Human Genetics Dispatch Fall 2023

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DOHG

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Chair's Corner

1 - Human Genetics Chair Peng Jin, PhD

Welcome to the fall edition of the Department of Human Genetics Dispatch for 2023.

I am pleased to recognize some of the excellent research communication and outreach efforts within our department. We had a strong presence at this year's American Society for Human Genetics meeting in Washington, DC, with five trainees delivering platform talks -- Shijia Bian, Tingyang Hu, Kelsey Robinson, Azalea Lee, and Katherine Westover -- along with 19 people delivering poster presentations.

This fall, the first-ever Medical Genetics Student Symposium allowed prospective geneticists and genetic counselors to get a taste of this challenging and exciting field, which combines human compassion and scientific puzzle-solving. The symposium, featuring a diverse career panel, captivating case presentations, and a comprehensive poster session, drew over 50 undergraduates, medical, and public health students on site, with a significant online attendance. This level of interest from across Georgia and the Southeast reflects the medical genetics field's pull and our medical professionals' versatility and approachability. Kudos to the organizing team, including medical students Meredith Fuchs, Wendy Lee, and Brandy Njai, and postdoctoral fellow Erkin Ozel, with support from faculty advisors Hong Li and Rossana Sanchez Russo.

In our ongoing efforts to recognize and celebrate excellence, I'm excited to share that the Department of Human Genetics is forming a Recognition Committee. This committee will focus on identifying and nominating deserving faculty, staff, and trainees for various departmental, School of Medicine, Emory institutional awards, and other accolades. Moreover, it will aim to put forward nominations for regional, national, and international professional organization recognition. I welcome your suggestions and ideas on how we can best steer the committee's efforts.

Enjoy the upcoming holiday season.

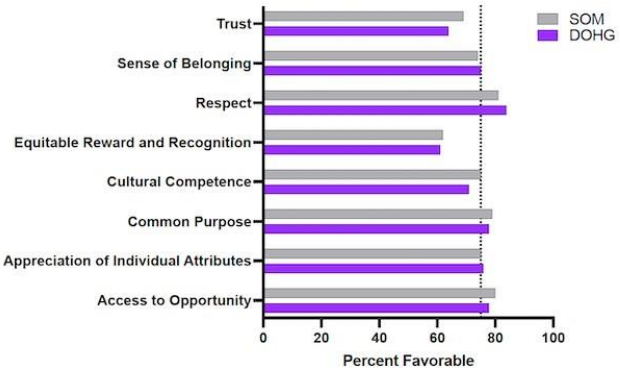
Peng Jin, PhD

Professor and Chair

From our DEI Committee

Survey data

Thanks to those who responded to the School of Medicine's recent Diversity Engagement Survey. Examining the results reveals a few tidbits. Mostly, our department's results were similar to the SOM as a whole. We displayed strong ratings as far as Respect and Sense of Belonging. Areas where the favorable rating was not as strong, both absolutely and in comparison to the SOM, were in Trust and Cultural Competence. Potential room for future improvement?



2 - Comparison of Diversity Engagement Survey results: DOHG vs SOM

Within DOHG, our cohorts are planning the rest of their meetings, and the DEI committee will need to evaluate and decide what's next. The DEI Book Club is reading Disability Visibility and plans to discuss it on Thursday, 11/30 at 1 pm. Also, welcome DEI committee chair Kate McCann, back from maternity leave!

Upcoming DOHG events

Upstander/Bystander training on Monday 12/11 at noon

Seminar Monday 1/29 at noon: Sarah Caston, PT, DPT, *Disability Inclusion in the Medical Sciences: Turning from Paradox toward Possibility*

SOM DEI office

Community Forum on Engagement, Equity and Inclusion

Thursday, 11/16, noon, Zoom/SOM153A

Department Spotlights

Get to know your DOHG colleagues. Each issue will feature randomly selected staff, faculty or trainee profiles. Also, we'd like to congratulate graduate student **Samantha Lanjewar** for the *2023 Outreach & Community Service Award* from GDBBS (the Graduate Division of Biological and Biomedical Sciences).

*3 - **Dawn Laney, MS, CGC***

My research interests revolve around unsolved mysteries in Fabry disease and other Lysosomal Storage Disorders. Currently, I'm finishing up a 5 year longitudinal study looking at medical issues and biomarkers in infants and young children living with Fabry disease, who were

diagnosed via family history or newborn screening. In addition to other clinical trials and projects, I am also working on an investigator-initiated project characterizing the phenotype and modifiers of a controversial variant in the *GLA* gene (A143T). The whiteboard in my office has a laundry list of additional patient-focused topics, should anyone like to collaborate!

