Neurophysiological Correlates and Biomarkers: Rett Syndrome, *MECP2* Duplications, and Rett-Related Disorders Consortium (aka 5212)

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Disclosures

1. RO1 NS076577 (Benke)

NIH/NINDS

Molecular mechanisms linking early life seizures, autism and intellectual disability

Role: PI.

2. Questcor Pharmaceuticals (Benke)

Whole-exome sequencing and ACTH responsiveness in Infantile Spasms

Role: PI.

3. 1U10NS077277(Vollmer)

NIH/NINDS

Rocky Mountain Network for Neuroscience Clinical Studies (NeuroNext Clinical Site)

Role: Co-I.

4. U54 HD061222 (Percy)

NICHD

Rett syndrome, MECP2 Duplication Disorder, and Rett-related Disorders Natural History.

Role: Site Director, Co-I.

5. Rett Clinic at Children's Hospital Colorado (Benke)

Rocky Mountain Rett Association

Role: PI/Medical Director

6. CDKL5 Center of Excellence (Benke)

International Foundation for CDKL5 Research

Role: PI

7. Neuren: Study of trofinetide, also known as NNZ-2566, for females with Rett Syndrome

Role: site PI

Topics today

- Background of 5212
- Purpose of 5212
- Outline of 5212

Participating Institutions and Investigators: 5212

Consortium Study Chair: Alan K. Percy, MD, UAB

Principal Investigator and Study Lead Investigator:

Eric Marsh, MD, PhD, Children's Hospital of Philadelphia

Principal Investigator and Study Co-Lead Investigator:

Tim Benke, MD, Ph, University of Colorado

Principal Investigator: Mustafa Sahin, MD, PhD, Boston Children's Hospital

Principal Investigator: Sarika Peters, PhD, Vanderbilt University

Principal Investigator: Alexander Paciorkowski, MD, University of Rochester

Principal Investigator: Steven Kaminsky, PhD, Rettsyndrome.org

Data Management and Coordinating Center Principal Investigator:

Jeffrey Krischer, PhD, University of South Florida

National Institutes of Health:

NICHD:

Program Officer: Melissa Parisi, MD, PhD

Project Scientist: Danuta Krotoski, PhD

NINDS:

Program Officer: Laura Mamounas, PhD

Neurophysiology Consultants:

Charles A. Nelson, PhD, Boston Children's Hospital

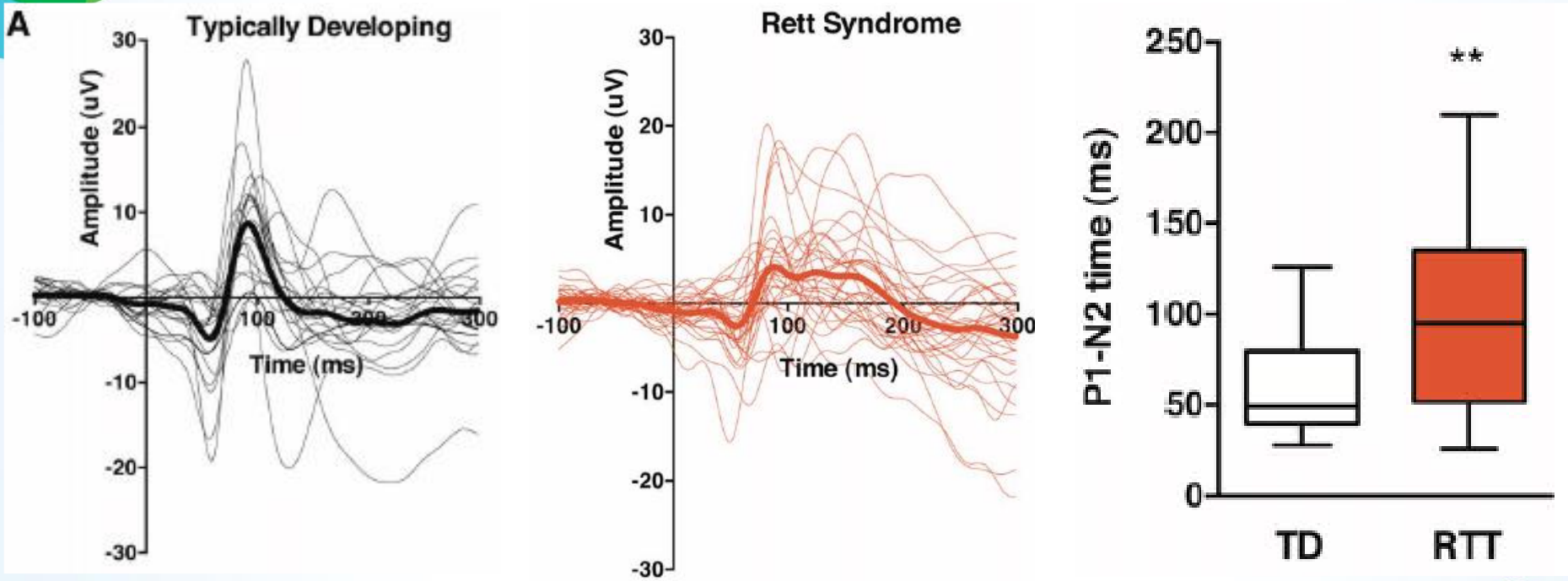
Michela Fagiolini, PhD, Boston Children's Hospital

