Human Genetics Dispatch Q1-2023

In this Issue

DOHG

In this issue:

Chair's Corner, July 2022

Welcome to the first edition of the Department of Human Genetics (DOHG) Dispatch for 2023. On February 28th, the world celebrated Rare Disease Day to increase awareness and support for the 300 million people living with rare diseases worldwide, along with their families and caregivers.

The CTCF protein was initially identified in the 1980s by researchers in Moscow who discovered its ability to bind to repeat elements that flank the chicken c-myc gene. CTCF has since gained attention for its multivalent DNA-binding zinc fingers and its role in transcriptional repression, and DOHG's own Victor Corces and his team confirmed its insulator activity in Drosophila. In a 2009 review, Corces referred to CTCF as a "master weaver" of the genome due to its capacity to organize chromatin in loops and insulate chromatin domains. Corces also emphasized the importance of genome-wide approaches in studying CTCF.

Medical geneticists, led by Hong Li, have now gained further insight into CTCF's function in human biology. CTCF mutations were found to have subtle and diverse effects on affected individuals. These studies were made possible by the basic research conducted by Corces and his team. With this knowledge, the investigators are now poised to develop new therapies for patients impacted by CTCF mutations.

This story highlights the long and rewarding scientific journey from basic research in fruit flies to identifying CTCF mutations in humans. It demonstrates how collaboration between basic and clinical researchers can generate valuable information and advance patient care.

Peng Jin, PhD

Professor and Chair

**Edited by ChatGPT*

From our DEI Committee

DOHG Events:

Cohorts are BACK for the spring. Cohorts are great learning opportunities and a chance to get to know others in our Department that you might not interact with on a regular basis. Cohorts are open to everyone (trainees, staff, and faculty). Please consider participating, even if you did it last year. Every conversation is different and an opportunity for learning (or unlearning). The time commitment is minimal (1 hour per month), but the impact is broad.

Lauren Lichten, representing the DEI Training and Awareness subcommittee, sent out a sign up form at the beginning of February. The plan is for cohorts to begin meeting in March. For questions, please email melanie.hardy@emory.edu.

The department's **DEI Book Club** is reading (and finishing) Histories of the Transgender Child. After two productive meetings, the last gathering is being scheduled for March/April.

Looking ahead to May 9, DOHG's clinical conference will host Melissa B. Davis, PhD, incoming Director of the Morehouse School of Medicine Genomics Institute and Georgia Research Alliance Distinguished Investigator.

1 - Melissa B. Davis, PhD

Emory events

Black History Month has gone by -- but you can still check out the Emory 2036 podcast with historian Carol Anderson.

March 16 – Remembrance and resilience event (2nd anniversary of spa shootings in Atlanta) with author Deepa Iyer

Social justice workshop Goizueta Business School 12 – 1:30 pm, Zoom webinar 4-5 pm

March 29, 11 a.m - 12:15 p.m, Racism: Public Health Crisis? How the Politics of Racial Resentment Undermine Individual and Societal Health and Well-Being -- Hybrid lecture and discussion with Jonathan Metzl of Vanderbilt. Register here.

Women's History Month is in March. See here for events

Ramadan is from March 22 to April 21

Surveys/opportunities

COACHE faculty satisfaction survey

Launched February 17, ends April 7. Eligible faculty received a personalized link.

Diversity Engagement Survey SOM Survey coming in March

This survey was last offered in 2020 and resulted in new affinity groups, Diversity Week and quarterly community forums to share updates.

The School of Medicine's Diversity, Equity and Inclusion office's website was recently revamped. Check it out.

DEI competency central to new performance management process for university managers and staff.*Learning and Organizational Development is offering upcoming training sessions (last one is March 1). A session will also be recorded and posted for those who are not able to attend.*

LGBT Health Workforce Conference, April 20-22, 2023**:** Online registration closes April 20. More info on the website.

SOM LGBTQ+ Mentoring Program: *The LGBTQ+ Faculty Affinity Group recently launched a mentoring program. Contact Jason Schneider (Department of Medicine) for more information.*

Free online course from the University of South Florida: Diversity, Equity, and Inclusion in the Workplace. More information can be found here.

Department Spotlights

Get to know your DOHG colleagues. Each issue will feature randomly selected staff, faculty or trainee profiles.

*2 - **Rossana Sanchez Russo, MD***

My hometown is Barranquilla, Colombia and my father was a pediatrician. When I was 7 years old, I saw the first patient with a genetic disorder who I can remember. He was a small child with a severe form of craniosynostosis, which causes a malformation of the skull's shape. This experience and the influence of my father led to my interest in genetics.

I attended medical school at Universidad del Norte in Barranquilla, followed by a pediatrics residency at Nicklaus Children's Hospital in Miami, and then a medical genetics residency and fellowship at Emory. For the last 5 years, I have co-directed the Human Genetics and Evolution course for first year medical students. In addition, I have been working with a multidisciplinary team at Children's Healthcare of Atlanta to help care for patients with rare vascular malformations, many of whom have rare somatic genetic disorders.

