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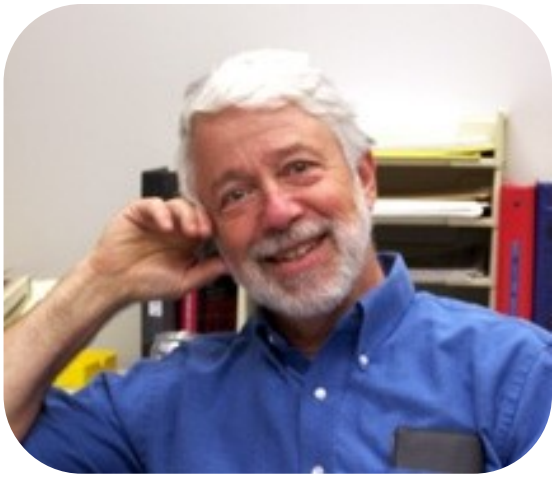
IOWA | Interdisciplinary Graduate Program in Genetics

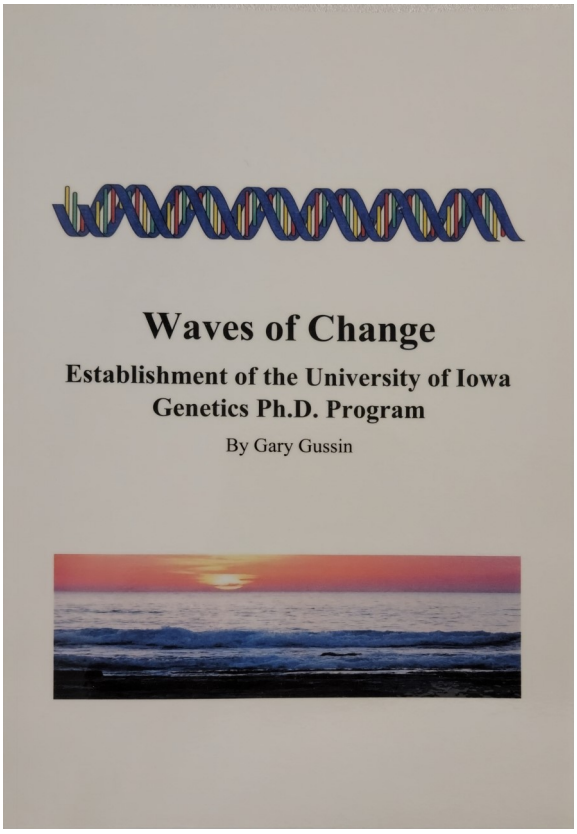
Dr. Gary Gussin
Professor Emeritus
Department of Biology

University of Iowa



Dr. Gary Gussin is a Professor Emeritus in the Department of Biology. Dr. Gussin was instrumental in the establishment of the Interdisciplinary Graduate Program in Genetics during the 1960's and was elected as the first Chairperson of the Program in 1975. Dr. Gussin published a book in 2021 titled *Waves of Change: Establishment of the University of Iowa Genetics Ph.D. Program*. The book recounts the early years of the program and successes, struggles, and contributions by the many faculty and administrators that helped develop the Program.

Wave of Change can be obtained by providing a minimum $20 donation to the Interdisciplinary Graduate Program in Genetics.



IOWA | Interdisciplinary Graduate Program in Genetics

STUDENT RETREAT

Keynote Speaker

Abby Dernburg Ph.D.

Professor of Molecular and Cell Biology

University of California Berkeley

Alumni Speakers

Dina Ahram MSc, Ph.D.(2014), FACMG, MB(ASCP), CGMBS

Chief Laboratory Officer
Insight Medical Genetics

Senior Clinical Laboratory Director—Molecular Genetics
Quest Diagnostics

Marwan Tayeh Ph.D.(2007), FACMG

Associate Professor
Department of Medical & Molecular Genetics
Director, Diagnostic Genomics Laboratory

Indiana University School of Medicine

Friday, October 7

Public Keynote Talk—Abby Dernburg

UI Art Building West

5:00pm Hors d'oeuvre

6:00 Public Talk

"Quality control during sexual reproduction - lessons from the nematode C. elegans"

Saturday, October 8

Genetics Program Events

8:00am **Check-in & continental breakfast**

8:30 **Opening Remarks**
Dr. Hatem El-Shanti, M.D.—Retreat Committee Chair

8:40 **Student oral presentations—Session 1**
* Maria Valdes Michel (Phillips lab, Biology)
* Sam Mellentine (Tootle lab, Anatomy & Cell Biology)
* Kristen Rohli (Stephens lab, Internal Medicine)

9:45 **Poster session 1**—odd numbered posters
(Refreshments available)

10:45 **Alumna Speaker**
Dina Ahram MSc, Ph.D., FACMG, MB(ASCP), CGMBS
"Carving out a path in clinical, diagnostic genetics"

11:15 **Alumnus Speaker**
Marwan Tayeh Ph.D., FACMG
"Somatic Mosaicism and Li-Fraumeni Syndrome"

12:00 **Lunch**

1:00 **Student oral presentations—Session 2**
* Yann Vanrobaeys (Abel lab, Neuroscience & Pharmacology)
* Emily Adelizzi (Dunnwald lab, Anatomy & Cell Biology)
* Nate Mullin (Mullins lab, Ophthalmology)

2:00 **Poster session 2**—even numbered posters
(Refreshments available)

3:15 **Keynote Speaker**
Abby Dernburg Ph.D.
"Spatial regulation of meiotic recombination: Counting to One"

4:30 **Closing Remarks & Award Ceremony**
Dr. Hatem El-Shanti, M.D.—Retreat Committee Chair

IOWA | Interdisciplinary Graduate Program in Genetics

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Program History

The Interdisciplinary Graduate Program in Genetics at the University of Iowa is a broad-based interdisciplinary training program that incorporates an ever-expanding range of techniques, model organisms and approaches to actively address critical issues in biology, medicine, evolution and genomics, with genetics as a common intellectual thread. Its purpose is to optimally prepare scientists that can be at the forefront of genetics research and become future leaders in any area of modern genetics, from bioinformatics and -omics to molecular genetics, gene discovery and mapping, cancer and medical genetics, and personal medicine. Our mission for society is to train a diverse cohort of graduate students in the broad discipline of genetics who are highly prepared and well-equipped to educate all members of society, who will increasingly need to understand genetic aspects of their own family's health care and individualized genomes.

The Genetics Program curriculum is designed to provide a solid and broad foundation in genetics and foster strong independent critical thinking skills and multidisciplinary training to equip students to meet modern challenges. Throughout the span of their educational training there is emphasis on rigor and reproducibility, responsible conduct and ethical and safe practices. The Genetics Program also provides flexibility tailored to individual needs to ensure student success. In addition, the program offers a Computational Genetics subtrack for students who want to develop particular strength in both the biological aspects of genetics and computational approaches to analyzing large and diverse sets of genomic and genetic data. Students thus equipped have been extremely successful in filling a growing niche in contemporary science. Research opportunities within the program span the spectrum of genetics, from bacterial to model organism to human genetics, and from developmental genetics to evolution, from epigenetics to genomics to disease mechanisms.

After several formative years of interdisciplinary research activity in Genetics on the University of Iowa campus, the Interdisciplinary Graduate Program in Genetics was approved as a degree-granting PhD program in 1975. This program that began with 7 primary faculty has now grown to currently having 73 faculty and 46 students in four colleges and 16 academic departments across our campus, with almost 200 graduates. While the history of the program makes the University and the state of Iowa proud, it is the continued pursuit to change and incorporate novel ideas, methods and societal needs that keeps successfully preparing our students. We have an enviable record of program completion, on-time graduation rates, publications and awards, as well as career advancement to postdoctoral fellowships and faculty positions at research-intensive universities. Since 1997, the Genetics Program has been supported by a T32 Predoctoral Training Grant from the National Institutes of Health, last awarded in July 2022.

Genetics Leadership

Josep Comeron, Ph.D.
Professor, Department of Biology
Interim Director, Genetics Ph.D. Program

Daniel Eberl, Ph.D.
Professor, Department of Biology
Director, Genetics Ph.D. Program

Rob DuBay
Program Administrator
Genetics Ph.D. Program

Mackenzie Goss
Program Associate
Genetics Ph.D. Program

IOWA | Interdisciplinary Graduate Program in Genetics

Genetics Retreat Chair, Hatem El-Shanti MD

Professor, Director of Division of Medical Genetics & Genomics

Dr. El-Shanti is a Professor of Pediatrics in the Stead Family Department of Pediatrics at the University of Iowa. He directs the Division of Medical Genetics and Genomics and holds the Richard O. Jacobson Foundation Chair of Pediatrics. Dr. El-Shanti graduated from Cairo University School of Medicine and trained in Pediatrics and Medical Genetics at the University of Iowa and Indiana University. He has 28 years of experience in the identification of genetic factors that are responsible for human disorders with the ultimate goal of identifying mechanisms and biologic pathways underlying physiologic and developmental processes. He has trained and mentored graduate students, medical students, fellows and junior investigators in different academic settings and countries and co-authored more than 100 manuscripts and book chapters.

Genetics Retreat Co-Chair, Anna Malkova, Ph.D.

