amino acid as R133C; MeCP2 complete
- Nonsense – DNA code change does not code for amino acid as R168X; MeCP2 incomplete
- Frameshift – insertion or deletion of DNA code; MeCP2 incomplete
- Large scale rearrangements – large part of DNA missing; MeCP2 incomplete

DOES MUTATION PREDICT OUTCOME?

- R133C, R294X, and R306C mutations and C-term truncations are associated with “better outcome”
 - Lower severity scores
 - Slower progression
 - Preserved speech variants

MOUSE MODELS

- Knock-out mouse: *Mecp2* deleted
- Knock-in mouse: Insertion of human mutation in *Mecp2*

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
 - Rapid re-expression in immature males resulted in death in 50%
 - Guy et al. *Science* 2007;315:1143-1147

KNOCK-IN MUTANT

- Enhanced anxiety and fear based on:
 - Elevated blood corticosterone levels
 - Elevated corticotropin-releasing hormone in hypothalamus, central nucleus of amygdala, and bed nucleus of stria terminalis
 - MeCP2 binds to *Crh* promoter methylated region
 - McGill et al. *PNAS* 2006;103:18267-18272

KNOCK-IN MUTANT

- Implications of *Crh* over-expression:
 - Anxiety plays central role in clinical RS
 - Amygdala has direct input into hypothalamus and brainstem autonomic nuclei correlating with clinical problems of respiration, GI function, and peripheral sympathetic NS
 - Suggests strategies for treatment

OTHER ACTIVITIES AND RESOURCES

NATURAL HISTORY STUDY

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

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

- Boston; St. Paul; Los Angeles

DATABASE RESOURCES

- 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

ON-SITE SURVEYS

- Chelsea Magee, a high school student from Montgomery, NY has a science project related to siblings. Please help her by completing her survey.
- Shaina Davis, a graduate student in nutrition at UAB, is conducting a survey on school nutrition programs. Please complete her survey as well
- Surveys are brief and take only a few minutes.

BIRMINGHAM EVENT – AUG 1, 2008

Southeastern Rett Syndrome Alliance



The TEAM Approach: Remembering Every Tender Touch

Sitting down on
the job, or...



...Rollin' with Curly





That's all folks!!!