3 - Example of pour painting

I enjoy spending time with my family, my two daughters and husband during my time off. My daughters and I like to craft and I taught myself pour painting during the pandemic. We also enjoy traveling to visit family abroad.

*4 - **Alyssa Long, PhD, Supervisor Research Specialist***

I work in the Caspary lab and I’m interested in intracellular signaling through the primary cilium during development. As a postdoc in Tamara’s lab, I identified a mutation in a gene that results in craniofacial abnormalities and perinatal lethality. Currently, I function as both a bench scientist and lab manager - keeping protocols up-to-date and the lab stocked with supplies, on-boarding new lab members, and contributing to manuscripts through experiments and writing assistance.

I earned my Emory PhD in Immunology in Jerry Boss' lab.

Hobbies / outside interests: When I’m not wrangling mice or cells in lab, I can be found enjoying sci-fi and fantasy books and shows, playing World of Warcraft, or cross-stitching.

*5 - **Michael Kelberman***

Throughout my undergraduate and graduate careers, I've been interested in understanding the locus coeruleus norepinephrine system's influences over diverse sets of behaviors, and how these normal processes go awry in disease. My current work with Dr. David Weinshenker seeks to describe how hyperphosphorylated tau affects locus coeruleus function in the context of Alzheimer's disease. To explore these questions, we employ a multifaceted approach including behavioral assays, electrophysiology, optogenetics, and functional magnetic resonance imaging in a rat model of Alzheimer's disease.

I obtained a B.S. in Biochemistry and Molecular Biology from University of Massachusetts Amherst, and my Emory Ph.D. in Neuroscience is in progress -- and close to completion. Outside of lab I like to play soccer and coach local youth teams, in addition to spending time with my cat, Lyla.

Key Discoveries: Human Genetics

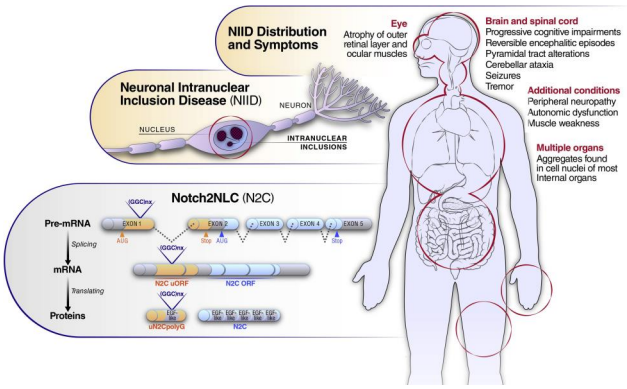
hnRNPM acts as "fulcrum" in neuronal intranuclear inclusion disease

-- Peng Jin, PhD

NIID (neuronal intranuclear inclusion disease) is a neurodegenerative disease whose genetic origins – an expanded GGC repeat within the gene *NOTCH2NLC* -- were identified in 2019. In partnership with Yongcheng Pan and Beisha Tang at Central South University in Hunan, Peng Jin's lab recently described a transgenic mouse model and a human neural progenitor cell model of NIID in *Science Advances*. Co-authors in the Jin lab, where the human cell culture model work was completed, include former graduate student Kailin Zhang and instructor Yunhee Kang.

Overall, the animal and human models mimic the clinical manifestations and pathological features of patients with NIID (see figure). The authors demonstrate that the pathophysiology of NIID partially resembles that of other repeat expansion-associated disorders such as myotonic dystrophy and ALS (amyotrophic lateral sclerosis), since nuclear inclusions of toxic homopolymer peptides are present in affected tissues. By analyzing patterns of alternative splicing in brain tissue, the authors deduced that sequestration of the RNA-binding protein hnRNPM (a "fulcrum molecule") drives pathology. This makes hnRNPM a potential therapeutic target.

Science Advances, November 23, 2022, *Expression of expanded GGC repeats within NOTCH2NLC causes behavioral deficits and neurodegeneration in a mouse model of neuronal intranuclear inclusion disease*



6 - The clinical manifestations of neuronal intranuclear inclusion disease (NIID) are quite variable: dementia/muscle weakness/sensory disturbance/ataxia/seizures. Before recent genetic studies, the disease was mainly diagnosed by skin biopsy.