Timothy P. Roberts, PhD, Children's Hospital of Philadelphia

Background

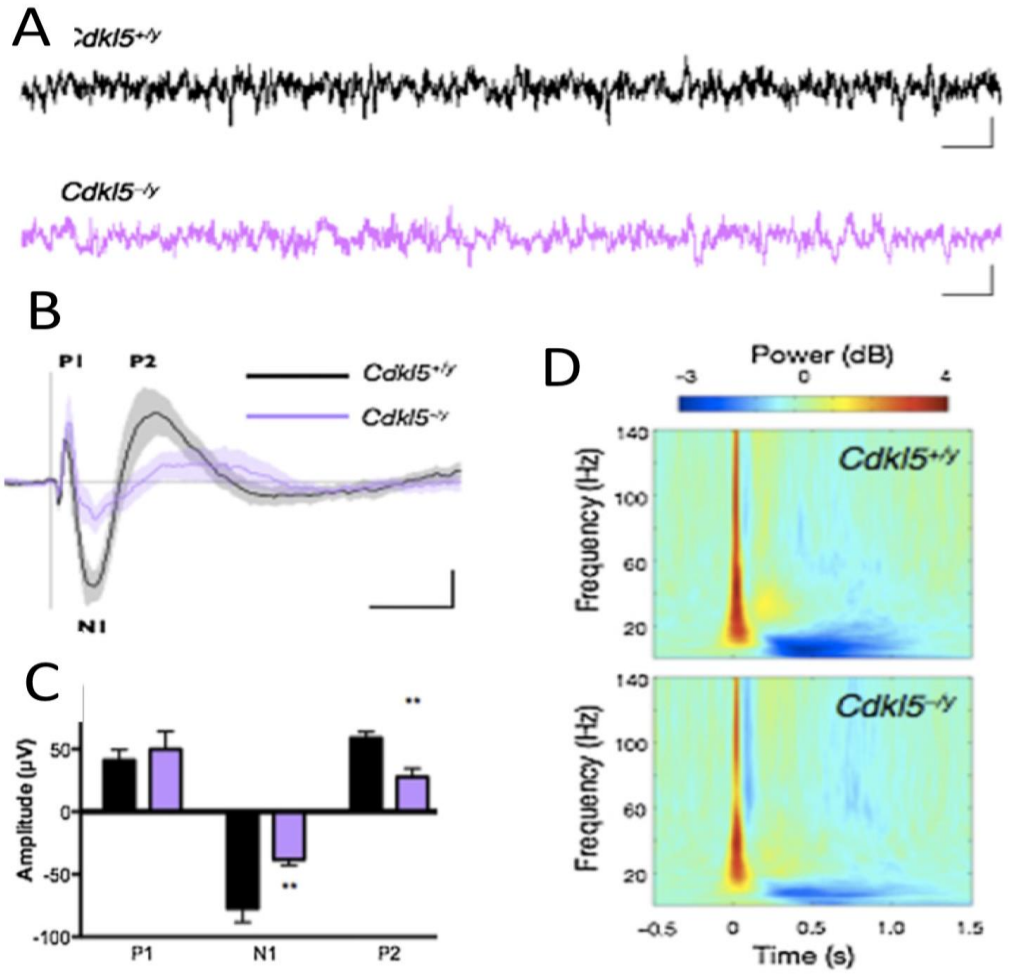
Multiple lines of evidence for synaptic pathophysiology resulting in network dysfunction in animal and humans with Rett and Rett-related disorders

