

1. Activities and Changes during Academic Year 2023/2024

Chromosome 18 Clinical Research Center Leadership

Director- Jannine Cody, PhD

Associate Director – Jonathan Gelfond, MD, PhD, MBA

Medical Director – Kameel Karkar, MD

Staff

Program Data Manager –Brittany Antopia, MPH

Participant Coordinator – Catherine McCarthy, MS

Laboratory Supervisor – Aamuktha Pentala, MPH

Administration – Gloria Matthews

Clinical Investigators

Bioinformatics

Jonathan Gelfond, MD, PhD

Psychiatry

Catherine Larson, MD**

Neuropsychology

Amy Werry-McFarlin, PhD

Child Neurology

Kameel Karkar, MD

Endocrinology

Daniel Hale, MD*

MRI

Peter Fox, MD

Mohamed Habes, PhD

Visual Evoked Potentials

Gabriel de Erausquin, MD

Ophthalmology

Martha Schatz, MD

Physical Therapy

Ann Newstead, PhD**

Speech Therapy

Fang-Ling Lu, PhD

Allergy / Immunology

Ed Brooks, MD

Sleep medicine

Karen Hentschel-Franks, MD

Bone Health

Alvaro Moreira, MD

Platelet Function

Andrew Meyer, MD

Translational Science Investigators

Stem cell editing

Donna Lehman, PhD

Mouse models

Noboru Hiroi, PhD

Mouse Behavioral Neuroscience

Georgianna Gould, PhD

Animal Electrophysiology

Jun Hee Kim, PhD

*Now at Milton S. Hershey Penn State Medical Center and Adjunct Faculty at UT Health

** In private practice and Adjunct Faculty at UT Health

% Salary Support

	Chromosome 18 Registry	Department of Pediatrics	Basic Science R03	Kids First R03	Total effort for Chr18 CRC
Jannine Cody	88	4	4	4	100
Jonathan Gelfond	10	-	-	-	10
Kameel Karkar	7	-	-	-	7
Britttany Antopia	25	-	-	75	100
Catherine McCarthy	75	-	-	25	100
Aamuktha Pentala	100	-	-	-	100

Space

Lab space is unchanged. One lab is used for molecular analysis and the other for tissue culture. Our office space includes 3 of the 4 offices in our main suite.

Major Equipment Purchases

Registry funding from Valero Energy funded the purchase of a -80-degree freezer and a centrifuge.

Current Enrollment

Syndrome	AY 23/24	Total
18q-	5	386
18p-	9	149
Ring 18	1	50
Tetrasomy 18p	4	89
Trisomy 18	0	37
18q+	1	11
18p+	0	5
TOTAL	20	727

Geographic Distribution		
North American Continent		622
	US (47 states)	564
	Canada (8 provinces)	49
	Mexico	5
	Barbados	1
	Puerto Rico	1
	Dominican Republic	2
South American Continent		7
	Brazil	6
	Columbia	1
Europe (18 countries)		58
Asia (4 countries)		6
Australasia		29
Africa (1 country)		2
Total		702

2. Publications and Education

Scientific Publications

Published

Larson CC, O'Donnell L, Soileau B, Van Riper M, Stark D, Hale DE, Cody JD. Understanding type and quality of relationships between individuals with chromosome 18 syndromes and their siblings. J Genet Couns. 2023 Oct 26. doi: 10.1002/jgc4.1823. Epub ahead of print. PMID: 37882415.

Mehl JM, Gelfond J, Carey JC, Cody JD. Causes of death in individuals with trisomy 18 after the first year of life. Am J Med Genet A. 2023 Oct 11. doi: 10.1002/ajmg.a.63436. Epub ahead of print. PMID: 37822198.

Cody JD. Ring Chromosome 18; Structural Variation and Clinical Consequences. In: Human Ring Chromosomes. A Practical Guide for Clinicians and Families. Li and Liehr eds. Springer Nature Publisher, 3/21/2024.

Submitted

Cody JD, Gelfond JL, Hiroi N. The impact of gene copy number on psychiatric disorders and its usefulness for gene discovery; chromosome 18 as a model. In: CNV and Psychiatric Disorders

Media releases

MD Briefcase – 3 10-minute interviews:

- Chromosome Abnormalities
- Personalizing a Care Plan
- Future Directions

Video presentations

12/3/2023 Research Update, World Chr 18 Day

Meeting Presentations

10/18/2023 Plenary Presentation, Am Society of Genetic Councilors Annual Meeting, Chicago, IL

7/8-10/2024 Chromosome18 Registry & Research Society Annual Family Conference, Charlott, NC.
Presentations by Drs. Cody, Gelfond, Karkar, Hale and Larson

Articles for the Chromosome 18 Registry newsletter

9/11/2023 Growth hormone deficiency and the chromosome 18 conditions. By D. Hale

12/7/2023 Deciphering Molecular Lab Reports

1/9/2024 What is happening with Tetrasomy 18p?

Part 1- The Long Road for Developing Novel Treatments for People with Chromosome 18

2/10/2024 Conditions

Part 2-The Long Road for Developing Novel Treatments for People with Chromosome 18

3/10/2024 Conditions

4/9/2024 Re-posting of World Chromosome 18 Day Research Update

5/10/2024 Ring 18 book chapter

6/10/2024 Introducing Drs. Gelfond and Karkar

7/30/2024 Analogies

8/12/2024 Smell test results

Research Center Tours

In 2016 the Research Center started providing tours (in-person and virtual) to anyone interested in seeing the labs and the offices where the magic happens. We have been pleased to meet with study participants as well as San Antonio community members.