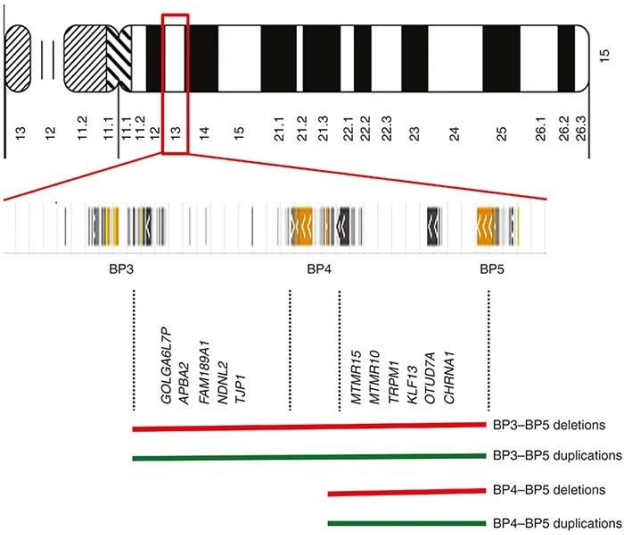
Homing in on causative mutations in 15q13.3-linked neuropsychiatric disorders

-- David Cutler, PhD, Michael Epstein, PhD, as well as Jennifer Mulle, PhD, Michael Zwick, PhD and Stephen Warren, PhD

Microdeletions in the 15q13.3 region have been associated with multiple neuropsychiatric conditions: schizophrenia, epilepsy, intellectual disability and autism. (Don't mix this up with Angelman and Prader-Willi, those are located at 15q11.) "15q13.3 microdeletion syndrome" was already an established term in the literature a decade ago, and more recently, several labs have been finding causative genes, with a focus on the *OTUD7A* gene.

Several DOHG members, current and former, are authors on this paper: a collaboration with Jubao Duan at University of Chicago. The authors identify three rare schizophrenia-associated loss-of-function mutations in the *OTUD7A* gene. Human iPSC work allowed assessment of this gene's roles in synapse development and neuronal function. Readers interested in 15q13.3 or *OTUD7A* should check out a 2023 Molecular Psychiatry paper, which uses proteomics to probe OTUD7a's deubiquitinase function.

American Journal of Human Genetics, August 4, 2022, *Loss of function of OTUD7A in the schizophrenia- associated 15q13.3 deletion impairs synapse development and function in human neurons*



7 - From 2016 review "The complex behavioral phenotype of 15q13.3 microdeletion syndrome". OTUD7A accounts for many characteristics of 15q13 microdeletions.

DSP-4 neurotoxicity as a model for locus coeruleus neurodegeneration

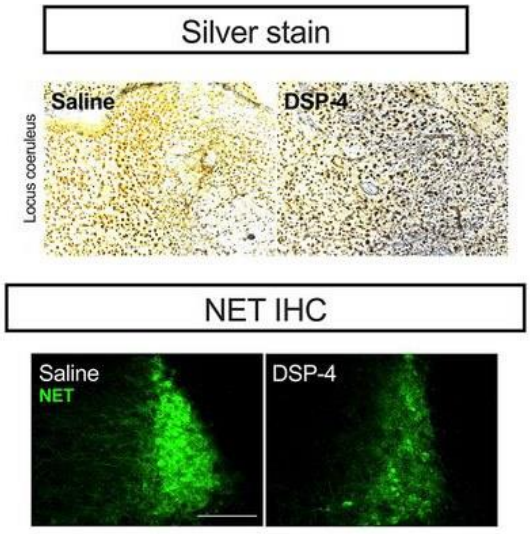
-- David Weinshenker, PhD

The locus coeruleus, the main source of the neurotransmitter norepinephrine in the brain, is an early site of neurodegeneration in Alzheimer's and Parkinson's. In this paper, the Weinshenker lab comprehensively assesses the early effects of the neurotoxin DSP-4 in mice, in terms of damage to the locus coeruleus, behavioral alterations, electrophysiology and gene expression. Neuroscience graduate student Alexa Ianitelli, who just defended her thesis on February 2, is the first author. (Congratulations Alexa!)

DSP-4 has been studied as a tool for depleting norepinephrine-producing neurons since the 1980s, but this paper shows in detail how DSP-4 first evokes hyperactive norepinephrine transmission, preceding outright cellular loss in the locus coeruleus. The results have important implications for understanding Alzheimer's and Parkinson's. They explain how early pathology in the locus coeruleus may manifest in neuropsychiatric symptoms such as anxiety and sleep disturbance, followed by more extensive neurodegeneration. They also remind other researchers to be aware of the time course of DSP-4's effects in experimental models.