Background



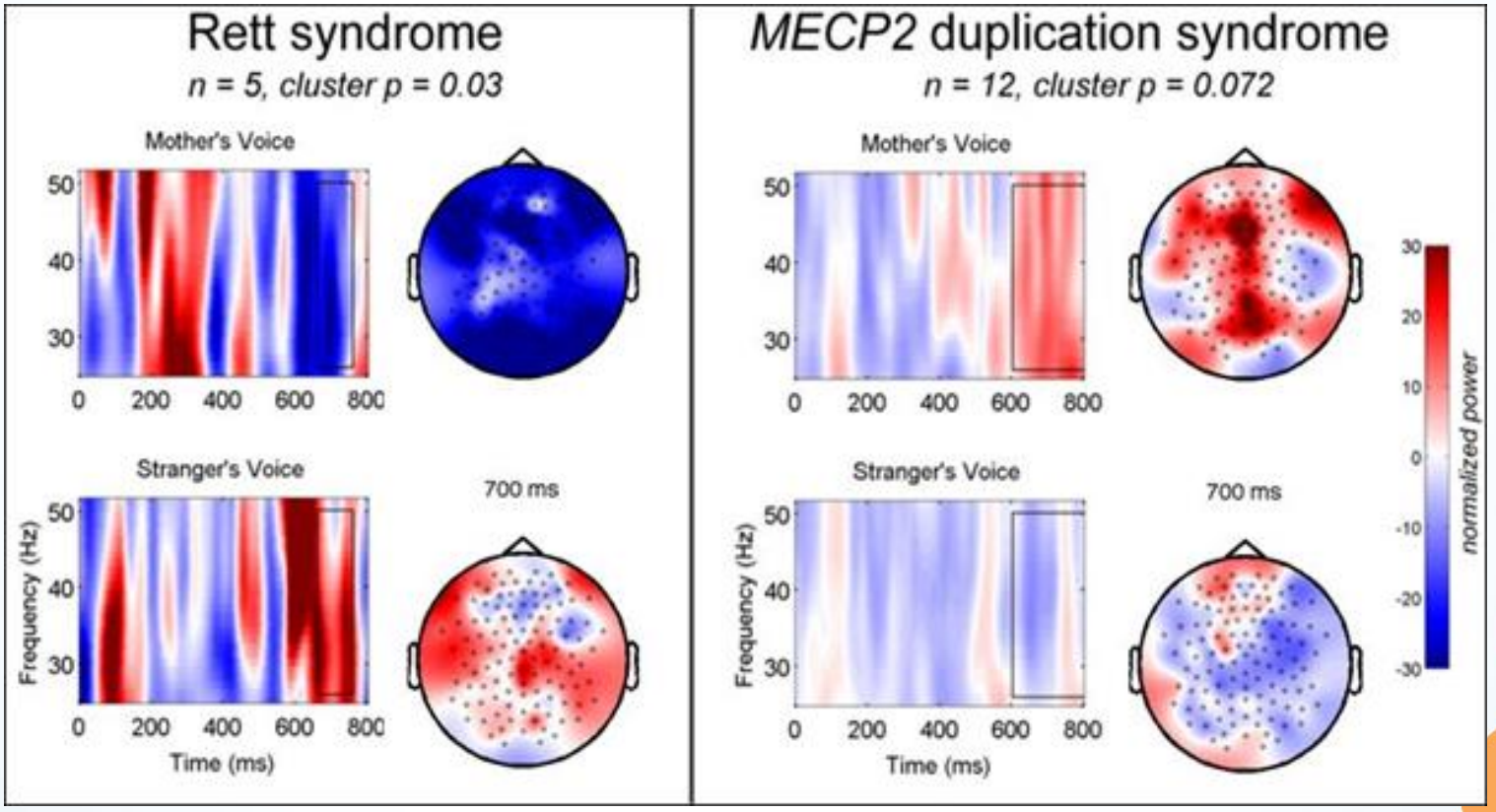
Abnormal VEP in RTT. *The red graph shows reductions in VEP (N1-P1) amplitude in RTT while the right graph depicts increases in latency in RTT, in this case P1-N2 time.* LeBlanc JJ, DeGregorio G, Centofante E, Vogel-Farley VK, Barnes K, Kaufmann WE, Fagiolini M, Nelson CA (2015) Visual evoked potentials detect cortical processing deficits in Rett syndrome. Ann Neurol 78: 775-786.