Professor, Biology

Roy J. Carver Professor of Biology at the Biology Department of the University of Iowa. Dr. Malkova graduated from St. Petersburg State University (Russia), where she obtained her Ph.D in Genetics. She received her postdoctoral training in Molecular Genetics at Brandeis University in the laboratory of Dr. James Haber. Before joining the University of Iowa in 2014, Malkova was Associate Professor in the Department of Biology at the Indiana University Purdue University Indianapolis. Dr. Malkova's research is aimed to unravel mechanisms of DNA repair. In particular, she is interested in repair of double-strand DNA breaks (DSBs), which are dangerous because their imprecise or faulty repair often leads to mutations and chromosome aberrations that cause genetic diseases and cancer. Her research focuses on one pathway of DSB repair called Break-Induced Replication (BIR), which she discovered during her postdoctoral research at Brandeis University. Dr. Malkova has trained many Ph.D students and authored more than 50 manuscripts published in high-impact journals including Nature, Cell, Molecular Cell and Nature Communications.

Genetics Student Committee Members

Marcelo Miranda Melo
El-Shanti Lab
Pediatrics

Tim Nguyen
Van Otterloo Lab
Periodontics

Past Oral & Poster Awardees

2021		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Tim Nguyen	Periodontics/Van Otterloo
2nd Place	Hayley Vaughn	Pediatrics/Darbro
3rd Place	Not awarded	
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Nate Mullin	Ophthalmology/Mullins
2nd Place	Kristen Rohli	Internal Medicine/Stephens
3rd Place	Jill Hauer	Otolaryngology/Smith

2020		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Tanner Koomar	Psychiatry/Jake Michaelson
2nd Place	Jacob Schillo	Anatomy & Cell Bio/Adam Dupuy
3rd Place	Jill Hauer	Otolaryngology/Richard Smith
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Taylor Thomas	Psychiatry/Jake Michaelson
2nd Place (Tie)	Nicole Recka Monique Weaver	Anatomy & Cell Bio/Rob Cornell Otolaryngology/Richard Smith

2019		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	James Mrkvicka	Anesthesia/Toshi Kitamoto
2nd Place	Alex Greiner	Internal Medicine/Barry London
3rd Place	Adam Hefel	Biology/Sarit Smolikove
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Tanner Koomar	Psychiatry/Jake Michaelson
2nd Place (Tie)	Nikale Pettie Jake Schillo	Biology/Llopart & Comeron Anatomy & Cell Bio/Adam Dupuy
3rd Place	Emily Fox	Anatomy & Cell Bio/Tina Tootle

2018		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Jessica Ponce	Internal Medicine/Grueter
2nd Place	Tyson Fuller	Biology/Slusarski
3rd Place	Kimberly Bekas	Biology/Phillips
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Ethan Bahl	Psychiatry/Michaelson
2nd Place	Leo Brueggeman	Psychiatry/Michaelson
3rd Place	James Mrkvicka	Anesthesia/Kitamoto

2017		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Emily Fox	Anatomy & Cell Bio/Tootle
2nd Place	James Mrkvicka	Anesthesia/Kitamoto
3rd Place	Melissa Marchal	Biology/Stipp
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Stephanie Haase	Biology/Lear
2nd Place	Alex Greiner	Internal Medicine/London
3rd Place	Patrick Lansdon	Anesthesia/Kitamoto

2016		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Patrick Lansdon	Anesthesia/Kitamoto
2nd Place	Matthew Strub	Pediatrics/McCray
3rd Place	Autumn Marsden	Biology/Slusarski
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Alex Greiner	Internal Medicine/London
2nd Place	Emily Fox	Anatomy & Cell Biology/Tootle
3rd Place	Wes Goar	Pediatrics/Sheffield Ophthalmology & Visual Sciences/

Past Oral & Poster Awardees

2015		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Lisa Harney	Biology/Manak
2nd Place	Eric Monson	Psychiatry/Willour
3rd Place	Fengxiao Bu	Otolaryngology/Smith
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Michael Molumby	Biology/Weiner
2nd Place	Allison Cox	Pediatrics/Bassuk
3rd Place (Tie)	Johnny Cruz Corchado Emily Toombs	Biology/Comeron Anatomy & Cell Bio/Tootle

2014		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Hung-Lin Chen	Anesthesia/Kitamoto
2nd Place	Emily Beck	Biology/Llopart
3rd Place	Katie Weihbrecht	Pediatrics/Sheffield/Seo
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Emily Petruccelli	Anesthesia/Kitamoto
2nd Place	Melissa Marchal	Biology/Houston
3rd Place	Scott Whitmore	Ophthalmology & Visual Sciences/ Scheetz/Mullins

2013		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Emily Petruccelli	Anesthesia/Kitamoto
2nd Place (Tie)	Dina Ahram Ashlyn Spring	Ophthalmology & Visual Sci/Kuehn Anatomy & Cell Biology/Frank
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Mathew Jorgenson	Microbiology/Weiss
2nd Place (Tie)	Lily Paemka Fengxiao Bu Samuel Trammell	Pediatrics/Bassuk Otolaryngology/Smith Biochemistry/Brenner

2012		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Pavitra Ramachandran	Internal Medicine/Davidson
2nd Place	Matthew Jorgenson	Microbiology/Weiss
3rd Place	Sara Hanson	Biology/Logsdon
Poster Presentation	**Student Name**	**Dept./Lab**
No Information Available		

2011		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Leah Biggs	Pediatrics/Dunnwald/Murray
2nd Place	Danielle Rudd	Psychiatry/Wassink
3rd Place	Elizabeth Leslie	Pediatrics/Murray
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Amber Hohl-Conell	Biochemistry/Geyer
2nd Place	Tara Maga	Otolaryngology/Smith
3rd Place	Juan Santana	Biology/Manak

2010		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Shyam Ramachandran	Pediatrics/McCray
2nd Place	Danielle Beekman	Biology/Logsdon
3rd Place	Megan Ealy	Otolaryngology/Smith
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Pamela Pretorius	Pediatrics/Sheffield/Slusarski
2nd Place	Leah Biggs	Pediatrics/Dunnwald/Murray
3rd Place	Heather Brockway	Biology/Smolikove/Tootle

Past Oral & Poster Awardees

2009		
Oral Presentation	**Student Name**	**Dept./Lab**
1st Place	Pamela Pretorius	Pediatrics/Sheffield/Slusarski
2nd Place	Erin Burnight	Pediatrics/McCray
3rd Place	Amber Conlee (Hohl)	Biochemistry/Geyer
Poster Presentation	**Student Name**	**Dept./Lab**
1st Place	Di Xu	Internal Medicine/Sigmund
2nd Place	Garrett Kaas	Anesthesia/Kitamoto
3rd Place	Lily Paemka	Pediatrics/Bassuk

Abby Dernburg, Ph.D.

Howard Hughes Medical Institute Investigator
Professor of Molecular and Cell Biology

University of California Berkley

Spatial regulation of meiotic recombination: Counting to One

Abby Dernburg is a Professor of Molecular and Cell Biology at the University of California, Berkeley, and an Investigator of the Howard Hughes Medical Institute. She also earned her undergraduate degree at UC Berkeley, and then moved across the Bay Bridge to UCSF for her doctoral studies. There she worked in the lab of Dr. John Sedat, who – along with Dr. David Agard and their colleagues – developed the wide-field deconvolution microscopy system that was later commercialized as DeltaVision. During her graduate work Dr. Dernburg developed robust 3D in situ hybridization methods and applied them to investigate interphase chromosome organization, focusing on the transcriptional phenomenon of position-effect variegation in Drosophila. She also initiated her studies of meiosis, probing the pairing and segregation of achiasmate (nonrecombinant) chromosomes in Drosophila oocytes, as well as segregation distortion in Drosophila males. For her postdoctoral work she joined forces with Dr. Anne Villleneuve at Stanford to develop the nematode Caenorhabditis elegans as an experimental model for meiosis. Research in the Dernburg Lab first elucidated the molecular basis for chromosome “Pairing Centers,” specialized sites important for homolog pairing, synapsis, and checkpoint signaling during meiosis in C. elegans. Their ongoing studies are also addressing the regulation of the meiotic cell cycle and the molecular basis for the phenomenon of genetic interference. Her lab currently investigates how chromosomes are physically remodeled during meiosis, how chromosomes pair and synapse with their homologs, how meiotic crossovers are regulated to ensure proper segregation, and how these mechanisms are coordinated and surveilled by the meiotic cell cycle machinery.

Alumni 2014

Dina Ahram MSc, Ph.D., FACMG, MB(ASCP), CGMBS

Chief Laboratory Officer
Insight Medical Genetics

Senior Clinical Laboratory Director-Molecular Genetics
Quest Diagnostics

Carving out a path in clinical, diagnostic genetics

Dina Ahram, PhD, FACMG, is board certified in Clinical Cytogenetics and Molecular Genetics (FACMG). She holds a New York State Certificate of Qualification in Cytogenetics and Molecular Genetic testing. With over 12 years of experience in academic research and diagnostic clinical care, she joined Insight Medical Genetics to serve as Chief Laboratory Officer in 2021. Recently, she went on to serve as senior clinical lab director in Molecular and Cytogenetics at Quest diagnostics. Alongside a highly skilled team, she leads laboratory operations to streamline the performance, and reporting of high quality molecular genetic and cytogenetic testing in prenatal and postnatal constitutional and cancer diagnostic genetic testing.