DSP-4 neurotoxicity can indirectly affect other regions of the brain. For example, it results in a decline in hippocampal neurogenesis in adult mice, as demonstrated in another recent publication in *IBRO Neuroscience Reports* – a Weinshenker lab collaboration with investigators in Mumbai.

eNeuro, December 9, 2022, *The Neurotoxin DSP-4 Dysregulates the Locus Coeruleus-Norepinephrine System and Recapitulates Molecular and Behavioral Aspects of Prodromal Neurodegenerative Disease*



8 - DSP-4 administration leads to neurodegenerative processes in the locus coeruleus, and loss of norepinephrine transporter (NET) immunoreactivity. From Ianitelli et al (2022)

Mutations in ubiquitin adaptor KLHL20: human neurodevelopmental phenotypes

-- *Jaime Vengoechea, MD, PhD*

DOHG's Jaime Vengoechea was a co-author on a December 2022 report describing individuals carrying pathologic variants in the E3 ubiquitin ligase adaptor KLHL20. The authors observe a genetic syndrome with patients having mild to severe intellectual disability, febrile seizures or epilepsy, autism spectrum disorder, hyperactivity, and subtle dysmorphic facial features. KLHL20 had been reported to regulate neurite outgrowth and synaptic development in animal models, but its role in human neurodevelopment had not been described.

The group was led by Hilde Peeters from KU Leuven in Belgium. 14 patients are described in the paper, and 11 had the same mutation (Gly357Arg). The patients were found through the website Matchmaker Exchange.

Genetics in Medicine, October 11, 2022, *De novo missense variants in the E3 ubiquitin ligase adaptor KLHL20 cause a developmental disorder with intellectual disability, epilepsy, and autism spectrum disorder*

9 - Logo for Matchmaker Exchange

Elevated homocysteine levels: What inborn errors of metabolism might we be missing?

-- Hong Li MD, PhD

High levels of homocysteine, a sulfur-containing amino acid and metabolic intermediate, are associated with increased risk for cardiovascular diseases. Elevated homocysteine can come from vitamin deficiencies, kidney disease, or inborn metabolic problems. In clinical practice, testing for plasma homocysteine level is widespread enough that a large body of data is available.

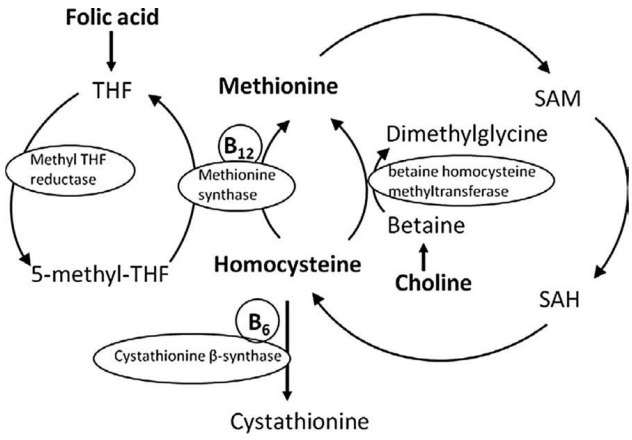
This led Hong Li and medical genetics fellow Aixa Gonzalez, now at University of Arkansas, to examine whether mining of homocysteine testing results might reveal unidentified cases of genetic metabolic diseases, such as CBS (cystathionine beta-synthase) deficiency. Their hypothesis was that some rare but treatable cases are currently being missed, because of variable presentation or lack of awareness. This idea turned out to be correct, at least for one person. This suggests that a larger multisite study could identify more undiagnosed patients with treatable metabolic diseases. Similar studies have been undertaken in Denmark and France.

Over a two-year period at Emory Healthcare, roughly 5 percent of all tests (103/1966) for plasma homocysteine were above the threshold of 30 µmol/L; normal is <15 µmol/L. Gonzalez and Li sifted through medical records and identified 22 candidates who did not have clear etiology for their elevated homocysteine. A large fraction of the others had end-stage kidney disease or vitamin B12/folate deficiency.

Genetic panel testing was offered to seven patients, and one was diagnosed with CBS deficiency, which had previously been missed. This patient had experienced placental abruption during her second pregnancy, leading to premature delivery and the death of the newborn. Hypercoagulation was suspected as the cause, leading clinicians to order a plasma homocysteine test during the patient's third pregnancy. She was prescribed low molecular weight heparin and folate supplementation and successfully delivered her baby.

Several years later, her homocysteine levels were elevated but had not been followed up. Genetic testing identified a pathogenic variant and a variant of uncertain significance in the CBS gene; the deficiency was confirmed by enzymatic testing. The patient's elevated homocysteine partially responded to vitamin B6, and then responded well to betaine supplementation.

American Journal of Medical Genetics A, October 22, 2022, *Elevated homocysteine levels: What inborn errors of metabolism might we be missing?*



10 - Homocysteine connects several metabolic pathways.