One of my favorite things about my current job is that every day brings something new. On any given day, I could be teaching genetic counseling students about human development and malformation, seeing one of the genetic counseling patients I have followed for over 20 years, coordinating subjects for a gene therapy study, planning out the 5 year vision for the Genetic Clinical Trials Center, brainstorming with the GCTC team, collaborating with patient advocacy groups on a manuscript, or moderating a symposium at a national meeting.

When I'm not working, I have a start-up with my family called ThinkGenetic that is working to identify patients at risk for genetic conditions. Between that and carpooling my teenagers around to everything from blacksmithing to marching band to Tae Kwon Do, my main hobby is sleeping. Someday, I'll return to my earlier hobbies of painting and writing books, but maybe not for a year or two. I started this journey with a BA in history and biology at Trinity College in Hartford, CT and then completed my training with a MS in Genetic Counseling from Sarah Lawrence College in Bronxville, NY.

*4 - **Genetic Counselor Fabienne Ehivet, MS, CGC***

My professional interests are to expand knowledge about the genetic counseling profession, facilitate access to and understanding of genetic testing, and to provide psychosocial support to patients and their families. Those are the reasons that drew me to the profession of genetic counseling.

I believe that what you give life is what you get back, so what I give patients is what I will receive. Whether it's respect, patience, empathy or understanding, it is well received and reciprocated. My greatest reward is to hear patients say: "I am glad I came to this appointment, I learned a lot. "

After being recommended by a former patient, I was part of a Pancreatic Cancer Action Network (PanCAN) panel discussion about early detection of pancreatic cancer. I was later invited to join PanCAN's Health Equity Committee. I have spoken about genetic counseling as a career at events sponsored by Morehouse School of Medicine and Fernbank Science Center. I have also spoken about family history and genetic testing options for the Center for Black Women's Wellness and the Eric & Deborah Dewitt VGJazz Foundation. All these activities have been very rewarding and I look forward to participate in more outreach activities.

I completed my B.S. in Biochemistry from the University of Cocody in Cote d'Ivoire, where I am originally from. I came to the US and completed a M.S in Food & Nutritional sciences at Tuskegee University and then completed a M.S in Genetic Counseling from Sarah Lawrence College. My hobbies include spending time with family and friends, listening to music -- especially gospel music, watching movies, and cooking.

*5 - **Neuroscience graduate student Abby Galvez***

My research focuses on understanding the underlying pathophysiology of major psychiatric disorders, with a focus on bipolar disorder (BP) in the lab of David Weinshenker. Our selectively bred Hyperactive (HYPER) rat model reflects the oscillating nature of BD through pronounced outbursts of hyperactivity and psychomotor retardation. We use genetic and molecular techniques to study differences in gene expression and protein localization that may contribute to the HYPER rat phenotype.

I completed my B.A. in Psychology and minored in Biology while at Cornell University. While there, I worked in the lab of Dr. Alexander Ophir, studying the role of the lateral septum (LS) in aggression. I then participated in Northwestern's PREP program, where I worked toward optimizing electrical stimulation to the hippocampal network to produce memory improvements in an Alzheimer's rat model in the lab of Dr. John Disterhoft. During my rotations with the Neuroscience faculty at Emory, I became increasingly interested in the function of

basal ganglia in motor control, reward processing, and decision-making before ultimately joining the Weinshenker lab.

During my free time, you will find me trying new restaurants in the Atlanta area, or recreating cooking and baking recipes.