She is a formally trained molecular geneticist with a publication track record that reflects her expertise in diagnostic genetics. She graduated with a PhD in Genetics from the University of Iowa in 2014. In 2016, she pursued a postdoctoral research fellowship at Columbia University- Division of Nephrology focused on the utility of precision medicine in guiding the clinical management of Nephropathies. She completed an American Board of Medical Genetics and Genomics (ABMGG) certification training in Clinical Laboratory Genetics and Genomics at Columbia University Medical Center in 2021, training extensively in the genetic diagnosis of constitutional and oncological disease.

She is best known for her research on the 1) Integration of rare and complex-common variant analysis models to identify the genetic underpinnings of congenital and adult renal pathologies, 2) Characterization of the genetic mechanisms associated with Neurodevelopmental disease (autism spectrum disorder and epilepsy) in inbred populations, and 3) Utilization of high throughput computational approaches to investigate the genetic causes of ophthalmic disease, including Ectopia Lentis (EL) and Primary Angle Closure Glaucoma (PACG).

Alumni 2007

Marwan Tayeh Ph.D., FACMG

Associate Professor
Department of Medical & Molecular Genetics
Director, Diagnostic Genomics Laboratory

Indiana University School of Medicine

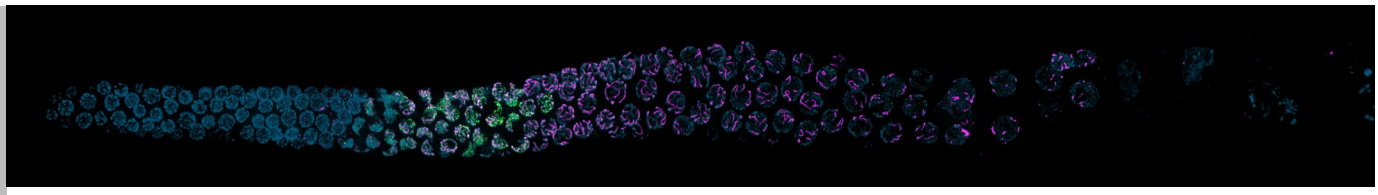
Somatic Mosaicism and Li-Fraumeni Syndrome

Alumnus Speaker: Marwan Tayeh

Marwan Tayeh, PhD, is currently the Director of the IU Diagnostic Genomics Laboratory, and an Associate Professor in the Department of Medical and Molecular Genetics at IU School of Medicine. Dr. Tayeh earned his PhD in Genetics in 2007 at the University of Iowa, and then completed ABMGG fellowship in Clinical Molecular Genetics and Genomics in 2009 at Emory University, Atlanta, GA. During his fellowship, Dr. Tayeh received the Richard King Award from the American College of Medical Genetics (ACMG) for best publication of the year for a manuscript entitled "Targeted comparative genomic hybridization (CGH) array for the detection of single- and multi- exon gene deletions and duplications".

In 2010, Dr. Tayeh joined Prevention Genetics, LLC, as a Clinical Molecular Geneticist, where he developed the first comprehensive clinical testing for ciliopathies among others genetic disorders. In 2011, Dr. Tayeh Joined the University of Michigan as the Director of the Molecular Laboratory of the Michigan Medical Genetics Laboratories, and as an Assistant Professor in the Department of Pediatrics at the University of Michigan School of Medicine, and then as an Associate Professor. During his 10 years at the University of Michigan, Dr. Tayeh has developed a wide variety of high-throughput diagnostic assays, such as gene-centric comparative genomic hybridization arrays (aCGH), Methylation assays, and next generation sequencing, to help advancing clinical Molecular Genetics and Genomics testing. Dr. Tayeh has also developed bioinformatics tools to improve Next Generation Sequencing (NGS) data analysis, variant calling, and variant annotation for clinical testing and research purposes.

Dr. Tayeh is also involved in national and international leadership efforts at the American College of Medical Genetics and Genomics (ACMG). His current interest is to help develop and implement diagnostic genetics and genomics testing across the globe.



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Beta-Catenin Centrosomal Clearance Regulates Wnt-Dependent Cell Fate and Inheritance

Sam Mellentine

Defining the Role of Prostaglandins in Collective Cell Migration

Kristen Rohli

Nutrient metabolism regulates insulin granule formation in the pancreatic islet beta-cell via ER redox homeostasis

Student oral presentations—Session 2

Yann Vanrobaeys

Spatial transcriptomics reveals unique gene expression changes in different brain regions after sleep deprivation

Emily Adelizzi

Deciphering the Tissue Specific Roles of Arhgap29 During palatogenesis

Nate Mullin

Mapping human photoreceptor development with rare pathogenic variants

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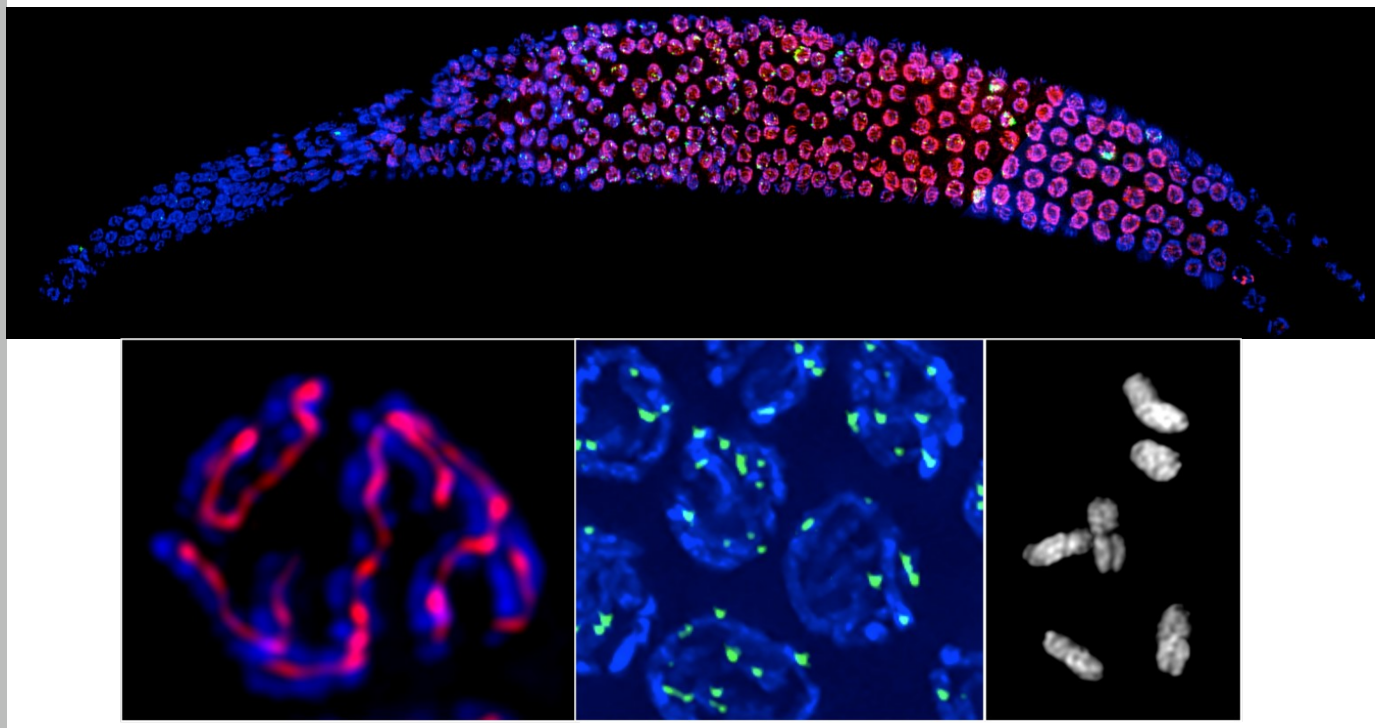
31	Hayley Vaughn	Ben Darbro	Pediatrics	45
32	Monique Weaver	Richard Smith	Otolaryngology	46



1. BETA-CATENIN CENTROSOMAL CLEARANCE REGULATES WNT-DEPENDENT CELL FATE AND INHERITANCE

M F Valdes Michel[1,2], B Phillips[1,2]

[1] Department of Biology, University of Iowa, Iowa City, IA 52242, USA

[2] Interdisciplinary Graduate Program in Genetics, University of Iowa, Iowa City, IA

Asymmetric cell division (ACD) allows daughter cells of a polarized mother to acquire different developmental fates. In *C. elegans*, the Wnt/β-catenin Asymmetry Pathway oversees many embryonic and larval ACDs; here, Wnt ligand induces asymmetric distribution of Wnt signaling components at mitosis. This polarity allows the daughter cells to differentially regulate Wnt target genes and gives rise to one Wnt-dependent lineage and one Wnt-independent lineage. The signaling component we study is the transcriptional activator β-catenin/SYS-1. SYS-1 is regulated in two different manners, (1) by negative regulation by a "destruction complex" targeting SYS-1 for proteasomal degradation, and (2) by mother cell centrosomal localization, which is required to limit daughter cell SYS-1 levels.

Previous work in the lab showed that SYS-1 centrosomal localization is enhanced by dynein minus-end microtubule trafficking. We tested this hypothesis by examining SYS-1-dependent cell fate after impairing SYS-1 centrosomal localization, dynein trafficking and centrosomal degradation. We showed, using ACDs of the somatic gonad (DTCs), that depletion of the dynein components leads to extra DTCs. Additionally, P_{hs}::SYS-1 acts as a sensitized background and enhances cell fate changes seen after disrupting trafficking in both DTCs and seam cells.