BPA-induced transgenerational obesity and the "fatso" gene

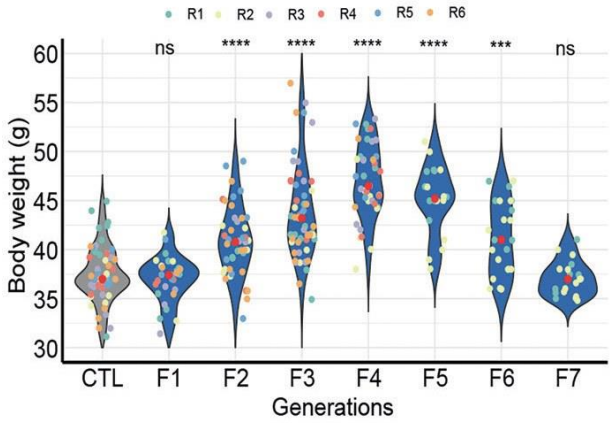
-- *Victor Corces, PhD*

Obesity is widespread in developed countries. Within an increasingly "obesogenic" environment, the influences of genetics on obesity are complex. A recent *PNAS* paper from Victor Corces' lab (first author: Yoon Hee Jung, now at Ajou University in South Korea) probes both genetic and environmental effects on obesity, and there are two ways to view it.

First, it's a disturbing reminder of the long-lasting -- indeed, transgenerational -- metabolic effects of the endocrine disruptor bisphenol A (BPA), which is still present in many consumer plastic products, even though BPA-based resins were banned from baby bottles and sippy cups a decade ago. Second, it's a contribution to the ongoing puzzle in the field over the function of FTO, the first gene connected with human obesity by GWAS.

The Corces lab's work implicates the mouse Fto locus as the site of chromatin interactions necessary for the transmission of BPA-induced obesity. However, their research doesn't directly deal with human exposure to BPA; the authors describe a mouse model of BPA exposure, in which pregnant animals receive daily peritoneal injections of BPA for a week. The resulting BPA levels are generally much higher than what humans are exposed to. And wow: the obesity-related effects of BPA exposure, driven by increased food consumption, persist for several

generations before fading. We can still infer something about nuclear mechanisms of endocrine disruption from the mouse model.



11 - Mice that are ancestrally exposed to BPA display obesity over several generations. From Jung et al. (2022).

The authors used ATAC-seq to map sites where changes in chromatin accessibility occur in the sperm of mice whose ancestors were exposed to BPA. Out of the differentially accessible 12 sites identified, only one was also present in oocytes. That site was in an intron of the Fto gene, and it becomes demethylated after BPA exposure. This cis-regulatory element contains a CTCF binding site; DNA binding by CTCF is methylation sensitive. The transcription factor CTCF has a nuclear "anchor" function regulating chromatin structure: sometimes it acts as an insulator, and sometimes it facilitates interactions between promoters and enhancers.

Back in 1999, FTO's cloners had prophetically named it "fatso" because the gene was large (>250 kb) and for its connection with the Fused toes (partial syndactyly of forelimbs) phenotype in mice. Several years later, an intronic variant in the FTO gene was shown to be associated with type 2 diabetes and obesity by GWAS. However, the mechanistic relationship between FTO function/expression (FTO encodes an RNA demethylase) and obesity has been difficult to unravel. Some studies suggest that the neighboring genes IRX3 and IRX5 may be the critical players instead. IRX3 and IRX5 interact with FTO by long-range enhancer loops and are involved in the differentiation of appetite-controlling neurons in the hypothalamus.

In the end, mice carrying a deletion of the CTCF site in the Fto intron are protected from obesity after ancestral exposure to BPA, indicating that that site is necessary for transgenerational inheritance. BPA may be provoking DNA binding by nuclear hormone receptors and inducing CTCF binding of the Fto intronic site, leading to long-lasting changes, the authors speculate.

Proceedings of the National Academy of Sciences, December 5, 2022, Recruitment of CTCF to an Fto enhancer is responsible for transgenerational inheritance of BPA-induced obesity

Three cheers for brain organoids

Fikri Birey co-authored three 2022 publications advancing organoid approaches for probing the intricacies of the human brain. One was an editorial in *Frontiers in Molecular Neuroscience*; another was a tour-de-force in *Nature,* with partner Jimena Andersen and led by Sergei Pasca and other Stanford luminaries (Maturation and circuit integration of transplanted human cortical organoids). The third describes technical protocols for high-resolution imaging of neuronal migration and calcium imaging of network activity in forebrain assembloids.

Highlighting genetics counseling theses

CF affects all population groups

Cystic fibrosis (CF) is the most common autosomal recessive genetic disease among Caucasians, and thus it has been known as a "white disease." But it is still possible for individuals who are not white to have CF. Genetics counseling student Kia Hutchins and her co-authors took on the misconception with a study of the experiences of minority adults with CF, surveying 82 patients from Emory Healthcare's Adult CF clinic.

The authors found that minorities with CF reported feeling they had a significantly lower understanding of their disease and more negative perceptions of their illness overall when compared to non-Hispanic Caucasian participants. A significantly higher endorsement of anxiety and depression was associated with disease experience in minority persons with CF. Minority participants perceived their support from family and community as significantly lower than non-Hispanic Caucasian participants, possibly due to unfamiliarity with CF, exacerbated by the lower prevalence of CF within minority communities.