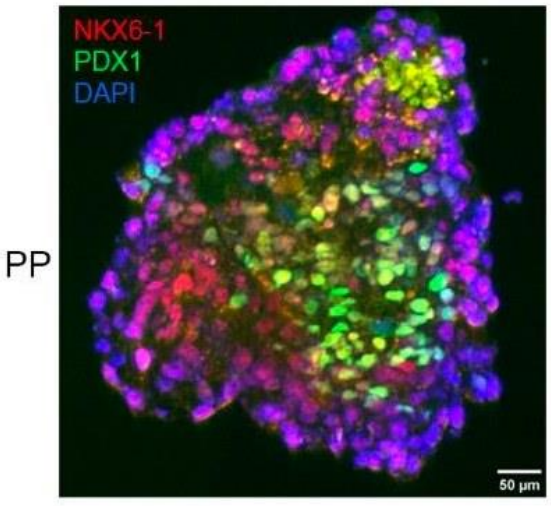
Key Discoveries: Human Genetics

Regulation of CTCF loop formation during pancreatic cell differentiation

-- Victor Corces, PhD

The DNA-binding protein CTCF performs an "anchor" function in chromatin, underpinning DNA loops that regulate gene expression. Xiaowen Lyu and colleagues in the Corces lab examined pancreatic cell differentiation through the lens of CTCF loop formation, using the Hi-C crosslinking technique to capture 3D interactions. Taking advantage of well-characterized model systems for pancreatic cell differentiation, they found that CTCF loops are dynamic throughout that process, forming and disassembling together with changes in other chromatin modifications such as DNA methylation and histone methylation.

Regulation of CTCF loop formation during pancreatic cell differentiation, Nature Communications, October 9, 2023



6 - Pancreatic progenitors, from Lyu et al (2023)

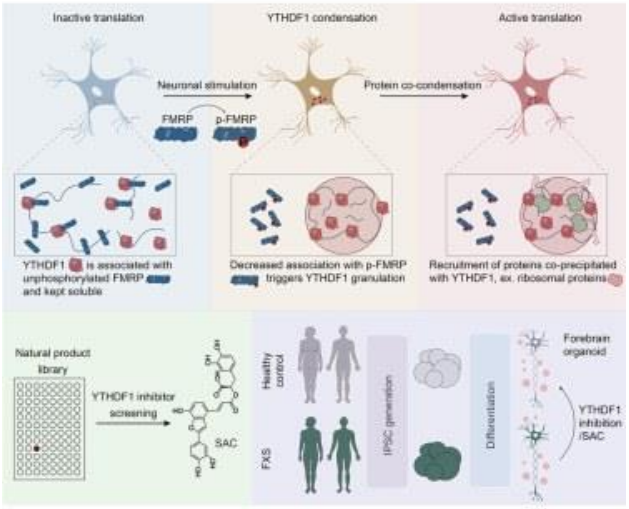
How m6A methylation of mRNA is connected to FMRP

-- Peng Jin, PhD

This tour de force from Chicago advances our understanding of how the fragile X protein (FMRP) regulates translation in neurons. Peng Jin's laboratory contributed with both forebrain organoid cultures and a FMRP-phosphorylation-blocked mutant mouse, whose full characterization is yet unpublished. FMRP was already thought to be a suppressor of mRNA translation, but the authors show how several molecular events -- N6-adenosine (m6A) methylation of mRNA, the m6A binding protein YTHDF1, and FMRP phosphorylation -- are connected together.

YTHDF1 and FMRP proteins both contain intrinsically disordered domains, and are prone to condensation and phase separation. In cells, their physical association and localization respond to depolarization. The paper also includes identification of SAC (salvianolic acid C) as an inhibitor of YTHDF1, with the ability to reverse hyperactive translation in FMR1-negative neurons and forebrain organoids. While the pharmacokinetic properties of SAC may not be ideal for a potential drug, SAC represents another lead worth investigation in the quest for fragile X therapies.

FMRP phosphorylation modulates neuronal translation through YTHDF1, Molecular Cell, November 9, 2023



7 - Graphical abstract from Zou et al (2023)

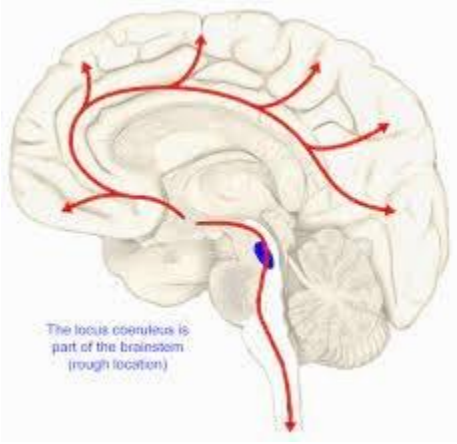
Part of my brain's got the blues

-- David Weinshenker, PhD

The name of the locus coeruleus, the Weinshenker lab's favorite part of the brain, means "blue spot." But what makes it blue – and particularly sensitive to neurodegeneration? This review

explores the biology of the neuromelanin pigment and approaches to studying its role in neurodegeneration. The first author was former graduate student Alexa Ianitelli.