These results suggest that impairing SYS-1 centrosomal degradation leads to increased SYS-1 daughter cell inheritance, a hypothesis we tested in the embryo using photobleaching. Using this technique, we identified two pools of SYS-1 in newly formed daughter cell nuclei, inherited SYS-1 and *de novo* translated SYS-1. To further test this hypothesis and directly measure SYS-1 inheritance we generated a strain with endogenously tagged photoconvertible SYS-1. Preliminary data shows successful photoconversion of SYS-1. Future work will examine turnover rates in the daughter cells of the inherited and the *de novo* translated SYS-1.

These data lead to a model where SYS-1 centrosomal localization and subsequent degradation limit beta-catenin inheritance to achieve successful cell fate specification.

2. DEFINING THE ROLE OF PROSTAGLANDINS IN COLLECTIVE CELL MIGRATION

S Mellentine[1], A Ramsey[1], O Rabab'h[1], and T Tootle[1]

[1] Anatomy and Cell Biology Dept., University of Iowa Carver College of Medicine

Collective cell migration – the coordinated movement of associated cells – is important for both normal development and tumor invasion. Prostaglandins (PGs) are short-range lipid signals that regulate cell migration and are up regulated in many cancers. However, their mechanisms of action during collective migration are poorly understood. Here we use the native, collective migration of the *Drosophila* border cells to uncover the roles of PGs. During Stage 9 of oogenesis a cluster of epithelial cells becomes specified as border cells, delaminates from the epithelium, and migrates collectively and invasively between the nurse cells. Prior work found that loss of Pxt, the *Drosophila* cyclooxygenase-like enzyme responsible for all PG synthesis, results in delayed migration and decreased cluster cohesion. However, the particular PG or PGs controlling border cell migration remain unknown. To begin to address this, we assessed the roles of three PGE_2 synthases (mPGES-1, mPGES-2, and cPGES) and the sole $PGF_{2\alpha}$ synthase (PGFS/Akr1B) in border cell migration. Our data support the model that cPGES and PGFS are required for on-time border cell migration. Specifically, loss of cPGES or PGFs delays border cell migration, but has no effect on cluster cohesion. We are currently using cell-specific RNAi knockdown to determine which cells produce PGE_s and $PGF_{2\alpha}$. Initial studies suggest that cPGES acts in the nurse cells to promote border cell migration. We are also assessing genetic interactions between the synthases and Pxt. We find that co-reduction of both Pxt and PGFS results in delayed border cell migration; supporting that the phenotype due to loss of PGFS is related to loss of PG signaling. Together our data lead to the model that PGE_2 and PGF2α both promote on-time border cell migration. As PG signaling is highly conserved, these studies provide critical insight into the specific functions of individual PG signaling cascades controlling collective cell migration and can be applied to understanding both developmental collective cell migrations and pathological migrations including cancer metastasis.

3. NUTRIENT METABOLISM REGULATES INSULIN GRANULE FORMATION IN THE PANCREATIC ISLET BETA-CELL VIA ER REDOX HOMEOSTASIS

KE Rohli[1,2,3], CK Boyer[1,4], SC Bearrows[1,3], MR Moyer[1,3], and SB Stephens[1,2,3,]

[1]Fraternal Order of Eagles Diabetes Research Center, University of Iowa, Iowa City, IA, USA

[2]Interdisciplinary Graduate Program in Genetics, University of Iowa, Iowa City, IA, USA

[3]Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Iowa, Iowa City, IA, USA

[4]Department of Pharmacology, University of Iowa, Iowa City, IA, USA

Defects in the pancreatic β-cell's secretion system are well-described in Type 2 diabetes (T2D) and include impaired proinsulin processing and a deficit in mature insulin-containing secretory granules; however, the cellular mechanisms underlying these defects remain poorly understood. To address this, we used an *in situ* fluorescent pulse-chase strategy to study proinsulin trafficking. We show that insulin granule formation and the appearance of nascent granules at the plasma membrane are decreased in rodent and cell culture models of pre-diabetes and hyperglycemia. Moreover, we link the defect in insulin granule formation to an early trafficking delay in ER export of proinsulin, which is independent of overt ER stress. Using a ratiometric redox sensor, we show that the ER becomes hyperoxidized in β-cells from a dietary model of rodent pre-diabetes and that addition of reducing equivalents restores ER export of proinsulin and insulin granule formation. Together, these data identify a critical role for the regulation of ER redox homeostasis in proinsulin trafficking and suggest that alterations in ER redox poise directly contribute to the decline in insulin granule production in T2D.

4. SPATIAL TRANSCRIPTOMICS REVEALS UNIQUE GENE EXPRESSION CHANGES IN DIFFERENT BRAIN REGIONS AFTER SLEEP DEPRIVATION

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Sleep deprivation has far-reaching consequences on behavior and bodily function. These alterations in function are rooted in changes in different brain regions that underlie these behaviors, where the consequences of sleep deprivation can be detected at multiple levels, including changes in gene expression. Some regions, like the hippocampus and cortex, have been extensively studied because of their vulnerability to sleep loss and for the importance of these regions to functions like memory. The large number of genes affected by sleep deprivation reflects the complexity of the response triggered by sleep, including cognitive deficits, general impairment of protein translation, metabolic imbalance, and thermal deregulation. However, much less is known about the location and intensity of those changes across the whole brain. Here we used the 10x Genomics Visium Gene Expression Solution platform to define the spatial topography of gene expression in sections of whole brain tissue from mice after sleep deprivation. By performing differential gene expression analysis, we showed spatially defined expression changes in each brain region and were able to reveal gene expression patterns and molecular pathways that were unique to each of these regions. The hippocampal region and hypothalamus were the most sensitive aeras in terms of significant reduction of gene expression with many molecular functions enriched for transmembrane transporter activity. The thalamus had a more balanced number of up and downregulated genes that enriched molecular functions related voltage-gated ion channel activity, as well as ATPase-coupled intramembrane lipid transporter activity. Interestingly, the neocortex displayed the greatest and strongest significant induction of gene expression including previously described immediate early genes and transcription factors. These results provide a detailed databank of genes altered in many regions of the brain acquired from the same animal and reveal interesting findings about the differences the brain responds to sleep loss.

5. DECIPHERING THE TISSUE SPECIFIC ROLES OF ARHGAP29 DURING PALATOGENESIS.

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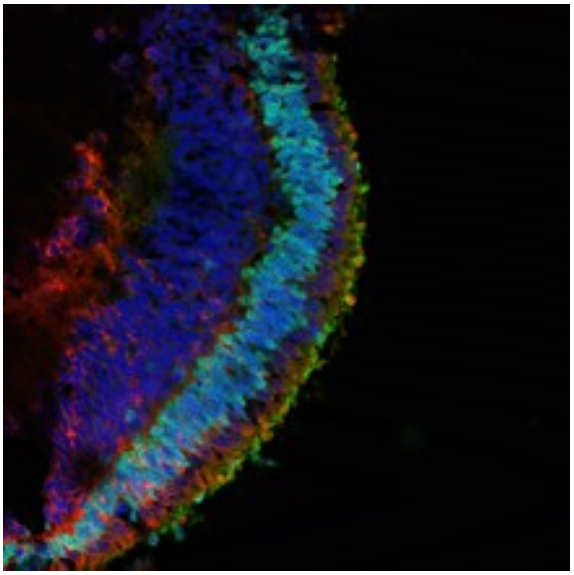
Craniofacial deformities, specifically non-syndromic cleft lip with or without palate (NSCL/P), are among the most common class of birth defects. Complex interactions between genetic and environmental factors contribute to the development of NSCL/P. Many genes have been associated with this disease, including *ARHGAP29*. ARHGAP29, Rho GTPase Activating Protein (GAP) 29, functions in the cyclical regulation of the small GTPase RhoA. Previous studies have identified genetic variants of *ARHGAP29* in NSCL/P and have found that ARHGAP29 levels were reduced in mice deficient for *Irf6*. Data from these studies suggest a role for ARHGAP29 in craniofacial morphogenesis but it remains unknown if ARHGAP29 is required for, or regulates craniofacial development. ARHGAP29 is detected in many tissues, including the oral epithelium. Using the Keratin14-driven Cre-recombinase allele, $Krt14^{Cre}$;$Arhgap29^{fl/fl}$ mice displayed a delay in palatal shelf elevation and did not exhibit a cleft palate. We hypothesized that the absence of a cleft palate was due to the late activation of the *Krt14-Cre* driver. EctCre drives Cre recombinase specifically in the ectoderm a couple of days before the *Krt14-Cre*. Our results show that Ect^{Cre};$Arhgap29^{fl/fl}$ mice survive to birth and display a non-mendelian pattern of inheritance. Interestingly, Ect^{Cre};$Arhgap29^{fl/fl}$ mice display a fully penetrant kinked tail phenotype, which has been described in other murine models of NSCL/P, and has been attributed to neural tube and skeletal defects. Additionally, at embryonic € day 14.5, while all the wild-type embryos showed adherent palatal shelves, 75% of Ect^{Cre};$Arhgap29^{fl/fl}$ mice displayed palatal shelves not elevated or adherent. Our preliminary data also identified one Ect^{Cre};$Arhgap29^{fl/fl}$ embryo out of 3 total analyzed with a cleft palate at E18.5. These data show that ARHGAP29 is required for on-time palatal shelves movement, supporting a role for ARHGAP29 in craniofacial development.