Hutchins and colleagues also found a significant age gap in CF diagnoses, with minorities having been diagnosed several years later – possibly because of clinician bias. As adults, participants in this study were unlikely to have been diagnosed via newborn screening, which was implemented over the last 20 years nationwide for CF.

Journal of Patient Experience, Published online July 14, 2022, Evaluating differences in the disease experiences of minority adults with cystic fibrosis

12 - Genetics counseling student Kia Hutchins, class of 2021, is now at Piedmont.

Randy Hunt, MD, physician in the Cystic Fibrosis Clinic, was Kia's senior focus capstone mentor.

Diagnostic experiences of women with FXPOI (fragile X-associated primary ovarian insufficiency)

The paper from Emily Allen, Nadia Ali and colleagues is a compelling read, mainly because of quotes from 24 women with FXPOI reflecting on their experiences. The quotes illustrate both the limited knowledge of FXPOI outside of academic medical centers, and the hurdles and biases patients face within the American health care system. The authors recommend implementation of a “FXPOI health navigator” as a resource for women with this diagnosis.

Here are two example quotes from different individuals:

“So I was having a lot of hot flashes, and it took probably four gynecologists, and essentially the first three basically said, “You’re too young…we’ve never heard of somebody your age having hot flashes. This makes no sense.” And all three of those doctors prescribed me anxiety medications, and then I went to a fourth gynecologist, OB-GYN, and she, essentially, said…I just read about this thing. I can test you for it…"

“I also asked her [genetic counselor],“Okay, well, what is your role in my ongoing care?” And she was like, “Oh, genetics is not involved in your day-to-day care. You should really go back to your OB-GYN…,” who at that point, had said…they weren’t gonna be responsible for my care, but that

endocrinology was. And the endocrinology said that genetics was, and then genetics sent me back to OB-GYN…"

Journal of Assisted Reproduction and Genetics, November 30, 2022, *The diagnostic experience of women with fragile X-associated primary ovarian insufficiency (FXPOI)*

13 - First author Bonnie Poteet finished the Genetics Counseling training program last year and is now a genetics counselor at Northside Hospital.

Barriers for genetic services use by PCPs

Given the limited number of genetic counselors and specialty-trained physicians, primary care providers are increasingly seen as a resource for identifying patients who would benefit from genetic services, coordinating subsequent referrals or testing. PCPs often recognize the benefit of genetic services for their patients, but do not feel comfortable with ordering tests or placing referrals. This discomfort can be compounded by logistical challenges or the need to interpret genetic test results.

Genetics counseling student Erin Seibel interviewed primary care providers in the Southeastern United States about barriers to genetic service usage. They reported a mix of lack of knowledge – both on the part of the provider and the patient – and structural barriers such as logistical challenges and scarcity of genetics providers.

Journal of Primary Care & Community Health, November 7, 2022, Primary care providers' use of genetic services in the southeast United States: Barriers, facilitators, and strategies

14 - Erin Seibel is now a pediatric hematology and oncology counselor at CHOA. Gwen Gunn and Aileen Kenneson shared senior focus capstone mentorship for Erin's project.

Newly Funded Research

Do genetic zombies (transposable elements) come alive in AD?

Bing Yao and Peng Jin were awarded an August 2022 R01 from the National Institute on Aging to elucidate the roles of transposable elements in Alzheimer's and related dementias. The RNA/DNA-binding protein TDP-43, well studied for its roles in ALS (amyotrophic lateral sclerosis) and FTD (frontotemporal dementia), has been identified as binding to transposable element-derived RNAs and repressing their transcriptional activity. Transposable elements make up more than half of the human genome and normally are repressed in heterochromatin.

TDP-43 protein loss of function appears to occur in Alzheimer's as well, as a result of sequestration in cytoplasmic inclusions. Tau pathology has been observed to reactivate transcription of transposable elements. A recent *Science Advances* paper outlines a role for TDP-43 in protecting preimplantation mammalian embryos from transposable elements' reactivation and retrotransposition.

In their grant, Yao and Jin have proposed that TDP-43 may be protecting brain cells from transposable elements' revival, and its loss of function in Alzheimer's may lead to disruptive activity from transposable elements. They plan to probe the roles of TDP-43 and R-loops, which are the three-stranded RNA/DNA structures formed by transposable elements.

15 - A zombie (from the Walking Dead)

Medical Genetics

16 - Rare Disease Day zebras sighted!

Rare Disease Day zebras were sighted at Emory University Hospital on Feb. 28!

Kristen Murphey, Hong Li, Meredith Fuchs and Rossana Sanchez Russo, with Jaime Vengeochea Barrios in the corner. Thanks to everyone who helped with the outreach activities!

