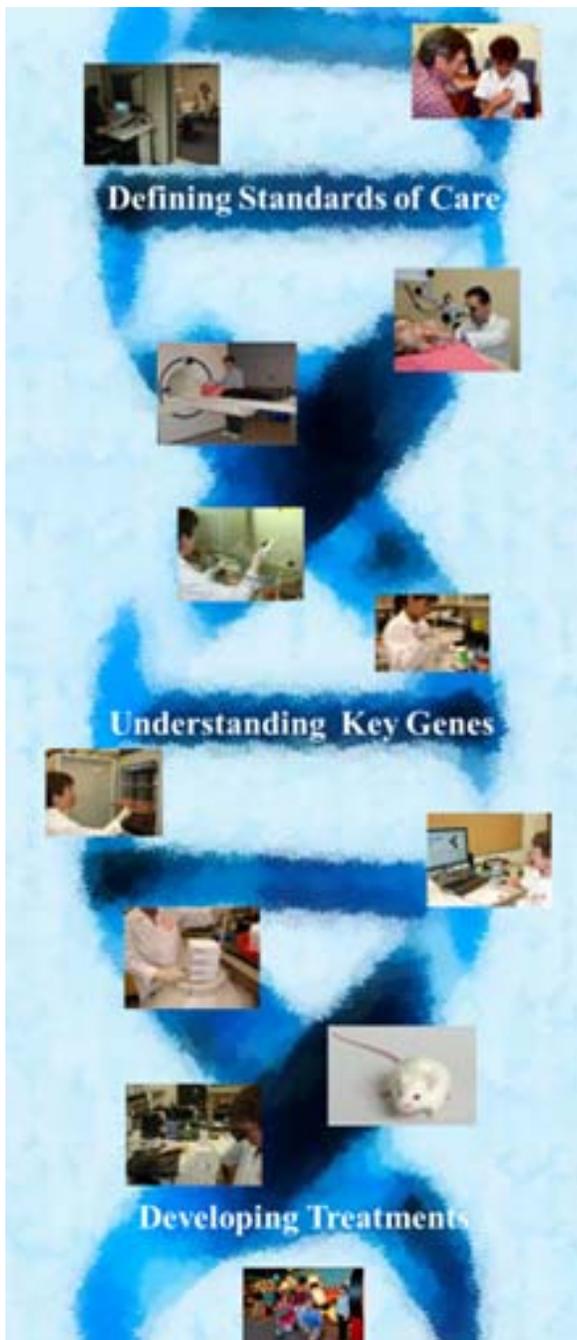


# The Chromosome 18 Clinical Research Center Annual Report

**Academic Year 2017/2018**

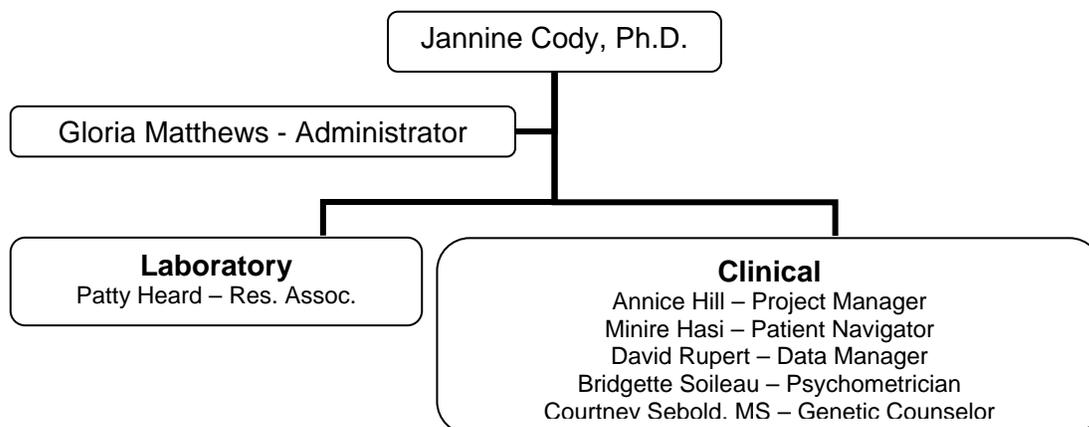
**Jannine D. Cody, Ph.D.**



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# 1. Activities and Changes during FY 2017

## Organizational Chart (as of 08/01/18)



### Volunteer Clinical Investigators

Medical Director  
Bioinformatics  
Psychiatry  
Neuropsychology  
Child Neurology  
Endocrinology  
MRI

ENT  
Ophthalmology  
Physical Therapy  
Gait Laboratory  
Speech Therapy  
Allergy / Immunology  
Sleep medicine  
Bone Health  
Platelet Function