Riddles in the dark: Decoding the relationship between neuromelanin and neurodegeneration in locus coeruleus neurons, *Neuroscience and biobehavioral reviews*, June 15, 2023



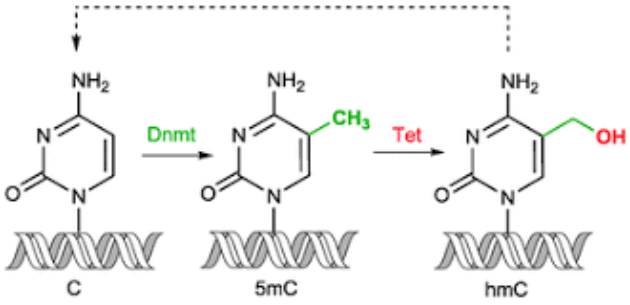
8 - The locus coeruleus is the source of most of the brain's norepinephrine

TET contributions to Alzheimer's pathogenesis

-- Peng Jin, PhD

Compromised TET enzyme function may contribute to Alzheimer's disease pathogenesis, former graduate student Matthew Armstrong and colleagues contend. The authors identify a significant enrichment of rare TET1 variants associated with early onset AD, and a disruption of hydroxymethyl-C patterns in late onset AD. In addition, they demonstrate that partial loss of Tet1 increases the amyloid plaque burden in 5xFAD mice.

Role of TET1-mediated epigenetic modulation in Alzheimer's disease, *Neurobiology of Disease*, September 27, 2023



9 - TET enzymes oxidize epigenetic marks on DNA, converting methyl-cytosine to hydroxymethyl

Insights into schizophrenia: Genetic risk factor impairs mitochondria

When a small portion of chromosome 3 is missing, called 3q29 deletion syndrome, it increases the risk for schizophrenia by about 40-fold. Former DOHG member Jennifer Mulle, now at Rutgers, has led the way in deciphering how schizophrenia develops by studying this risk factor.

In a collaboration including the Sloan lab along with the Bassell and Faundez labs in Cell Biology, scientists analyzed how patterns of altered gene activity overlap in two models of 3q29 deletion syndrome: in mice and in human brain organoids. They spotted an unexpected change in brain cells: impaired mitochondrial function.

The findings converge with work on another genetic risk factor for schizophrenia, 22q11 deletion syndrome or DiGeorge syndrome, which has also been found to involve disrupted mitochondrial function. More information here. Co-first authors: Ryan Purcell, PhD in the Department of Cell Biology and Esra Sefik, PhD (now at Princeton).

Cross-species analysis identifies mitochondrial dysregulation as a functional consequence of the schizophrenia-associated 3q29 deletion, Science Advances, August 16, 2023

10 - Genetic risk factors for schizophrenia converge on mitochondria. 3q29 deletion

Choline intake linked to working memory in PKU

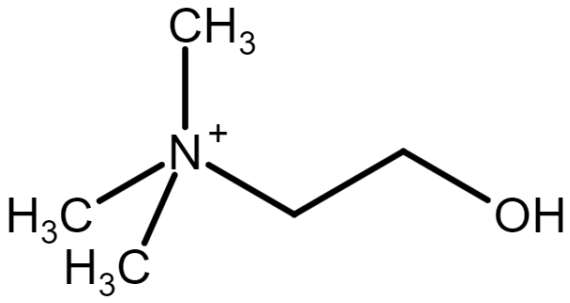
-- *Rani Singh, PhD*

Choline is an essential nutrient for brain development whose intake comes mainly through high-protein foods, which are limited in the prescribed diet for people with phenylketonuria (PKU). Meriah Schoen, Rani Singh and colleagues investigated whether insufficient choline intake may contribute to the neurological and memory deficits displayed by many people with PKU.

While choline intake did not predict a difference in working memory performance in the group studied overall, increased choline intake was associated with better memory performance in a subgroup with well-controlled Phe levels. This study is the first to evaluate the association

between working memory and choline intake in individuals with PKU. The results support clinical monitoring of choline intake in people with PKU.

Total choline intake and working memory performance in adults with phenylketonuria, *Orphanet Journal of Rare Diseases*, July 29, 2023



11 - Dietary intake for choline is considered insufficient for many in the general population, in addition to people with PKU

Galactosemia is not a progressive disorder

-- Judy Fridovich-Keil, PhD

Despite early detection and dietary avoidance of galactose, many patients with the classic form of galactosemia experience long-term developmental complications, such as speech, motor, and cognitive deficits. In the galactosemia community, whether those deficits are progressive – that is, worsening over time as the patient gets older -- has become a point of uncertainty and confusion.