Recognition for Margie Leathers

Margie Leathers, BSN, RN, CPN, senior nursing manager for clinical services, recently received two awards. One was the internationally recognized and prestigious DAISY Foundation award for extraordinary care, and the second was the departmental Genetics Excellence award.

"Margie is a patient advocate that goes above and beyond for those she serves," wrote clinical administrator Tamario Lenoir in his nomination letter. "She is kind, thoughtful and is motivated to serve our patients and staff members alike. She appreciates and continues to find the humor and joy in simple patient care, but also operates with precision when a patient's condition demands expert attention. She's brilliant, steadfast, and compassionate."

17 - Margie getting DAISY award with Deena Gilland, Emory Healthcare's vice president of patient services and chief nursing officer

The evolution of the CTCF-related disorder community

The National Organization of Rare Diseases catalogs more than 7,000 rare diseases – most of them genetic in origin. For Rare Disease Day (February 28), we are spotlighting how advances in sequencing technology makes it possible to diagnose and understand otherwise mysterious conditions. At the same time, parents are thrust into new roles as community organizers and amateur geneticists.

It started with an email from a persistent mom, who was worried about her son's seizures. Courtney, a high school teacher in Walton County, GA, unexpectedly found allies at Emory. They ended up creating a new community, recruiting families affected by a rare genetic mutation from across the country and around the world. Their goal: to provide parents and clinicians with the accurate information Courtney had lacked four years ago.

In 2019, several weeks after his birth, Courtney's son had begun to experience seizures, and the doctors they'd seen were slow to react. They first thought he was displaying signs of acid reflux. Courtney, who works in special education, had experience with kids with learning differences. But her son's seizures were the first she had witnessed. (To shield her son's future privacy, we are using her first name only.)

After pushing for more information and then agreeing to pay out-of-pocket* for genetic testing, she and her family received an extensive report, but they needed help making sense of it. The report said that her son's genome carried a mutation in the gene encoding the protein CTCF. However, no information was available about what parents might expect. Searching online, Courtney found references to Victor Corces, an Emory geneticist who had published several papers about CTCF.

"There were 39 cases known in the whole world," she says. "I was just a mom asking for help. I didn't know what CTCF was."

When she contacted Corces, Courtney was surprised to see an answer come back the same day. Corces did have plenty of experience studying CTCF's functions, both in Drosophila fruit flies and in mice. He was willing to help, although he wasn't a medical doctor.

"He was my only ally at the time," she says.

From Corces, she learned something about what CTCF does. Picture DNA in the cell nucleus as an unruly pile of extension cords in the garage. CTCF organizes the DNA into manageable loops. Tinker with CTCF, and genes shaping brain, heart or skeletal development might be on or off at the wrong time or in the wrong cells. That might explain why some people with CTCF mutations had intellectual disability, cardiac defects or changes in their craniofacial structure.

Learning more together

In an initial effort to gather information about CTCF mutations, Courtney wrote hundreds of emails. Many were to genetics specialists, asking them to share her information with their patients. She participated in Facebook groups for parents of children with special needs, and eventually started her own. In this way, she found her first compatriot, a mom in New York

whose child also had a mutation in CTCF. Other families she found had received diagnoses years before, but also felt alone. Once they met others dealing with the effects of similar mutations, they could compare notes. But the symptoms weren't the same in each individual, which was confusing.

"When you're dealing with a genetic mutation that nobody understands, there's nothing better than reaching out to someone else who knows what you're going through," Courtney says.

Soon after their email exchange, Corces conferred with Hong Li, a medical geneticist at Emory, at a Department of Human Genetics retreat. Courtney's son was already scheduled to see Li at the Emory genetics clinic in two weeks. Li was intrigued, even though information about the clinical effects of CTCF mutations was limited. Meeting the family confirmed her interest.

"I was very impressed by the connections she had already made," Li says. "I said: 'Maybe we can learn more about this disease together.'"

Li eventually recruited Gabriella Valverde de Morales, an Emory genetics counseling student, to systematically gather information about people with CTCF mutations. Hsiao-Lin Wang, a postdoctoral fellow in Corces' lab, joined in too. Together with the contacts Courtney had made via social media, it began to feel like a community.

"Dr. Li will answer my phone call when we are in the emergency department at midnight, and will tell the other doctor what's going on," she says. "It really helps, because most doctors – even pediatric neurologists -- have not encountered someone with a CTCF mutation."

For Rare Disease Day in 2020, the group visited the Georgia state capitol to advocate for greater attention to rare diseases. Researchers and families from around the world recently held a Zoom conference, with plans for an in-person gathering next year.

Li and colleagues recently published a paper in the American Journal of Medical Genetics describing more than 100 people with CTCF mutations, recruited from North America, several European countries, Australia and Israel. Most have some form of intellectual disability or developmental delay, such as motor or speech delay. While some are severely affected, a few attend college. One distinctive aspect of the paper: a face. Using computer modeling, the authors created an image of typical patient's facial features, which could facilitate clinical recognition and diagnosis.