3. Core activities

There are two aspects that make the Chromosome 18 Clinical Research Center such an amazing resource. First, the large number of participants with one of these ultra-rare conditions is truly unique. This cohort is about 40 times larger than any other reported cohort. Second, is the participant partners commitment to the longitudinal nature of the research. We continue to learn more about the genes on chromosome 18 and can apply that knowledge to help the participants. Also, the participants continue to provide information about new achievements and setbacks in their lives. All of which can be used to inform the wider audience of people with chromosome 18 changes around the world. The core activities that make this possible are:

1. Enrollment

- Medical records review documenting a chromosome 18 abnormality.
- Whole blood for:
 - DNA
 - Establishment of permanent cell lines
 - Nuclei preparation for chromosome analysis
- Medical History and Developmental survey

2. Longitudinal follow-up

- Developmental milestones and school achievement surveys

- Annual Medication survey
- Behavioral surveys and tasks (web-based or paper)
- Medical record collection updates. These are abstracted (key information entered in the database) and copies of the original documents are scanned into the server folders.

3. Gene Dosage Maps

- Gene Dosage Map - a map of every gene on chromosome 18 classified by its potential to cause an abnormality when deleted or duplicated.
- Phenotype Map – a map of the abnormalities associated with a deletion or duplication of a specific region of chromosome 18 for which the exact causative gene is yet to be discovered.
- Clinical Dosage Map – a map of only the small number of genes known to be causative of an abnormality when deleted or suppllicated.

4. Research Projects

Kids First Program

One hundred fifty of the chromosome 18 deletion participants who have structural birth defects were selected by the Kids First Program for whole genome sequencing by the Broad Institute of MIT and Harvard. We also were required to submit their birth defect data to the NIH. Both the genetic and medical information is available to other NIH approved investigators.

We are collaborating with Dr. Santhosh Girirajan at Penn State University who is helping us with the genome data analysis. The amount of data is massive, and we and they have been applying various algorithms to sort through the data to identify variants with potential deleterious effects. They have no specific funding to support their work. However, an R01 NIH grant is being planned.

The follow-up grant for this program is to update all the medical records for the 150 participants. Progress is well ahead of schedule to be completed by 2/28/2025.

Trisomy 18 Long-term survivor's survey

We conducted a survey asking about the lives of people with trisomy 18 over the age of one year to learn more about long term health and management. There were 242 responses, 166 of those concerned someone with full Trisomy 18 and 21 of those were deceased. The paper on the cause of death in this group was published last year. The data on the long-term health issues and the medical management of these children and adults has been analyzed and a draft of the manuscript is being edited by our long-time collaborator Dr. John Carey from the University of Utah.

Dysmyelination genetics project

One of the issues that affects the greatest number of people with a chromosome 18q deletion is dysmyelination of the brain. Up until recent years, it was thought that the consequences of this would mostly result in slow reaction time. But recently it has been determined that insufficient myelination of the brain can lead to many conditions such as attention deficit, seizures, intellectual disability, autism and potentially accelerate age-related cognitive decline. Because this is an anatomical issue with behavioral consequences, it is a good candidate for potential funding from the National Institutes of Health (NIH). This project has two different aspects, the basic science and the clinical science.

1. Basic science – With Drs. Donna Lehman and Noboru Hiroi, we have an R03 grant from the NIH (\$75,000/yr for 2 years; 6/1/2023- 5/30/2025) to identify the genes responsible for dysmyelination

and to investigate the cellular mechanism of dysmyelination using participant derived cerebral organoids and mouse models. We are beginning to make plans to apply for a larger R01 grant to complete this work.

2. Clinical Science - We are writing an NIH R21 grant (\$275,00 over 2 years) to support a more precise investigation into dysmyelination in study participants. The goal of this grant (due 10/17/24) would be to define potential clinical trial endpoints in preparation of future treatment trials.

18p- Video assessments

Data on the function of two different genes on 18p lead us to believe people with 18p- are at risk for Facioscapulohumeral Dystrophy, Type 2 (FSHD2) and Spinocerebellar Ataxia, Type 28 (SCA28). We are monitoring facial movement and speech as a screening tool using participant acquired videos conducted following a specific protocol. The videos are being evaluated by Dr. Karkar, and Dr. Rabi Tawil at the University of Rochester who is a leading expert in FSHD2 and by Dr. Ling Lu the director of speech Pathology at UT Health. This project is ongoing with plans to do follow-up assessments every 5 years or as families have new concerns.

5. 2024/2025 Plans

Seizure survey

Dr. Karkar developed a seizure survey to be sent to all participants beginning the week of 9/23/2024.

Medical Record Updating

We plan to continue to update the medical records of the Kids First participants and expand to update records for all participants. One aspect of the grant being planned with Dr. Girirajan is to automate the process of generating an individual participant prepopulated medical history survey out of REDCap that will be electronically sent to the participant and their submitted data will go directly into the database after review by a staff member. We are already working on this process with regard to medication updates.

Management Guide Updates.

It will have been 5 years since the last revision to the Management Guides. With the transition of data to REDCap, an update should be much less labor intensive. But at the same time there are more types of data to add. This project will require the significant staff time over the year.

18p Driver Genes

We are in discussions with Dr. Donna Lehman about strategies for using participant derived cerebral organoids to identify driver genes on 18p that can impact cognition and behavior when in 1 or 4 copies.