Background



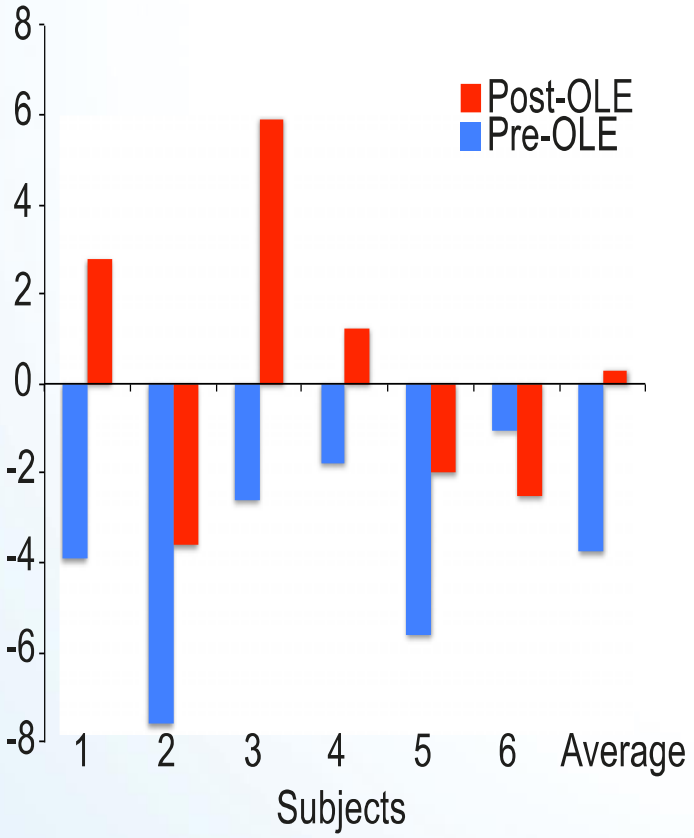
Cortical physiology of Cdkl5 mice. *A. EEG from Cdkl5 ko and wt animals. B and C. Raw AEP wave form and quantification of AEP amplitude. D. Gamma band frequency is calculated and different between genotypes.* Wang IT, Allen M, Goffin D, Zhu X, Fairless AH, Brodkin ES, Siegel SJ, Marsh ED, Blendy JA, Zhou Z (2012) Loss of CDKL5 disrupts kinome profile and event-related potentials leading to autistic-like phenotypes in mice. Proc Natl Acad Sci USA 109: 21516-21521.

Background



Grand average time-frequency representations and topographies from the preliminary data auditory EEG paradigm. *Induced gamma power differed for familiar and unfamiliar voices in the RTT group (left) and the MECP2 Dup group (right), showing opposite trends.* Peters SU, Gordon RL, Key AP (2015) Induced gamma oscillations differentiate familiar and novel voices in children with MECP2 duplication and Rett syndromes. J Child Neurol 30: 145-152.