6. MAPPING HUMAN PHOTORECEPTOR DEVELOPMENT WITH RARE PATHOGENIC VARIANTS.

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Rod and cone photoreceptors are specialized, light-sensitive neurons that convert light entering the eye into a nerve signal that is eventually conveyed to the brain. Photoreceptor cell development is controlled by a cascade of transcriptional regulatory events. Photoreceptors are specified out of a multipotent progenitor pool that also gives rise to the other cell types of the retina. Mutations in the genes encoding the transcription factors that participate in photoreceptor specification are known to cause vision loss in patients. However, the precise molecular abnormalities of the cells born of this pathologic specification process are not fully understood. As a result, prognosis and treatment of such diseases is limited. Here, we used induced pluripotent stem cells (iPSC) to model Enhanced S-Cone Syndrome and identify the transcriptional changes undertaken by abnormal photoreceptors during retinal development. *NR2E3* is a nuclear receptor gene known to harbor variants causative for Enhanced S-Cone Syndrome. We generated retinal cells *in vitro* from three iPSC lines; one homozygous for a loss-of-function mutation in *NR2E3*, a CRISPR-corrected isogenic control, and an unrelated healthy control line. We sampled developing retinal cells across a 160-day time course with single-cell RNA sequencing to understand how and when NR2E3 acts in human photoreceptor development. Using gene expression profiles of over 80,000 individual cells across five timepoints, we identified a unique developmental detour away from normal rod photoreceptor maturation taken by cells lacking functional NR2E3. Differential gene expression analysis shows that the resulting abnormal cells lack expression of some, but not all, genes present in normally functioning rod photoreceptors while remaining transcriptionally distinct from normal cone photoreceptors. These results show that NR2E3 loss damages normal rod photoreceptor development through misexpression of a specific subset of normal rod genes, yielding a divergent photoreceptor lineage unique to the disease state.

7. SEQUENCE-BASED DEEP LEARNING MODEL LINKS NON-CODING ACTIVITY-DEPENDENT REGULATORY POTENTIAL TO EFFECTS ON EDUCATIONAL ATTAINMENT.

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The transcriptional and epigenetic response to neural activity permits lasting changes to structure and function of cells and brain circuits, serving higher cognitive functions such as learning and memory. While extensive work in mice has characterized genes involved in activity-dependent (AD) transcriptional regulation, little is known about the non-coding regulatory grammar orchestrating this response. More importantly, the effect of non-coding variation on AD regulatory potential is unknown.

We used publicly available data to train a sequence-based deep learning model capable of inferring AD regulatory potential of a DNA sequence. The convolutional neural network was trained on non-coding DNA sequences showing increases in chromatin accessibility following learning in mice. We applied our model to compare AD-regulatory potential of hg19 reference sequences to sequences containing variants tested for association with educational attainment (EA). For each gene, we fit a weighted linear regression between the GWAS coefficients of proximal SNPs and the predicted change in activity-dependent regulatory potential of those SNPs.

308 genes showed a significant relationship between predicted changes in AD-regulatory potential of proximal SNPs and their effects on EA. We also found a significant enrichment of known immediate early genes among genes where predicted decreases in AD regulatory potential were significantly and positively correlated with effects on EA, thus identifying long-term potentiation (LTP) as a plausible molecular mechanism contributing to this trait.

In ongoing work, we are applying these techniques to GWAS data in order to estimate the contribution of AD gene regulation to liability for bipolar disorder, schizophrenia, and other conditions where learning and memory are shown to be affected. Our model of AD regulatory potential shows promise in identifying genetic variation associated with biological capacity to adapt, and may yield biomarkers informative in predicting clinical outcomes of neuromodulation treatment.

8. COMPARING GENETIC BURDEN TECHNIQUES ON A TURNER SYNDROME COHORT

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Turner Syndrome (TS) is a rare genetic condition that affects 1 in every 2,500 live female births. TS is caused by an absent or structurally abnormal X chromosome. Individuals with TS have short stature due to haploinsufficiency of *SHOX;* however, there is variable expressivity of other associated characteristics of TS. A spectrum of left-sided congenital heart disease occurs in up to 50% of patients that is only partially explained by X chromosome mosaicism. Because of this unaccounted for phenotypic heterogeneity, genetic modifiers are believed to play a role. Genetic modifiers are a confounding genetic variation that when present for a specific disease can explain phenotypic heterogeneity in some cases. Complicating their study, genetic modifiers exhibit genetic and allelic heterogeneity and do not necessarily have to be a rare genetic finding. Measuring genetic burden is a methodology used to better understand each separate phenotype in complex genetic diseases. Burden can be calculated on either the disease gene itself (perhaps across a cohort of individuals) or across a functional pathway or network that includes modifier gene(s). Here, we utilized two common gene burden models to elucidate modifier genes in TS: Variant Annotation, Analysis Search Tool (VAAST) and Sequence Kernel Association Test (SKAT). SKAT uses a linear regression model to determine association between a given SNP-set (like a gene) and a phenotype by aggregating SNP level p-values. VAAST uses an aggregative variant association test that combines amino acid substitution data, phylogenic conservation, and allele frequencies into its calculation. From this study, we found very little to no overlap in significant genes, possibly in part due to the way these algorithms handle directionality of variants. This study highlights the importance gene burden methodology used as well as current differences in gene burden testing techniques.

9. OVEREXPRESSION OF PLACENTAL *IGF-1* RESULTS IN SEX SPECIFIC EFFECTS ON GENE EXPRESSION IN SIGNALING PATHWAY

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Placental gene expression can significantly influence fetal neurodevelopment. Our lab found that prenatal stress, a risk factor of autism spectrum disorder (ASD), increased placental *Igf-1* expression in mice. The placenta is the primary source of *Igf-1,* a crucial growth factor for brain development, to the fetus prior to birth. We hypothesized that in addition to the impact on fetal development caused by overexpression of placental *Igf-1*, other genes in this signaling pathway and functionality of the placenta would be altered subsequently contributing to the etiology of ASD. We have analyzed gene and protein expression in E14 male and female placenta.

We identified that we can successfully induce overexpression of placental *Igf-1* via direct insertion of a SAM CRISPR plasmid but that the significantly increased expression in manipulated placentas is driven by effects in females. We further investigated the impact of placental *Igf-1* expression on other genes within its signaling pathway and found significant sex differences. No difference in *Igf-1r* expression was found, but a significant correlation between *Igf-1* and *Igf-2r* expression was found in overexpression samples. Male overexpression samples showed a significant decrease in *Igfbp3* but not *Igfbp4*. Females showed no difference in Igf binding proteins gene expression. A significant correlation was found between *Igf-1* and *Igfbp4* expression in overexpression samples, driven by females. Overexpression male and female samples displayed inverse changes in expression of System A Amnio Acid Transporter genes, factors essential for growth. Overexpression male samples showed a significant or trending decrease, and females showed a significant or trending increase in *Snat2* and *Snat4*. The expression differences found in male and female overexpression samples may explain why females display an increase in body weight and placental efficiency and males do not. Overall, this may contribute to brain development as we have identified that E14 females show different Ki67 staining in the ganglionic eminence and E18 females have increased striatum volume.

10. GENETIC ARCHITECTURE OF LANGUAGE IMPAIRMENT IN AUTISM INTERSECTS WITH PSYCHOSIS RISK FACTORS

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Autism is a highly genetic neurodevelopmental condition, affecting an estimated 1 in 44 children. Phenotypically, autism is associated with high rates of language impairment (up to 30%). Due to this high comorbidity, we hypothesized that language impairment in autism would be positively associated with autism polygenic propensity scores (PGS). To test this, we generated a quantitative language impairment trait (controlled for confounds) for analysis with genetic risk factors (N=15,577). Surprisingly, we found these language impairment scores had no relationship with autism genetic liability, while schizophrenia PGS were positively associated ($Z=4.3$, $p=2 \times 10^{-5}$). A Genome-Wide Association Study (GWAS) was conducted on language impairment scores for 14,728 individuals with ASD. A genome-wide significant locus (rs11147928, $p=1 \times 10^{-8}$) maps to a schizophrenia risk variant in the *ENOX1* gene.

Downstream analysis of our GWAS results identified significant genetic correlations between our language impairment trait, left-handedness, and psychotic disorders (schizophrenia and bipolar). A meta-analysis was conducted to re-weight GWAS loci based on the genetic correlations, providing a “meta-language” PGS. These meta-language PGS were more predictive of language impairment in ASD in an independent sample when compared to the original language impairment PGS. Interestingly, the “meta-language” PGS was portable to children without autism as well; showing significant associations with verbal IQ, mania, and family history of psychosis. Together, these results suggest language impairment in autism is associated with psychosis risk factors, not autism risk. This work provides evidence that common genetic variation impacting language skills in children intersect with risk for psychotic disorders.