Daniel E. Hale, MD  
Jonathan Gelfond, MD, PhD  
Catherine Larson, MD  
Louise O'Donnell, PhD  
Sid Atkinson, MD  
Daniel Hale, MD  
Peter Fox, MD  
Jack Lancaster, PhD  
Brian Perry, MD  
Martha Schatz, MD  
Ann Newstead, PhD  
Gail Walden, PhD  
Fang-Ling Lu, PhD  
Ed Brooks, MD  
Karen Hentschel-Franks, MD  
Alvaro Moreira, MD  
Andrew Meyer, MD

### Translational Science Investigators

Mouse Behavioral Neuroscience  
  
Electrophysiology  
Stem cell editing

Georgianna Gould, PhD  
Elizabeth Cody  
Jun Hee Kim, PhD  
Donna Lehman, PhD

## Financial status

### Chromosome 18 Clinical Research Center (Registry funds) - (\$225,000)

- 80% of Patty Heard (Research Associate)
- 0% of Gloria Matthews (Administrator)
- 40% of David Rupert (Data Manager)
- 15% of Courtney Sebold (Genetic Counselor)
- 100% of Annice Hill (Project Manager)
- 100% of Bridgette Soileau (Psychometrician)
- 100% of Minire (Mimi) Hasi (Patient Navigator.)

### Chromosome 18 Research Activity (fka MacDonald account)

- 90% of Jannine Cody, PhD

### Long School of Medicine Pilot Project funding

\$50,000 for Sept 2017 – Sept 2018. **Identification of a new gene essential to CNS myelination.**

The focus of this project is the identification of myelin genes on 18q. A full description is found in the Ongoing Projects section.

## Personnel changes

There have been no personnel changes in 2018

## Space

Lab space is somewhat changed. The total lab space for all 3 labs is 1350 square feet. One lab is now also used as the processing lab for Pediatric Clinical Research, which Dr. Cody directs. Our office space is within the same 3 office suites – we have 3 of the 4 offices in our main suite, with 2 in the administrative suite and 1 office and a conference room in the 3<sup>rd</sup> suite. We share the second two suites with Division of Endocrinology faculty and staff.

## Enrollment

Syndrome	AY 17/ 18	Total
18q-	6	364
18p-	3	129
Ring 18	1	42
Tetrasomy 18p	1	76
Trisomy 18	1	36
18q+	1	7
18p+	0	3
<b>TOTAL</b>	<b>13</b>	<b>657</b>

Geographic Distribution		
North American Continent		565
	US (47 states)	511
	Canada (8 provinces)	47
	Mexico	4
	Barbados	1
	Puerto Rico	1
	Dominican Republic	1
South American Continent		6
	Brazil	5
	Columbia	1
Europe (18 countries)		50
Asia (3 countries)		5
Australia		22
New Zealand		7
Africa (1 country)		2
<b>Total</b>		<b>657</b>

## Publications

1. **Monosomy 18p is a risk factor for FSHD.** Balog J, Goossens R, Lemmers RJLF, Straasheijm KR, van der Vliet PJ, van den Heuvel A, Cambieri C, Capet N, Feasson L, Manel V, Contet J, Kriek M, Donlin-Smith CM, Ruivenkamp CAL, Heard P, Tapscott SJ, Cody JD, Tawil R, Sacconi S, van der Maarel S. *J Med Genet.* 2018 Jul;55(7):469-478. doi: 10.1136/jmedgenet-2017-105153
2. **The Chromosome 18 Clinical Resource Center.** Cody JD, Hasi-Zogaj M, Heard P, Hill A, Rupert D, Sebold C, Soileau B, Hale DE. *Mol Genet Genomic Med.* 2018 May;6(3):416-421. doi: 10.1002/mgg3.385.

## Submitted

1. **Genetic Changes on Chromosome 18p Affect Platelet Aggregation.** Meyer AD, Rishmawai AR, Heard P, Meledeo MA, Cody JD.
2. **Chromosome 18 Gene Dosage Map 2.0.** Cody JD, Heard P, Rupert D, Hasi-Zogaj M, Hill A, Sebold C, Hale DE
3. **Abnormal Bone Mineral Content and Density in People with Tetrasomy 18p.** Moreira A, Hasi-Zogaj M, Soileau B, Hill A, Bruder J, Hale DE, Cody JD

## Additional accomplishments

The Management Guides need to be advertised, so to speak. We have submitted revised syndrome information that refers to the Management Guides to, Up To Date an EMR-based medical information resource. We have also submitted new information to the NIH Genetics and Rare Disease (GARD) website. In both cases, we are waiting to hear back on a decision.