Background



Right-sided frontal alpha band EEG asymmetry is common in RTT and shows a trend toward reversal with IGF-1 treatment. *Six subjects evaluated before IGF-1 treatment (Pre-OLE) demonstrated R > L asymmetry. Although the degree of asymmetry was variable after treatment (Post-OLE), five of the six showed a decrease in the asymmetry index and in three there was a reversal. A paired-samples t test revealed significant group differences Pre- and Post-OLE.* Khwaja OS, et al (2014) Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human-IGF1) for the treatment of Rett syndrome. Proc Natl Acad Sci U S A 111: 4596-4601.

Purpose of 5212

Gap addressed:

The relationship(s) between neurophysiological findings:

- Visual evoked potentials
- Auditory evoked potentials
- EEG

and

- disease evolution,
- severity and
- specific clinical features

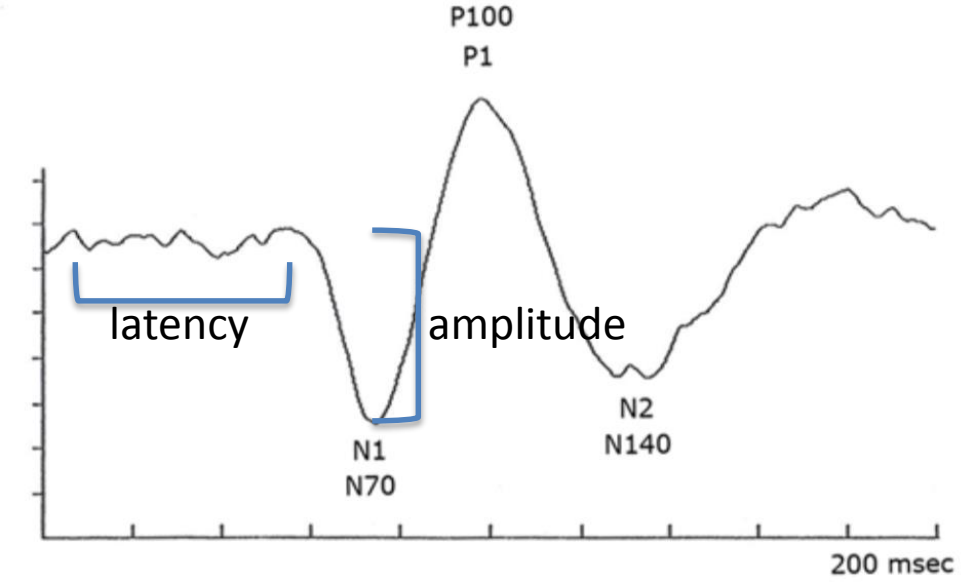
in Rett and Rett-related disorders is unknown.

Purpose of 5212

- Advance understanding of the neurophysiological features of:
  - Rett syndrome (RTT)
  - MECP2 Duplication (MECP2 Dup)
  - CDKL5
  - FOXG1
- Gain insight into disease pathogenesis
- Identify biomarkers of disease evolution and severity
- Intertwined to the core study Natural History of Rett Syndrome and Related Disorders (RTT5211)
- Serve as basis of future translational investigations
  - Refinement of biomarkers & development of outcome measures

Primary Outcome measures

1. Auditory Evoked Potential (AEP) latency (ms)
2. Auditory Evoked Potential amplitude of P1, P2 and N1 peaks (uV)
3. Visual Evoked Potential P1-N2 time (ms)
4. Visual Evoked Potential (VEP) amplitude of N1-P1 (uV)



Secondary Outcome Measures

1. AEP: Change in power of gamma band activity (delta dB at 30-70Hz band between pre-stimulus and post-stimulus).
2. Frontal alpha band activity asymmetry index
3. Other AEP and VEP parameters.

Enrollment: Inclusion criteria

Females and males of all ages must have:

Testing for *MECP2, CDKL5*, and /or *FOXG1* genetic changes.

AND must meet these requirements:

Gene positive for a sequence change, duplication or deletion in one of these 3 genes.

AND

Those with Rett syndrome phenotype should meet consensus criteria for typical or atypical Rett syndrome.