To address this question, Nikki Smith, Judy Fridovich-Keil, and colleagues analyzed Vineland scores (a measure of adaptive behavior, or everyday capabilities), medical records, and family responses to customized surveys. The authors concluded that galactosemia-related complications are not progressive for most affected patients. They also showed that children with galactosemia, while gaining milestones, tend to reach them at a slower pace than metabolic-typical counterparts. Normed scores may thus give parents the false impression of a decline in ability when in reality the child is still gaining milestones – just slowly.

Note: a small group of galactosemia patients and controls who experienced extremely severe neonatal symptoms was excluded from the analysis in this paper. Results for this group will be reported in the future, Fridovich-Keil says.

A related paper in *Journal of Inherited Metabolic Diseases* shows that galactosemia is associated with a grip strength deficit both in human patients and model GALT-null rats. Additional analysis suggests this phenotype may be secondary to growth delay, and is not evidence of a muscle abnormality.

Long-term complications in classic galactosemia are not progressive, Molecular Genetics and Metabolism, October 2023

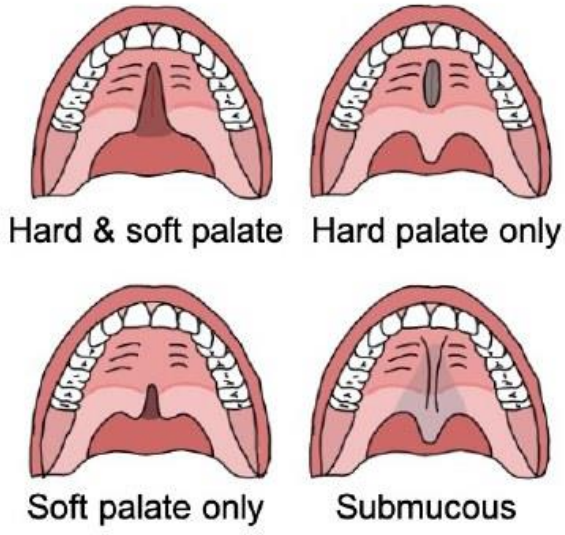
12 - In the galactosemia community, whether developmental deficits are progressive has become a point of uncertainty and confusion, Fridovich-Keil says.

Cleft palate risk genes: divide and conquer yields fruit

-- Elizabeth Leslie, PhD

Kelsey Robinson, the Leslie lab and a long list of colleagues reported the results of their GWAS of cleft palate, using a cohort of 435 case-parent trios. The authors demonstrated that the "divide and conquer" strategy (separating hard/soft palate) can identify subtype-specific risk loci. They found one new risk locus, *ANGPTL2*, which is associated with any cleft of the hard palate. *ANGPTL2* plays a role in osteoblast differentiation and is expressed in craniofacial tissue. They also identified several other loci of suggestive significance conveying an increased risk for any type of cleft palate and subtype-specific risk loci.

Trio-based GWAS identifies novel associations and subtype-specific risk factors for cleft palate, *Human Genetics and Genomics Advances*, August 25, 2023



13 - Separating orofacial clefts by hard/soft palate can identify subtype-specific risk loci

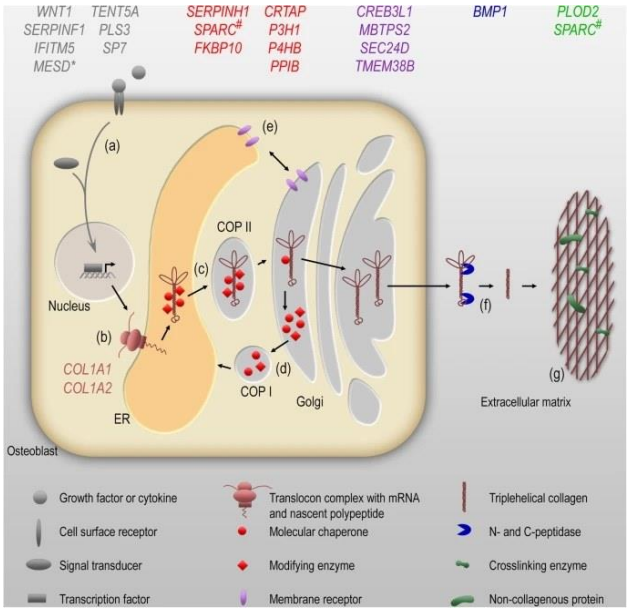
Indirect tweaks to collagen expression lead to cleft lip

-- Elizabeth Leslie, PhD

How do synonymous variants drive a particular type of structural birth defect? These cleft lip-assocated variants don't change protein sequence, but they can either destroy or create new transcription factor sites in an enhancer. That enhancer regulates expression of *SEC24D*, which is critical for bone formation and necessary for the export of type 1 procollagen.