11. IMPUTED TRANSCRIPTOME OF FOURTY-FOUR TISSUES FOR AUTISM SPECTRUM DISORDER

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It is well-established that the majority of risk for autism is genetic. However, the mechanisms through which these genetic risk factors change neurodevelopment remains unclear. One mechanism in particular has been under-explored: genetic regulation of gene expression. Here, we present a full imputed transcriptome (44 tissues) for ASD patients and healthy controls from the SPARK cohort (~51,000 samples), based on their common variant genotypes. The UTMOST package provided a linear model that was previously fitted on genotypic data and gene expression in an independent sample (GTEx). The estimated weights from this analysis were pulled from the model and used to impute transcription for the SPARK cohort. The case/control comparison of imputed gene expression provided a list of significant differentially regulated genes (pvalue < 0.05, some with FDR <= 0.1) in all tissues. In addition, an in-silico evaluation for the output was done using forecASD, a machine-learning model that provides a single score indexing for gene's involvement in the etiology of ASD.

A combination of ~ twenty-nine thousand genes were identified as significant in all tissues. Among these genes, some of them have been previously linked to ASD, including SCN2A, DISC1, SLC6A1, and RELN. Almost 10% of significant genes -in every tissue- have more than 0.375 score indexing in forecASD, and the other ~90% are still under exploration with previous literature. Some of the significant genes have not been reported in previous GWAS, although the imputed transcriptome is only based on common variant genotypes.

12. DEVELOPMENT OF AN *IN-VITRO* MODEL FOR AXONAL PROTEOSTASIS.

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Maintenance of proteostasis is critical for preserving cell integrity and ensuring an appropriate response to a changing environment. Impairments in proteostasis can lead to a deleterious imbalance in protein concentration, localization, and degradation. Deficiencies in proteostasis have important consequences for neurons, which must persist and function for an entire human's lifespan. In the axonal compartment, isolation from the soma necessitates a unique approach to sustaining proteostasis within this compartment. Many studies on neuronal proteostasis focus on the soma rather than the axon such that specialized mechanisms residing in the axon compartment are still unknown. To fill this important gap, I've developed an in-vitro model to investigate local proteostasis networks in the axon. This model utilizes cultured neurons from the dorsal root ganglion of embryonic mice and genetically encoded fluorescent reporters-fused with axon-targeting 3'UTRs to visualize newly synthesized proteins in axons. I am employing live-cell imaging to track the fate of newly synthesized proteins and protein aggregates in both axon and soma. With this model, I am investigating how neurotoxic stressors and human disease models impact local proteostasis networks. For example, I've introduced mutated forms of a tRNA synthetase linked to Charcot-Marie-Tooth disease in primary neurons and observed extensive axon degeneration and neuronal cell death. I am determining how these disease-linked mutations impact different elements of axonal proteostasis. With this model system, genetic and pharmacological screens will identify critical nodes in the axonal proteostasis network. These findings will have broad relevance to the growing list of proteinopathies and other neurological disorders characterized by loss of proteostasis.

13. AUXIN'S ROLE IN DEVELOPING APICAL STEM CELLS IN THE MERISTEM OF *CERATOPTERIS RICHARDII* GAMETOPHYTES

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Plant stem cells are located in specialized structures called meristems that control plants' growth throughout life with a complex network of signals distinct from those used in animals. The model fern Ceratopteris's (*Ceratopteris richardii*) haploid gametophyte generation consists of a single layer of cells with one stem cell in the meristem, making it accessible for observation and manipulation.

The phytohormone auxin is known to have an important role in meristem development in seed plants, though its role in stem cell identity is unclear. Preliminary results show that *TAA* and *YUC*, two genes encoding enzymes known to catalyze auxin biosynthesis in the flowering plant model Arabidopsis, are expressed surrounding the single stem cell of Ceratopteris gametophytes. Similar expression patterns were observed for PIN, a protein involved in auxin transport.

The Cheng lab previously established a system to ablate the stem cell of a gametophyte, resulting in the formation of a new stem cell within a certain distance from the original one. Visualizing cell-specific expression of *TAA, YUC,* and *PIN* before and after ablation can provide insight into how auxin is involved in the development of a new meristem. We expect to see the expression of these genes disappear from the ablated meristem and reappear where the new meristem forms. To further examine auxin's role in this process, we blocked auxin synthesis post-ablation with KYN, a known competitive inhibitor of the enzyme TAA.

14. DESCRIBING CAUSATIVE AND/OR PROTECTIVE GENETIC DETERMINANTS PRESENTING IN SARS- COV-2 RELATED MULTISYSTEM INFLAMMATORY SYNDROME (MIS-C) IN CHILDREN

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SARS-CoV-2 infection commonly causes COVID-19 disease which is categorized as a pandemic in recent times. Patients at different age groups having unique co-morbidities differ in COVID-19 clinical presentations and outcomes, suggest that specific genes and co-existing factors determine the differences.

Some COVID-19 specific human genes have already been delineated in adult populations as the patient sample is bigger. Whereas fewer human genetic determinants were explained in COVID-19 infections among pediatric populations due to nonspecific corresponding respiratory clinical presentations and smaller sample populations. Pediatric clinical presentations are often asymptomatic or show mild respiratory symptoms.

But few children showed more serious symptoms like Kawasaki disease involving hyperinflammation, multi organ infections and high fevers. These symptoms are called as multisystem inflammatory syndrome (MIS-C). In this study, we hypothesize that specific risk and/or protective genetic determinants cause the MIS-C like symptoms or lack of them in pediatric COVID-19 infections.

To study this hypothesis, we recruited 38 children who are tested positive for SARS-CoV-2 infection. Among them, 19 showed MIS-C symptoms forming our test group and 19 showed no MIS-C symptoms, forming our control group. We collected the whole genome sequencing (WGS) data for these 38 recruited children along with detailed clinical data. We used the Illumina DRAGEN Bio-IT platform for analysis to obtain germline genetic variants among our test and control groups.

We, then, utilized a specific bioinformatics tool called "Variant Analysis, Annotation and Search tool (VAAST)" to identify and rank both inflammation-related risk and protective variants within genes including *CD2, MMP24, SELPLG, PDCD1, ADGRE2, CDCP1 and NOTCH3* which showed statistical significance in our test and control groups.

The results from this study will aid in scientific understanding of gene variants and clinical presentation linkages in the understudied pediatric COVID-19 infections. This understanding will enable optimal treatment planning and appropriate resource usage.

15. DROSOPHILA MODELS OF *SNRNP200*-ASSOCIATED RETINITIS PIGMENTOSA EXHIBIT PHOTORECEPTOR ABNORMALITIES.

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Retinitis pigmentosa (RP) affects 1:4000 individuals worldwide and represents a collection of genetic eye disorders with progressive loss of photoreceptors in the retina. Photoreceptor death occurs via apoptosis, with evidence of oxidative stress. RP33 is non-syndromic form of RP caused by mutations in the *SNRNP200* gene, which encodes an RNA helicase that is a pre-mRNA splicing factor. To understand the function of *SNRNP200* in the retina, we developed Drosophila models of *SNRNP200*-associated RP. The Drosophila genome possesses an orthologue of human *SNRNP200*, which we call *dSnrnp200*. Human and Drosophila SNRNP200 exhibit a remarkable 74% amino acid identity and 89% similarity. The objective of our research is to understand how mutant *SNRNP200* causes retinal defects and identify potential treatments. To accomplish this objective, we introduced patient mutations into Drosophila *dSnrnp200* using CRISPR mutagenesis. These mutants encode dSNRNP200 with single amino acid substitutions in the active RNase helicase cassette and exhibit increased apoptosis in larval eye imaginal discs, relative to controls. Furthermore, the *dSnrnp200* mutants show progressive loss of photoreceptor function, as evidenced by abnormal electroretinograms of adult eyes. Immunohistochemical staining shows that *dSnrnp200* mutants have abnormal photoreceptor organization. In addition to the CRISPR generated mutant alleles, RNAi was used to knockdown *dSnrnp200* in the eye. Depletion of *dSnrnp200* increase apoptosis in eye imaginal discs and produced a “rough eye” phenotype in adults, an easily scorable phenotype. Given the connection between RP and oxidative stress, flies were treated with either the antioxidant N-acetylcysteine (NAC) or water as a control. NAC-treated flies showed dosage-dependent suppression of the rough eye phenotype. Taken together, Drosophila models of *SNRNP200*-associated RP have been generated and recapitulate aspects of the human disease. These models have provided novel insights on disease mechanisms and suggest antioxidant treatments as a treatment to lessen the severity of *SNRNP200*-associated RP.

16. MISSENSE VARIANT IN *KRT32* IS RESPONSIBLE FOR INEFFICIENT ANCHORING OF ANAGEN HAIR SHAFT TO ITS FOLLICLE

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Loose Anagen Hair Syndrome (LAHS) is characterized by excessive shedding or easily pluckable terminal hair during its active growth (anagen) phase. Although the prevalence of LAHS is estimated to be 2 cases per million, we believe that this is an underestimate due to under-reporting. This disorder is thought to be due to abnormal anchoring of the hair shaft to the hair follicle. Several genes have been implicated in LAHS, including pathogenic variants of *KRT75* (keratin 75) as well as pathogenic variants in *PPP1CB* and *SHOC2* in Noonan syndrome with loose anagen hair (NSLH). Our group identified a likely pathogenic variant in *KRT32* (keratin 32) that is responsible for autosomal dominant LAHS and segregating with the disorder in a large kindred. The identified *KRT32* missense variant (NM_002278.3; c.296C>T; NP_002269.3; p. Thr99Ile) replaces a highly conserved threonine at position 99 with an isoleucine residue. This amino acid is evolutionarily conserved, specifically in mammals, suggesting that variation has a high likelihood of being pathogenic. We are currently examining a cohort of LAHS patients for variants in *KRT32* and performing downstream cell biology functional assays that provide functional evidence of the pathogenicity of the identified mutation. The understanding of the pathophysiology of LAHS would provide insight into the mechanism(s) that anchor the anagen hair shaft to its follicle. This may have a broader implication on other causes of anagen hair loss, which are more common, such as chemotherapy, radiation therapy, and heavy metal poisoning.