## YouTube videos

The following YouTube videos have been created:

- 2017 Registry conference research update: <https://www.youtube.com/watch?v=oQ0FENT3IHs&t=3s>
- 18p- pre-conference update: <https://www.youtube.com/watch?v=MrBmLMLJcn4&t=1s>
- 18q- pre-conference update: <https://www.youtube.com/watch?v=PMAbVtPQyTY&t=1290s>
- Ring 18 pre-conference update: <https://www.youtube.com/watch?v=uOPI340-yo0&t=8s>
- Tetrasomy 18p pre-conference update: <https://www.youtube.com/watch?v=pWzW9h7SbBw&t=119s>
- An Introduction to chromosome 18: <https://www.youtube.com/watch?v=1Hy-kPDMtE8&t=10s>
- How to use the chromosome 18 gene dosage maps:  
<https://www.youtube.com/watch?v=FrPRccpIBws&t=15s>
- Gene Dosage Map Examples: <https://www.youtube.com/watch?v=V0w4LYt2Mwg&t=21s>
- How to use the dosage maps 2.0: <https://www.youtube.com/watch?v=nJsR906DBIM&t=40s>
- Gene Dosage Map 2.0 Examples: <https://www.youtube.com/watch?v=ZIQKANvd7E0&t=62s>
- Seizure survey results: <https://www.youtube.com/watch?v=eSfopNI8ySI&t=2s>

## Research Center Tours

In 2016 the Research Center started providing monthly tours to anyone interested in seeing the labs and the offices where the magic happens. We have been pleased to meet with more than 40 study participants as well as San Antonio community members.

## 2. Core Activities

### Primary Enrollment

We continue to enroll anyone with any chromosome 18 abnormality. As a part of the enrollment we collect:

- Medical records. These are abstracted (key information entered into the database) and copies of the original documents are scanned into the database. (Mimi)
- Whole blood. DNA is isolated to be analyzed using microarrays with 180,000 features to characterize each affected person's chromosome 18 change (Patty).
- White blood cells are isolated and used to develop permanent cell lines. These allow us to undertake a variety of other activities, some of which will be described subsequently (Patty).

### Gene Dosage Map

One of our most important and less visible Core activities is to keep up with the scientific and medical literature on what is known about every gene on chromosome 18. At least once each year all of the information on every known or suspected gene on Chromosome 18 is reviewed (Cody). The purpose of this review is primarily to determine if there might be a potential effect of an abnormal copy number of each gene. During the gene review this year it became apparent that the emerging scientific information would allow a classification system describing the actual potential for a clinically meaningful outcome from an abnormal gene copy number. Both the gene map and the phenotype regions map were completely revised to be less mechanism-based and more probability-of-effect-based. A manuscript describing the Gene Dosage Map 2.0 is under review.

### Molecular Analysis

We paused the microarray molecular determination of the chromosome 18 abnormalities due to lack of funding.

## **3. Selected Ongoing Projects**

### **SMCHD1 / FSHD2**

We continue to collaborate with the international group of investigators trying to understand how a gene on 18p, *SMCHD1*, causes Facioscapulohumeral Dystrophy, type 2 (FSHD2). This collaboration is led by Silvère M. van der Maarel at Leiden University Medical Center. FSHD2 results when someone has a combination of 2 different genetic changes: one on chromosome 4 and a deletion of the *SMCHD1* gene on 18p. Given what is known about the molecular basis of FSHD2, we believe that people with 18p- as well as the risk variant on chromosome 4 are at an increased risk to have FSHD2. We continue to monitor study participants as they get older. This year at the Registry family conference we recorded scripted speech interviews that will be evaluated for subtle signs of FSHD2. We plan to send our iPad out to individual families for them to perform the evaluations. We will also do follow-up evaluations in the years to come to look for changes.

### **Mouse models to identify genes involved in behavior**

In order to better understand a specific gene on 18q-, we established a colony of *Neto1* knockout mice. Based on our own data as well as previously published mouse data, we think the *NETO1* gene may be important for learning. More importantly there are promising pharmacologic compounds that have completed Phase 2 clinical trials in humans that are likely to counteract the effects of a deletion of this gene. We had some pilot funding for this project to acquire the preliminary data to submit an NIH grant. The data are being analyzed and needs to be written up for publication.

### **Myelin genes**

Although it has been known for many years that people with terminal deletions of 18q have dysmyelination of the brain, the exact gene responsible has been elusive. We think that dysmyelination is caused by a combination of the deletion of the *MBP* gene in addition to another nearby gene. We will be using CRISPR/Cas9 molecular scissors technology to snip out the *MBP* gene in combination with other genes one

at the time to determine which cells fail to form myelin. These experiments have just gotten started in the last 6 months so there is still much to finish before we can have enough data to apply for an NIH grant.