In this paper, Sarah Curtis and colleagues demonstrate how rare variants in *SEC24D* are associated with cleft lip, in comparison with cleft lip and palate. Many of the variants are in a craniofacial-specific enhancer. Missense mutations in *SEC24D* can cause osteogenesis imperfecta (OI) in humans; most OI cases are caused by mutations in collagen genes.

Rare variant modifier analysis identifies variants in SEC24D associated with orofacial cleft subtypes, *Human Genetics*, September 7, 2023



14 - OI genes involved in collagen biosynthesis and maintenance of bone homeostasis. SEC24D is *necessary for the export of type 1 procollagen.*

Exome sequencing of multiplex OFC families: an inclusive strategy

-- Even more publications from the Leslie lab!

Orofacial clefts are highly heritable, but with complex penetrance; sometimes family members display subclinical alterations of the mouth or palate anatomy. The Leslie lab and collaborators took the strategy of performing exome sequencing in 31 multiplex OFC families, including some individuals with subclinical phenotypes. They identified likely causal variants in six genes: COL11A2, IRF6, SHROOM3, SMC3, TBX3, and TP63. The first author was former Leslie lab graduate student Kimberly Diaz-Perez, now at University of Michigan.

Rare variants found in multiplex families with orofacial clefts: Does expanding the phenotype make a difference?, American Journal of Medical Genetics A, June 23, 2023

"Sporadic" OFC cases: assessing what diagnostic yield would be

This paper represents the opposite side of the coin for OFC cases (compared to the situation above), when the proband doesn't have other family members displaying related phenotypes. Sequencing is usually not performed in this case; the Leslie lab dove in anyway to assess how often an un-revealed variant might be playing a causal role.

Collecting sequencing data from more than 800 OFC cases, the authors checked a list of 418 genes thought to be associated with OFCs. Overall, around 9 percent of cases contained "likely pathogenic" variants; the percentage was higher for cleft palate (>17%) compared to cleft lip

(<3%). The variants clustered in nine genes accounting for most of the yield. Kimberly Diaz-Perez was first author for this one too.

Rare variants found in clinical gene panels illuminate the genetic and allelic architecture of orofacial clefting, *Genetic Medicine*, June 15, 2023

Making a long list of craniofacial genes

The Leslie lab teamed up with Justin Cotney's lab from UConn to analyze RNA sequencing data from human fetal craniofacial tissue. The authors assembled a list of more than 500 genes likely to contribute to craniofacial disorders -- the listed genes contain increased levels of de novo mutations in patients with orofacial clefts.

Integrative analysis of transcriptome dynamics during human craniofacial development identifies candidate disease genes, *Nature Communications*, August 2, 2023

Healthcare experiences of African American women with the fragile X premutation

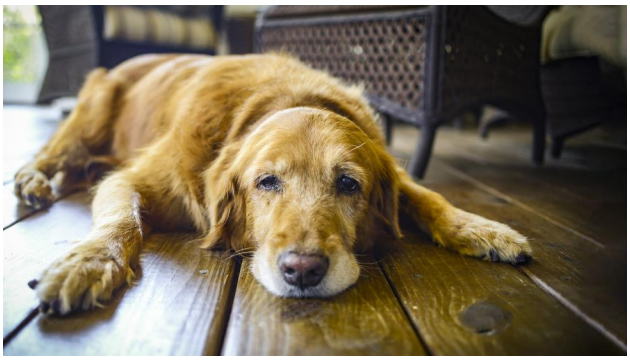
-- Emily Allen, PhD, Nadia Ali, PhD, Cecelia Bellcross, PhD, Fabienne Ehivet, MS, CGC

Eight African American women with a fragile X premutation were interviewed to explore disparities in receiving healthcare and to learn about psychosocial experiences during and after their diagnoses. Almost all of them had children with fragile X syndrome. Participants reported concerns about not being taken seriously by providers, as well as mistrust of medical institutions. The first author of this paper was genetics counseling student Andrew King. This work builds on previous related DOHG papers from Poteet et al and Visootsak et al.

Several of the interviewees had to explain their premutation to the medical professionals they saw, the authors report: “The doctor was not open to understanding fragile X… an old dog who didn’t wanna know new tricks.”

Within families, interviewees reported denial, insensitivity, and isolation. The authors propose that interventions designed for African American women, such as family counseling sessions and inclusive support from national organizations, could ease the impacts of a premutation.