AND

Enrolled in RTT5211.

Enrollment: Rett syndrome

60 female subjects evaluated up to 3 times (annual evaluations)

- 20 in stage 2 (active regression) or <12 months since last skill loss (~2-5 y.o.)
- 20 children in stage 3 (post-regression, ≥12 months since last skill loss; ~5-12 y.o.)
- 20 adolescents/adults (all in stage 3, post-regression; >12 y.o.)

The stage/age groups above will attempt to distribute genetic changes type/severity and clinical severity as follows:

30 with milder *MECP2* changes (R133C, R294X, R306C, C-terminal deletions)

30 with more severe *MECP2* changes (R106W, T158M, R168X, R255X, R270X, large exons 3+4 deletions)

30 with more severe clinical profile (≥22 CSS*)

30 with less severe clinical profile (<22 CSS*)

**Median CSS score from the Natural History Study (Protocol RTT5201)*

Enrollment: MeCP2 duplication

18 male subjects evaluated three times (annual evaluation)

- 9 in early childhood, prior to onset of epilepsy (~2-10 y.o.)
- 9 adolescents/adults, post onset of epilepsy (>10 y.o.)

Enrollment: CDKL5 syndrome

CDKL5 Disorder:

18 female subjects evaluated three times (annual evaluation)

- 6 in infancy, during the period associated with infantile spasms (~2mo-2 y.o.)
- 6 in childhood, after the cessartion of infantile spasms (~2-12 y.o.)
- 6 adolescents/adults (>12 y.o.)

Enrollment: FOXG1 syndrome

FOXG1:

14 male/female subjects evaluated three times (annual evaluation)

- 6 in infancy, during the period associated with infantile spasms (~2mo-2 y.o.)
- 5 in childhood, after the cessation of infantile spasms (~2-12 y.o.)
- 3 adolescents/adults (>12 y.o.)

Enrollment: Controls

30 females evaluated up to 3 times (annual evaluation)

- 10 females in early childhood (~2-5 y.o.)
- 10 females in late childhood (~5-12 y.o.)
- 10 female adolescents/adults (>12 y.o.)

30 males evaluated up to 3 times (annual evaluation)

- 10 males in early childhood (~2-5 y.o.)
- 10 males in late childhood (~5-12 y.o.)
- 10 male adolescents/adults (>12 y.o.)

Timeline

NIH approval of 5212 protocol: 5/13/2016

Local IRB approvals: submitted/in-process. Due 9/1/2016

Validation of local data/technology

- Human “phantoms” (Marsh and Roberts)
- Visits to establish cross-site data parity: 9/2016

Initial visits: September 2016 (year 1)

- 2nd visit/Year 2: September 2017
- 3rd visit/Year 3: September 2018

Challenges and Limitations

Technical:

- Establishing uniformity across sites
- Translating protocol into clinical practice

EEG:

- Not a surrogate for epilepsy assessment
  - limited sample (no sleep or other behaviors)
  - EEG “e-bank” needed
- Frequency analysis:
  - Alternative behavioral correlates (other than AEP/VEP)

Patient numbers/statistical power

- Phenotypic & genotypic variability
- RTT versus Rett-related

Special Thanks!!!

Tristen Dinkel
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Rett Clinic Team

Our patients and families

NHS-Natural History Study:

Eric Marsh, Alan Percy, Jeff Neul, Alex Paciorkowski, Laura Mamounas, Tim Roberts, Chuck Nelson, Sar Peters, Michela Fagiolini, Walter Kaufmann, etc

IFCR COE: Heather Olson, Elia Pestana-Knight, Sumit Parikh

Rocky Mountain Rett Association

Ponzio Family Chair in Neuroscience Research

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RETTSYNDROME.ORG • EAGLEWOOD RESORT, ILLINOIS • 2016
RESEARCH SYMPOSIUM (JUNE 22-24)

Rettsyndrome.org

The 4Q1 Project CURE MECP2 DUPLICATION SYNDROME

International Foundation For CDKL5 RESEARCH

INTERNATIONAL FOXG1 FOUNDATION


questions