

Natural History Study

Presented by Alan K. Percy, MD

University of Alabama at Birmingham



Natural History Study I, USA

- Disorders: RTT, Angelman, And Prader-Willi
- Goal: Enroll 1000 girls or women with RTT
- Meet clinical criteria or have *MECP2* mutation
- Purpose: expand phenotype-genotype studies and set stage for clinical trials
- Principal sites: Baylor, Greenwood Genetic Center, and UAB
- Travel Clinics: Oakland, Chicago, New Brunswick, Florida (Miami and Tampa)
- DMCC: Contact Registry
 - rarediseasesnetwork.epi.usf.edu

Natural History Study II, USA

- Disorders: RTT, Angelman, and Prader-Willi
- Continuation grant funded in 2009
- RTT included Classic and Variant RTT, MECP2 Duplication Disorder, and *MECP2* positive, non-Rett individuals
- Enrollment goal now 1350
- Principal sites: Children's Hospital Boston, Baylor, Greenwood Genetic Center, and UAB
- IRSF provides support for Rett travel clinics

Natural History Study

- Current enrollment = 1191 participants
 - ~40% enrolled at travel clinics
- Rett syndrome = 927
- Variant forms = 166
- *MECP2* positive, non-Rett = 98
 - Females = 51 (8 with *MECP2* duplications)
 - Males = 47 (27 with *MECP2* duplications)

Lessons learned!

- >95% of classic RTT have *MECP2* mutations
- 8 mutations account for ~ 60%
- Deletion or insertions about 15-18%
- Incidence: ~1:10,000 female births
- Mainly sporadic
- Familial Rett syndrome is <<1%
- Variant forms account for ~15%
 - 75% with *MECP2* mutations
- And much more

NHS 1 and 2 Team

- **Baylor College of Medicine**

- Daniel Glaze
- Kay Motil
- Jeff Neul (UCSD)
- Judy Barrish

- **Greenwood Genetic Center**

- Steve Skinner
- Fran Annese
- Lauren Baggett

- **NIH: ORDR/NICHD**

- **CHB**

- Walter Kaufmann
- Daniel Tarquinio (Emory)
- Katherine Barnes
- Heather O'Leary

- **UAB**

- Alan Percy
- Jane Lane
- Suzie Geerts
- Jerry Childers

- **Girls and women with RTT and their families**

Natural History Study 3, USA

- Now only RTT, MECP2 Duplication, CDKL5, FOXP1: Refunded through 2019
- Longitudinal and neurobehavioral assessments related to core features
- Biomarker and clinical outcome measures
- Evaluate neurophysiologic and neuro-imaging correlates
- Develop specific behavioral outcome
- Metabolomics approach

NHS 3 Team

- Baylor College of Medicine
- Boston Children's Hospital (Harvard)
- Children's Hospital of Philadelphia (Univ. of Penn)
- Greenwood Genetic Center
- Rush Medical Center (Chicago)
- University of Alabama at Birmingham (**lead site**)
- University of California San Diego
- University of California San Francisco (Oakland)
- University of Colorado
- University of Rochester
- Vanderbilt University

Rett Clinics in North America

Presented by: Paige Nues, Rettsyndrome.org



*Kathy Hunter, Katie Nues, Paige Nues
One Handful of Clinics in the United States, March 2004*

Rett Clinics in North America: 2015

- **Countries:** United States and Canada
- **Rett Clinics Total: 22**
 - **United States: 19**
 - 11 comprise the NIH-funded Natural History Study Consortium for Rett syndrome, MECP2 Duplications disorder, CDKL5 disorder, and FOXP1 syndrome
 - **Canada: 3**
- **All clinics are connected to a hospital or medical university**
- **The majority are at a Children's Hospital**

* **RED** indicates a clinic designated as Natural History Study Consortium Site



For details: www.rettsyndrome.org/our-role-and-impact/blog

Rett Clinics in North America

	USA-State	Institute	Medical Director
1	Alabama	Birmingham, Civitan International Research Center	Alan K. Percy, MD
2	California	Children's Hospital Los Angeles	Larry Yin, MD
3	California	University of California San Diego Rady Children's Hospital	Jeffrey L. Neul, MD PhD
4	California	University of California San Francisco Benioff Oakland Children's Hospital	Mary Jones, MD
5	Colorado	Children's Hospital Colorado	Timothy A. Benke, MD PhD
6	Florida	University of Florida Jacksonville Pediatric Multispecialty Center	Anthony Perszyk, MD
7	Illinois	Rush University	Peter Heydemann, MD
8	Maryland	Kennedy Krieger Institute, John's Hopkins School of Medicine	SakkuBai Naidu, MD Constance Smith-Hicks, MD
9	Massachusetts	Harvard Medical School Children's Hospital Boston	Walter Kaufmann, MD
10	Minnesota	Gillette Children's Specialty Healthcare	Tim Feyma, MD Art Beisang, MD
11	Missouri	St. Louis Children's Washington University	Dr. Robin Ryther (Rett) Dr. Judy Weisenberg (CDKL5)