Some families report cardiac defects, cleft palate or hearing loss, but these are not universal features of CTCF-related disorder. The group has developed a list of tests and examinations newly diagnosed patients should undergo to catch potential problems. Armed with this information, one family discovered their child had a heart defect and was able to intervene before it became severe.

And through research in Corces' lab conducted by Hsiao-Lin Wang, Courtney now has some answers – still incomplete – to her original questions about why her son experiences early onset seizures and how best to control them. Her son's unique mutation in CTCF appears to perturb the activity of sodium channel genes, which control electrical signals in brain cells. This information could guide discussion with neurologists about optimal medications, she says.

In the fall of 2022, Li and Corces obtained a grant from the National Institute of Dental & Craniofacial Research to study in greater detail how the effects of CTCF mutations are connected with the protein's function. Li says she wants to examine other factors that may influence the symptoms a child with a CTCF mutation may experience, such as cleft palate or seizures.

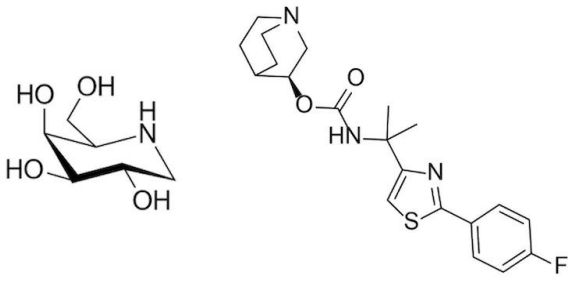
*The family later received a grant from GeneDx's Odyssey program for exome sequencing, which is often not covered by insurance.

NOTE: a similar effort organizing families affected by GRIN (glutamate receptor) mutations has been facilitated in recent years by the Department of Pharmacology and Chemical Biology's Center for Functional Evaluation of Rare Variants.

New horizons in the therapeutic landscape for Fabry disease

DOHG's William Wilcox appeared as co-author on two multi-site studies of Fabry disease, both published near the end of 2022. These publications provide a view of the therapeutic landscape for Fabry disease. Enzyme replacement therapy became available in 2001 in Europe and 2003 in the United States. Although enzyme replacement therapy was a significant advance, Fabry disease patients can describe its limitations, and issues such as the optimal dose, when to start therapy, and the clinical impact of anti-GalA antibodies remain unresolved. Development of a variety of additional medications and gene therapies continues today (including a gene therapy study here).

Migalastat or Galafold was approved in 2018 (after initial rejection). Migalastat, a simple iminosugar molecule, is not an enzyme replacement; instead, it rescues the function of "amenable" GalA mutations by binding and chaperoning the misfolded protein. The newly published study, sponsored by migalastat's maker Amicus Therapeutics, was meant to address the contrasts between findings from real-life studies and results of the pivotal clinical trials that led to FDA approval. It collects data on the frequency of Fabry-associated clinical events (FACEs) from several phase III studies, in comparison with long-term historical data.



18 - Molecular structures of migalastat (left) and venglustat (right)

The story with venglustat – fast-tracked for Fabry but not FDA-approved -- is not as advanced as with migalastat. Venglustat is an inhibitor of the enzyme glucosylceramide synthase, which catalyzes an early step in the synthesis of glycolipids. Inhibition of GBS lowers substrate availability, and thus reduces the accumulation of glucosylceramide, the driver of lysosomal dysfunction and organ damage in Fabry and other lysosomal storage diseases.

With venglustat, GBS's critical position in glycolipid synthetic pathways led manufacturer Sanofi to study the drug's efficacy for more prevalent conditions. Until 2021, Sanofi was developing venglustat for autosomal dominant polycystic kidney disease (ADPKD) and Parkinson's, but flat clinical trial results pushed the company into abandoning both programs. For Fabry disease, investigators were able to measure positive effects on cellular and biochemical markers of lipid accumulation, but longer-term outcomes remain to be evaluated.

The tricky thing about this field is comparing events from different studies – the migalastat authors cite "the clear need for standardizing the definitions of FACEs to allow for better evaluation of treatment outcomes across studies, as well as the need for data sharing across multiple industry and academic partners."

Journal of Medical Genetics, December 21, 2022, Long-term multisystemic efficacy of migalastat on Fabry-associated clinical events, including renal, cardiac and cerebrovascular outcomes

Molecular Genetics and Metabolism, November 9, 2022, Venglustat, an orally administered glucosylceramide synthase inhibitor: Assessment over 3 years in adult males with classic Fabry disease in an open-label phase 2 study and its extension study

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DOHG technical editor Quinn Eastman is serving as newsletter editor. To reach him with questions, ideas or submissions for the Human Genetics Dispatch, please email **qeastma@emory.edu**.