Healthcare Experiences of African American Women with the Fragile X Premutation, Journal of Racial and Ethnic Health Disparities, September 15, 2023



15 - One interviewee described her physician as "an old dog who didn't wanna know new tricks," when it came to the fragile X premutation and its associated health issues for carriers.

A critical look at medical students' genetics curriculum

-- Kate Garber, PhD, Nadia Ali, PhD, Lauren Lichten MS, CGC

How much do medical students remember of what we (geneticists and genetic counselors) teach them? While students understand the core concepts, they don't remember many of the clinical applications that are carefully presented to them, the authors conclude ruefully. This paper emerged from genetics counseling student and first author Sunaina Kapur's capstone project; Kapur is now at Piedmont.

The authors held focus groups with Emory medical students in 2020, and provide some dispiriting quotes from those sessions. As a result of their findings, the authors are planning to modify the preclinical curriculum, so that clinical applications of genetics and problem-solving methods, rather than static facts, are stressed. Additional interventions will introduce genetics in a more dispersed way throughout the clinical curriculum. The authors also highlight potential contributions by genetic counselors in medical education.

Poor recall of genetics curriculum by medical students highlights barriers to use in clinical practice, *Journal of Genetic Counseling*, September 21, 2023

16 - Emory medical students in SOM lecture hall

Newly Funded Research

Probing the roles of cilia in astrocyte development

Rachel Bear, a Neuroscience graduate student in Tamara Caspary's lab, was awarded an F31 predoctoral fellowship from the National Institute of Neurological Disorders and Stroke. She will use mouse models to genetically ablate cilia at distinct timepoints. She will determine how cilia regulate astrocyte proliferation, differentiation and gene expression.

Genome-wide dysregulation of R-loops in ataxia telangiectasia

The inherited neurological disorder ataxia telangiectasia (AT) is caused by mutations affecting the ATM kinase, which plays a crucial role in DNA damage responses. Katherine Westover, a GMB graduate student in Bing Yao's lab, will investigate the role of dysregulated R-loops – RNA/DNA hybrid structures – in AT, using patient-derived cellular models. Westover will test whether METTL3, a recently identified substrate of ATM that methylates adenosine residues in RNA, plays a role in AT DNA repair problems. NIH reporter link (F31)

Ten genes, one disorder: convergence in autism risk pathways

Forebrain assembloids offer an advanced model system for studying the biology of neurodevelopmental disorders in human cells. Fikri Birey was awarded an "explorer track" grant to examine the effects of introduced mutations in 10 high-risk ASD (autism spectrum disorder)

genes. His lab will probe functional connectivity in mutated forebrain assembloids via imaging, electrophysiology and opto/chemogenetics tools. Birey's group was one of 15 teams who were funded under the Simons Foundation Autism Research Initiative's request for applications. The award is for $400,000 over three years.

Medical Genetics

Awards

Rossana Sanchez Russo was selected for the 2023 Adam Bailey Service Award from Emory Healthcare, based on her "intent, compassion, and overall commitment to improving the quality of care for our patients." She was chosen from several video submissions by the Adam Bailey Steering Committee and Patient Experience Team.

Adam was a team member at The Emory Clinic until his tragic passing in January, 2016. In his memory, a $2,000 annual award was created to honor the qualities he so strongly possessed: service, compassion, and community.

17 - Photo after EHC Service Hero Award ceremony. *From left to right: Hong Li, MD, PhD, Margie Leathers, BSN, RN, CPN, Caitlin Flatley, MS, RD, Rossana Sanchez Russo, MD, Juanita Neira, MD*

*18 - **Photos from the first Medical Genetics Student Symposium***

Poster session top, career panel bottom

"In medical genetics, we like to put the pieces together, to make a larger picture," said Rana Al-Jaberi, MD, a current medical genetics resident and one of the career panelists.

One highlight was a memorable case presentation from Jaime Vengeochea, describing a patient with Li-Fraumeni syndrome (high cancer risk) who came to the clinic with her sister.

All of Us "Lunch and Learn" events (both noon - 1 pm)

Tuesday, 11/21 Genomic Data/Researcher Workbench, CNR4001 RSVP Link

Wednesday 1/24, Your DNA story - Emory Student Center, in collaboration with Atlanta Black Nurses Association Link

PMF Duckrace and Family Pool Day

What started out as a fundraiser for a patient assistance fund turned into a lighthearted memorial for a beloved teacher: Paul Fernhoff, former head of medical genetics, who died in 2011.