17. ATF4-MEDIATED ACTIVATION OF CDKN1A (P21) PROMOTES SKELETAL MUSCLE ATROPHY

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Skeletal muscle atrophy impairs the health and quality of life of tens of millions of people worldwide. Aging, muscle disuse, malnutrition, and essentially any serious illness or injury cause skeletal muscle fibers to undergo atrophy, which leads to a loss of muscle mass and strength. Despite broad clinical impact, the molecular basis of muscle atrophy remains poorly understood and there are no effective or approved pharmacologic therapies to prevent or reverse this debilitating condition. In young, healthy skeletal muscle, cyclin-dependent kinase inhibitor 1a (p21) is weakly expressed, but p21 expression rises dramatically during multiple clinically relevant conditions that cause muscle wasting. Using in vivo mouse models, we discovered that, in response to limb immobilization, the transcriptional regulator ATF4 activates p21 mRNA expression in muscle fibers by binding to an evolutionarily conserved enhancer element located approximately 15kb upstream of the p21 transcription start site. Furthermore, forced ATF4 or p21 expression in young healthy muscle is sufficient to induce skeletal muscle fiber atrophy. Because terminally differentiated skeletal muscle fibers are post-mitotic, it is unlikely that p21 causes muscle atrophy through its canonical role of inhibiting the cell cycle. To investigate the mechanism by which p21 causes muscle atrophy, we biochemically isolated skeletal muscle proteins that associate with p21 in mouse skeletal muscle fibers. This analysis revealed that 70% of high confidence p21-interacting proteins in muscle fibers represent cyclin-CDK complexes. Targeted inhibition of one p21-associated cyclin-dependent kinase (Cdk1), but not the other four (Cdk2, Cdk4, Cdk5, Cdk6), was sufficient to induce muscle fiber atrophy in vivo. Collectively, these results identify a molecular pathway by which ATF4 promotes skeletal muscle atrophy through p21, providing molecular-level insights into the etiology of this widespread condition.

18. DOUBLE TROUBLE: AN EXPLANATION FOR PHENOTYPIC VARIABILITY AMONG INDIVIDUALS WITH THE SAME *LMNA* MUTATION

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Mutations in the human *LMNA* gene encoding A-type lamins cause a collection of diseases known as laminopathies. These diseases affect many types of tissues, including skeletal and cardiac (striated) muscle. A hallmark of these striated muscle laminopathies is their phenotypic variability. Individuals with the same *LMNA* mutation can have clinically distinct diseases. Furthermore, individuals with the same clinical diagnosis are likely to have high variation in the severity of their muscle disease phenotypes.

Here we describe a multi-generational family passing an *LMNA* mutation in which individuals with the mutation can present with Limb Girdle muscular dystrophy (LGMD), dilated cardiomyopathy (DCM), both, or be entirely asymptomatic. To determine the cause of this phenotypic variability, whole genome sequencing (WGS) was used to identify other genetic variants that could be contributing to the LGMD phenotype in the family.

WGS of LGMD-affected family members identified 22 variants of uncertain significance (VUS), of which the top candidate was a variant in *CCDC78*, a gene that has previously been linked to muscle disease. Skeletal muscle biopsies of these individuals were found to contain aggregates of CCDC78 and RyR1 co-localized at muscle cores. Muscle cores are an abnormal pathological feature for patients with *LMNA* mutations but have been found in patients with pathogenic *CCDC78*, further strengthening the case for *CCDC78* as a contributor to disease in this family. Overall, our findings suggest that LGMD is a digenic disease in this family in which two variants, one in *LMNA* and one in *CCDC78*, are needed to cause skeletal muscle disease (double trouble).

19. ANALYSIS OF CHIRALITY AND DE NOVO MUTATION IN ASEXUAL SNAILS

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Potamopyrgus antipodarum, also known as the New Zealand mud snail, is a freshwater species native to New Zealand. These snails exist either as an obligately sexual diploids or obligately asexual triploid or tetraploids. Both sexual and asexual snails are found coexisting throughout their native habitat.

In 2019, we discovered a *P. antipodarum* individual, nicknamed Sinistra, that has a shell that spirals to the left ("sinistral"). Sinistra is the first-ever *P. antipodarum* individual ever found to depart from the typical right-spiraling (dextral) chiral form. This individual was produced within an otherwise dextral asexual *P. antipodarum* lineage, suggesting that her unique phenotype arose within an asexual context. We are now using whole-genome sequencing data to compare Sinistra to her clonemates, with the goals of (1) uncovering the genetic basis of chirality, an important question in biology, as well as (2) estimating the rate of *de novo* mutation in an asexual line. *De novo* mutation is of broad interest both as the source of the raw material for evolution as well as the only mechanism by which asexual lineages can access new genetic variation.

20. TELOMERE LENGTH OF RPE AND CHORIOCAPILLARIS IN YOUNG VS OLD VS AMD HUMAN EYE TISSUE

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Age-related macular degeneration (AMD) is a leading cause of blindness in adults over 50. AMD is characterized by a loss of central vision caused by pathogenic angiogenesis and/or atrophy. As AMD is a disease of aging, we sought to address the possibility that cellular senescence-- an irreversible arrest of the cell cycle strongly linked to many aging phenotypes—plays a role in its initiation and or progression. Even though age is the most important risk factor for AMD, the relationship between senescence and AMD remains an incomplete field of study. To that end, one of our initial goals is to evaluate telomere length between cells involved in early AMD (choriocapillaris and retinal pigment epithelium (RPE)) in human donor eyes from young, old and AMD donors. For initial studies, we used laser capture microdissection to collect samples of RPE and choriocapillaris from sections of aldehyde-fixed macula from human donor eyes which were compared to unfixed flash frozen samples (n=2). DNA was extracted from each sample and telomere length determined using the Absolute Human Telomere Length Quantification qPCR Assay Kit (ScienCell #8918). Absolute quantification was determined by comparing the samples to a genomic reference standard of known telomere length. Preliminary data confirms that this approach is suitable for amplifying the very small amount of DNA yielded by LCM samples, and that telomere length readouts are within a predicted range. Additionally, fixed and flash frozen unfixed tissue gave comparable results on the qPCR assay readout, further supporting the validity of the approach and expansion of the project to more samples.

21 TFAP2 PARALOGS OPERATE IN A FRONTONASAL DYSPLASIA-RELATED *ALX1/3/4* GENE REGULATORY MODULE

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Cranial neural crest cells (CNCC's) give rise to the facial skeleton during embryonic development, and their contributions to forming unique structures are endowed by positional gene regulatory networks. Disruption of these networks leads to a high prevalence of craniofacial anomalies, the 2nd leading structural malformation to appear at birth. While pathways controlling formation of the lower face elements (e.g., jaw) have been widely characterized, the midface programs are poorly understood. Here, we show that combined loss of *Tfap2a* and *Tfap2b* in CNCC's leads to a severe midfacial cleft not seen by loss of a single *Tfap2* member. Cellular analyses and temporal gene inactivation strategies suggest the midface cleft arises not from impaired CNCC migration from the neural tube, but rather from defective post-migratory CNCC developmental processes. The combination of scRNA-seq, RNA-seq, and targeted gene expression approaches revealed that loss of *Tfap2a* and *Tfap2b* decreases *Alx1/3/4* transcript levels, whose expression is enriched in midface CNCC's, mutations cause Frontonasal Dysplasia (FND), and gene functions regulate midfacial CNCC survival and patterning. ChIP-seq revealed TFAP2 occupancy at *Alx1/3/4* loci, and our preliminary analyses provide evidence for *Tfap2a* and *Alx3* genetic interactions. Together, our findings illuminate a model with TFAP2 paralogs directly activate *Alx1/3/4* gene expression during midface morphogenesis. Interestingly, *Tfap2* inactivation did not compromise expression of FND-related *Six2*, whose gene product is implicated to regulate *Alx1/3/4* levels. Unexpectedly, we observed *Six2* weakly interact with *Tfap2a* and *Tfap2b* in the midface skeleton. Thus, our ongoing work is testing the hypothesis that TFAP2 and SIX2 factors operate in largely distinct transcriptional pathways in midface CNCC's while converging at the *Alx1/3/4* gene regulatory module.

22. CHARCTERIZATION OF UNLOADING DEFECT MUTANTS IN *C. ELEGANS* MEIOSIS

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Genomic instability is caused by both exogenous and endogenous sources of damage. External agents include various sources of radiation whereas internal agents can include endonucleases and reactive oxygen species. Germline DSBs are endogenously induced by a programmed pathway that disperses them throughout the genome (SPO-11-mediated DSBs in meiosis). Efforts have been used to identify meiotic hotspots in various species (e.g., modENCODE Project in C. elegans via RAD-51 antibody). Such a technique may also be able to map DSBs generated by inducible endonuclease systems to identify sites that cut most efficiently, thereby allowing ease of study of particular sites.