### **EMILIN2**

This is one of the projects that arose from information about the function of a gene on chromosome 18p. Mice with deletions of both copies of this gene had abnormal blood clot retraction times. No information was provided about the heterozygous mice: which is analogous to 18p-. We obtained blood from people with 18p deletions and Tetrasomy 18p to see if they have clotting or bleeding abnormalities. We worked closely with Dr. Andrew Meyer to do the analysis. These data show platelet function abnormalities but more work needs to be done to determine exactly what the molecular basis is of this dysfunction. Although this work started because of emerging knowledge of the function *EMILIN2* gene, we don't know if it is that gene or another gene on 18p that is responsible for the platelet problems. A manuscript describing these data has been submitted. Stay tuned.

### **Tet18p bone data**

We collected survey data from Tetrasomy 18p families about bone health as well as bone density X-ray (DEXA) and clinical laboratory blood test data. We have survey data from 54 families and complete data from 21 individuals. These data show that people with tetrasomy 8p do in fact have low bone mineral density that appears to be helped to Vitamin D supplementation. A manuscript reporting the details of this finding has been submitted.

### **Trisomy 18 long term survivors**

We are in the midst of reviewing medical records and the literature to determine the common issues faced by the long-term survivors (over age 4) with Trisomy 18. This project has been moving slowly for two reasons. We have not enrolled very many new families with an older child with Trisomy 18. And we don't have someone with sufficient time to dedicate to this project.

### **Seizure survey**

We recently completed a survey on seizure history across all the chromosome 18 conditions. This data are analyzed and a report has been sent to the participating families along with a video explain the results. A manuscript is in preparation.

### **AFG3L2 effects**

This gene causes spinocerebellar ataxia type 28. We hypothesize that a deletion involving this gene, as seen in individuals with 18p-, leads to progressive dysarthria. The longitudinal evaluation of dysarthria in people with 18p- over the age of 12 years was begun this year at the Chromosome 18 Registry family conference and combine with the FSHD2 evaluation described above.

### **Tetrasomy 18p constipation**

We recently initiated a survey about constipation in individuals with Tetrasomy 18p. This is in preparation for expanding the information in the Physician Management Guides to emphasize the importance of this issue and the potential long-term effects.

## **4. New Initiatives**

New initiatives are focused on identifying the most economical ways to collect data. We continue to design surveys and other remote mechanisms to learn more about people with chromosome 18 conditions without them having to travel to San Antonio. This type of data is particularly useful in identifying new areas in need of more intense investigation.

## **5. Next Steps Toward Treatments**

We have a long list of projects that we would like to undertake that would move our treatment focused agenda forward. Here are the top projects for each of the chromosome 18 conditions.

### **18q-**

Characterize mice with deletions of the key genes on 18q to better understand the abnormal behaviors and physiology associate with a single gene deletion. These mice will also be essential for early testing of compounds that could potentially normalize the behaviors.

The cost of this study is about \$100,000 per year and will take several years to characterize multiple different strains of mice.

### **18p-**

Create an in-depth clinical and behavioral understanding of people with 18p- centromeric breakpoints. We would do this by performing comprehensive assessments of 15 teenagers and adults with 18p-(cen). To date we have primarily relied on medical records and have very little data from on-site evaluations. This study would cost the Registry approximately \$60,000 to conduct.

### **Tetrasomy 18p**

We are acquiring skin samples from individuals who are mosaic for Tetrasomy 18p. Those samples will be sub-cloned create cell lines with normal chromosomes and cell lines with tetrasomy18. Our collaborators in Leiden will perform limited experiments to look at specific differences between these cells. However, there are numerous other characterizations that can be done to help understand how the cells from someone with Tetrasomy 18p are different from cells with normal chromosomes. Because there are multiple directions these experiments could take, it is difficult to make a cost prediction. However, we believe that each increment of experiments will probably cost about \$50,000.

### **Trisomy 18**

Clinical evaluations of 20 individuals over the age of 4 with full Trisomy 18 to determine their unique characteristic associated with survival.

This study would cost the Registry approximately \$100,000 to conduct. This project is more expensive per participant because we propose to perform exome sequencing in these participants.

## **6. Chromosome 18 Clinic**

We have very limited funding for clinical visits as a part of the research study. However, we appreciate that our team is made up of clinicians who have seen more children and adults with chromosome 18 conditions than anyone else in the world. We need to make their expertise available to families. We will help coordinate and schedule clinical appointments for the families enrolled in the research study to see members of our team. The families are responsible for the costs of their travel and lodging; however, we can provide guidance and local information. The families are also responsible for the costs of their clinical appointments and need to get the necessary pre-authorizations from their health insurance company. The families can also meet with the research team members who are not clinicians for advice and consultation at no cost. Because we have the medical records for families who are enrolled in the study, the research team can advise the families about which clinical appointments will be most beneficial to them.