Rett Clinics in North America

	USA-State	Institute	Medical Director
12	New York	Children's Hospital at Montefiore (CHAM) / Albert Einstein Medical School	Aleksandra Djukic, MD
13	New York	University of Rochester Medical Center	Alex R. Paciorkowski, MD, FACMG
14	Ohio	Cincinnati Children's Hospital Medical Center	Shannon Standridge, MD Patty Manning, MD
15	Oregon	Oregon Health and Sciences University	Mario Petersen, MD
16	Pennsylvania	University of Pennsylvania Children's Hospital of Philadelphia	Eric D. Marsh, MD PhD
17	South Carolina	Greenwood Genetics Center	Steve Skinner, MD
18	Tennessee	Vanderbilt University Medical Center	Sarika Peters, PhD
19	Texas	Baylor College of Medicine Texas Children's Hospital	Daniel Glaze, MD
		* Natural History Study Consortium sites	
	CANADA- Province	Institute	Medical Director
20	Ontario, London	South Western Ontario Rett Syndrome Clinic	Dr. Victoria Siu
21	Ontario, Ottawa	Children's Hospital of Eastern Ontario Rett Syndrome Clinic	Dr Peter Humphreys
22	Ontario, Toronto	Holland Bloorview Kids Rehabilitation Hospital, Hospital for Sick Children (SickKids)	Dr. Melissa Carter

Rett Clinics in North America

- How many girls, boys and adults are seen each year?
 - Approx 2,234 combined
 - Example large clinic: 500+ regular patients (4 clinics per week)
 - Example smaller clinic: 19 regular patients (1 clinic every 3 months)
- Where and how is the diagnosis carried out?
 - Primarily by the local neurologist or geneticist
 - Rett Clinics see families primarily post-diagnosis, may also schedule to confirm clinical diagnosis, Atypical RTT, and sometimes Undiagnose

Rett Clinics in North America

- The specialists are in total:
 - Anesthesia
 - Behavioral Psychology and Developmental Pediatrics
 - **Cardiology,**
 - **Communication (SLP, AAC, AT),**
 - Dentistry
 - Endocrinology (bone health)
 - **Gastroenterology,**
 - Gynecology
 - **Medical genetics and genetic counselling,**
 - **Neurology,**
 - **Nurse Case Management,**
 - **Nutrition, swallow therapy,**
 - Ophthalmology
 - **Orthopedic surgery,**
 - Paediatrics,
 - Palliative care (pain management)
 - **Physical medicine and rehabilitation (PT, OT, Music, Seating, Equipment),**
 - Pulmonology,
 - Social Services, parent volunteer family support
 - Transitional Care Physician
- Each clinic capacity varies for specialists, in **BOLD** are the most common

Rett Clinics in North America

- What are the clinical exams carried out:
 - Behavioural assessment,
 - Blood panels,
 - Cardiology, autonomic function monitoring,
 - Communication,
 - EEG, epilepsy monitoring,
 - Gait analysis, motor function,
 - GI, nutrition and swallowing,
 - Osteodensitometry,
 - Scoliosis, hip dysplasia,
 - Sleep monitoring,
- Each clinic varies in what standard exams are carried out at a regular clinic visit, referrals always made as needed

Rett Clinics in North America

- All have the ability to connect to a research lab and have a PCRC (Pediatric Clinical Research Center) for support. All have research goals.
 - Only a handful are doing both clinical and animal model research
 - Approximately ½ are currently conducting research such as Clinical Trials, Clinical Research, Natural History Data Collection, or Outcome Measure Development Tools
- Almost all clinics engage in:
 - Multi-Disciplinary Care
 - Health Management
 - Community Education
 - Advocacy: patients and families
- The clinics are financed in a variety of ways:
 - Fee based services, billed to insurance
 - Rett foundation research grants
 - NIH research grants
 - Industry research support
 - Donations: community, private, local Rett organizations

Role of Rettsyndrome.org

- Rettsyndrome.org has made it a priority to support a collaborative NETWORK of Clinics.
- Parents struggle watching their children struggle; not knowing what to do, they turn to our foundation, listservs, the Rett Syndrome Handbook, and social media for advice. These resources are all wonderful, but do have their limitations.
- Local physicians unfamiliar with Rett syndrome also struggle; they too turn to us for information and insight. We often refer them to our Rett experts for clinician-to-clinician consultation.
- Our strategy to build bridges across specialty centers was initiated in 2004, gained traction with our funding of the Natural History Study travel sites, and accelerated further in 2009 with the organization of regular clinic-inclusive conference calls.
- We started by bringing a handful of Rett Center medical directors in the U.S. together for “deep dives” on specific symptoms or issues that were raised again and again by the parents supported by Rettsyndrome.org
- By early 2015, we will help inspire the development, growth and networking of 22 Rett specialty centers in North America, all passionately supporting our children and rapidly spreading the news that care and cure are linked hand in hand.
- Our commitment and dedication mean that these NETWORKED centers will grow, conference calls will continue, and meetings will convene.
- Better treatments, interventions and a cure will happen because when you bring a group of passionate people together who care about one thing. the health of our children, amazing things happen.