On September 10, Dawn Laney and family held the annual Duck Race event at their home swimming pool (it was previously held at the Student Activity/Academic Center pool). The contributed funds now benefit student scholarships in honor of Fernhoff, and genetics counseling students enjoyed the fruit of the grill.

Dawn was also nominated for Invitae's 2023 Heart of Genetic Counseling award.

*19 - **Go ducks!***

Deep dive into SYNGAP1

Jansen Jones is a Georgia teenager whose neurodevelopmental disorder was diagnosed by Emory medical geneticists led by Rossana Sanchez Russo. This summer, she was featured on local television, and her story touches on some common themes for medical genetics and rare diseases.

Jansen's parents first noticed developmental delay and hypotonia at infancy, and they submitted her DNA for genetic testing at age 3. Although the results were inconclusive, her parents kept pushing for explanations, despite being advised by some doctors to give up and focus on day-to-day care. Her family finally got an answer in 2021, with a more comprehensive genetic sequencing approach. It turns out that previous sequencing efforts -- very thorough: whole exome and several panels -- had missed a variant in the SYNGAP1 gene.

The new information, while it did not change Jansen's daily life or medications, was still a big deal. It provided causal information her family didn't have before, and it led her parents to jump into fundraising and advocacy. They were welcomed by a rare disease community that has grown with impressive speed. Suzanne Jones, Jansen's mother, became the chair of the board of directors for the SynGAP Research Fund. Jansen's family has already put a lot of material out there already; here we will focus on three issues.

20 - SynGAPians like Jansen Jones are reported to have "an unusual affinity for the sensation of water on their skin."

What was special about the sequencing?

Jansen's SYNGAP1 variant is on chromosome 6, close to an intron boundary. Previous whole exome sequencing didn't pick up the variant because of poor coverage. Variantyx, which performed the more recent sequencing, attributes success to its PCR-free approach. PCR-free is supposed to have more uniform coverage, but it is not unique to Variantyx and is offered by other companies.

What is distinctive about SynGAP1?

SYNGAP1 encodes a synaptic protein that is a part of the Ras pathway and a molecular hub for the regulation of synaptic strength. It makes sense that a missense mutation in this gene leads to "neurons firing wildly" (as her mother explains) and developmental delay, intellectual disability, seizures and the rest of the reported symptoms. SynGAP is on the Simons Foundation Autism Research Initiative's list of autism risk genes and is one of the genes whose functions our own Fikri Birey will probe in his SFARI-funded project.

It's clear that Jansen's family has put major effort into supporting her care and designing an educational/therapeutic program for her. In her family's videos, Jansen can be seen riding horses and swimming comfortably.

The SynGAP Research Fund maintains an updated census of people with the diagnosis: almost 1,300 worldwide and more than 300 in the United States. They have estimated that the true prevalence may be comparable to that of other genetic disorders such as Dravet syndrome, Rett syndrome and Angelman syndrome. Difficulties in sequencing SynGAP1 variants might have complicated past diagnoses.

What are the prospects for therapeutic development?

The SynGAP Research Fund was started around 2018. But anyone familiar with medical genetics has observed how communities like it have proliferated in recent years. An entire ecosystem has grown up to support them, with non-profit groups such as Global Genes and the National Association of Rare Diseases, along with biotech and pharmaceutical companies.

Until recently, pharmacologists might look at SynGAP1's place in neuronal signaling and throw up their hands. Maybe some small molecule drug could counterbalance the lack of an important synaptic protein. But the advent of splice-switching oligonucleotides (SSOs) changes that picture. Now it is possible to envision customized therapies.

This summer, a team in Boston published a framework for individualized splice-switching oligonucleotide therapy, using the spectrum of ataxia-telangiectasia mutations as a model. A similar approach has been validated in cell culture models for SynGAP1 mutations. Labs at Penn and University of Chicago have demonstrated that antisense oligonucleotides can

promote expression from the intact SynGAP1 allele, by disrupting interactions with PTBP splicing proteins.

Earlier this year, Penn and Children's Hospital of Philadelphia announced a $25 million gift establishing a Center for Epilepsy and Neurodevelopmental Disorders, which has SYNGAP1 as one of its focus areas. The company Stoke Therapeutics has named SynGAP1 as one of its targets for RNA-based therapies (along with Dravet and Rett). The bottom line: there's a lot of momentum around SSOs -- and SynGAP1 in particular.

In Other Department News

- DOHG Website (link)
- DOHG Events (link)
- More DOHG News (link)
- **SOM News** (link)

Contact Us

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**.