However, the RAD-51 antibody used in the modENCODE Project is no longer available to use for such experiments. Here, we propose to use a tagged version of RAD-51 as an alternative approach. Attempts to tag Rad-51 have been successful in our hands but these tagged versions of RAD-51 behave differently than wildtype RAD-51. Here, we describe the distinctions between different tagged versions of RAD-51, with a focus on RAD-51::FLAG. To determine if tagged RAD-51 behaves as wildtype in terms of loading and unloading during meiosis, we survey foci resolution through the germline. To see if RAD-51 is loading in the normal locations, we look at its distribution along the chromosomes. We also screen for checkpoint activation to see if these tagged RAD-51 proteins trigger a feedback response to increase DSBs. To see if chromosomal pairing occurs, we assess DAPI bodies at diakinesis-1. We demonstrate that there are abnormalities with the tagged versions of RAD-51, however, we may still be able to utilize them for mapping sites of DSBs from inducible endonuclease systems.

Developing tools to aid in surveying where DSBs occur may be helpful in furthering our understanding of how DSBs are repaired.

23. INTEGRATED GENOMIC APPROACHES TO CHARACTERIZE THE BIOLOGY OF LOW-GRADE SEROUS OVARIAN CANCER

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Ovarian cancer accounts for more deaths in women than any other gynecological cancer. Due to lack of screening methods for early detection, more than 80% of women with ovarian cancer have already developed advanced-stage disease prior to diagnosis, a major reason for the disease's high mortality. In addition to late diagnosis, few therapeutic advances have been made within the last 30 years, in part due to a lack of actionable targets in the most common subtypes of ovarian cancer.

Low-grade serous ovarian cancer (LGSOC) is an exception to this trend, as it shows frequent genetic alterations in the MAPK pathway (e.g. *KRAS, BRAF*) that can be targeted therapeutically. Although LGSOC accounts for <5% of ovarian cancers, the age of onset is younger (~45 years) than other subtypes and most patients eventually progress on standard of care therapy. The frequent MAPK pathway mutations have motivated several recent clinical trials testing MEK inhibitors in relapsed LGSOC patients, with trametinib producing the best outcome. However, all patients eventually progressed on trametinib, emphasizing the need to understand adaptive and/or genetic mechanisms of trametinib resistance in LGSOC. Here we describe our efforts to characterize these resistance mechanisms using integrated genomic approaches including CRISPRi and Sleeping Beauty mutagenesis screens in a panel of LGSOC cell lines. Based on results from our CRISPRi kinome screen, we hypothesize that LGSOCs develop resistance to MEK1/2 inhibition by upregulating PI3K-Akt signaling, thereby promoting cell survival.

24. GENETIC ASSOCIATION OF ANOSMIA AND AGEUSIA SYMPTOMS WITH COVID-19

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The COVID-19 pandemic has impacted the state of global health and economics consisting of over 600 million infections and accounting for just under 6.5 million deaths. COVID-19 has a diverse presentation of symptoms across patients including the possibility of cold-like symptoms, loss of smell (anosmia), and loss of taste (ageusia), along with displaying a spectrum of severity from asymptomatic infections to hospitalization and death. Prior studies have established genetic associations to more severe manifestations of COVID-19. However, the genetics involved with the COVID-19 symptoms of anosmia and ageusia have yet to be investigated. In this study, we performed whole-genome sequencing and gene-based variant association analysis on 191 individuals with confirmed SARS-CoV-2 infections to determine variants and genes associated with the development of anosmia and the development of ageusia. Our gene-based variant association analysis found 204 and 243 suggestive associations with gene variants that may increase risk of developing anosmia and ageusia respectively. We found suggestive associations with 168 and 138 genes that may provide protection to the development of anosmia and ageusia respectively. Pathway analysis was performed with the candidate genes and the top significant GO term for anosmia is “negative regulation of response to stimulus,” the top term for ageusia being “epithelium development.”

An examination of asymptomatic cases found several suggestive genes, one previously reported as being associated with COVID-19 severity, validating our methodology. These results contribute to understanding the genetics involved with COVID-19 and provide a start to understanding the anosmia and ageusia symptoms. Further refining of these results may provide insight for the development of better treatments to COVID-19.

25. SPATIAL TRANSCRIPTOMICS OF CARDIOMYOCYTES

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Many RNAs show asymmetrical distribution within the cells. Their localization is mediated by a set of protein called RNA binding proteins (RBPs). This localization is important for many physiological and normal developmental processes which can be dysregulated by Mislocalization of RNAs. Cardiomyocytes are the functional contractile cells that generate the required force for heart pump. These cells are connected through specialized structure called intercalated disc (ICD) to couple them electrically; so, their contraction can be synchronized and function as one unit. Aberrant localization or expression of ICD proteins is involved in many heart diseases. Many ICD proteins turn over rapidly, so they need to be replenished continuously. This could be energetically and functionally unfavorable for cardiomyocytes given their large size. Notably many RBPs are also expressed near ICDs which suggest the presence of RNA pool there. We hypothesize that intercalated disc territory is enriched with RNAs related to intercalated disc function which enable local translation of the proteins they encode. In this study we aim to identify the transcriptomic of intercalated discs region in physiological and pathological conditions. Intercalated discs will be isolated using laser capture microdissection; and RNA will be then isolated and sequenced.

26. IDENTIFICATION OF A NOVEL ROLE FOR THE PROTEIN PRMT5 IN ORAL AND SKIN EPITHELIAL DEVELOPMENT.

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During development, the initially single-layered epithelium of the skin and oral cavity requires a precise coordination of cell proliferation and differentiation to execute epidermal stratification. Defects in these events can lead to a range of congenital epidermal anomalies. Moreover, the accumulation of harmful mutations can lead to uncontrolled epithelial proliferation—often through reactivation of developmental programs—and carcinoma. Thus, uncovering molecular regulators of epidermal development can provide novel avenues for cancer therapies. Protein Arginine Methyl Transferase 5 (PRMT5)—an enzyme that catalyzes methylation of arginine residues in critical proteins, including histones and transcription factors—is upregulated in cancer and correlates with poorer prognosis. While inhibition of PRMT5 has been shown to have anti-cancer properties, the mechanisms behind this effect are unknown. Interestingly, PRMT5 has been identified as necessary to maintain a progenitor, stem-cell fate in both germ-cell and limb development as well as a variety of cancers. Therefore, we hypothesize that PRMT5 driven methylation of histones and transcription factors drives a gene expression program that impedes differentiation allowing the maintenance of a stem-cell phenotype. To test this hypothesis, we have used conditional mouse genetics to delete Prmt5 from the early (~E7.5) ectoderm. Consistent with a critical role for PRMT5 during this process, epithelial loss of Prmt5 resulted in gross skin and oral epithelial defects, reduced skin barrier function, and reduced postnatal viability. Histological analyses of control and mutant skin revealed severe defects in epidermal stratification, including the loss of the proliferative basal layer. To further probe the molecular underpinnings of these defects, we are currently profiling changes in gene expression (RNA-seq), chromatin accessibility (ATAC-seq), and histone methylation. Collectively, our findings have identified a critical role for PRMT5 in epithelial development and provide a novel model in which to dissect its molecular function in this process, providing insight into its role during tumor progression.

27. MECHANISMS OF DISEASE-MODIFYING EFFECTS OF NALTREXONE, A MU-OPIOID RECEPTOR ANTAGONIST, IN A JUVENILE MOUSE MODEL OF POST-TRAUMATIC EPILEPSY

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Traumatic brain injuries (TBIs) trigger mechanisms that cause neuroinflammation, glial cell activation, neuronal network remodeling, and post-translational synaptic protein modification that can cause deficits in cognitive function. Sustained disruption of normal homeostasis can ultimately result in dementia, anxiety, and post-traumatic epilepsy (PTE), with PTE developing in more than 50% of severe TBI cases. First-line pharmacological agents such as anti-epileptic drugs (AEDs) are commonly prescribed following TBIs, however, their efficacy is still disputed. Using high throughput transcriptome profiling, we identified Naltrexone (NTX) as a potential candidate for preventing or slowing the progression of epileptogenesis. Recent work evaluated the effect of NTX in a pentylenetetrazol (PTZ)-induced mouse model of epilepsy and found that mice pre-treated with Naltrexone were resistant to PTZ-induced seizures, suggesting that NTX may mitigate TBI-induced neuroinflammatory changes and prevent the development of PTE.

To test this, four-week-old C57BL/6J mice were subject to diffuse brain injury using a free-fall weight drop model. Mice were given two doses of Naltrexone or vehicle for 3 days, followed by a single dose for four more days. After euthanasia, serum was collected and brain tissues were harvested for neuroinflammation and neuroprotection evaluation, respectively. Results show that acute administration of Naltrexone following traumatic brain injury suppresses neuroinflammation, neurodegeneration, epileptiform discharges, and spontaneous recurrent seizures. These findings suggest that Naltrexone can be a potential disease modifying agent for epilepsy.

28. WHY DO TRANSCRIPTION FACTORS DEPEND ON COACTIVATORS?

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Transcription factors (TFs) are the center of any gene regulatory network, and their evolution has the potential to rapidly rewire the entire network, leading to functional divergence. One prevalent feature in eukaryotic gene regulation is combinatorial regulation, or the requirement of two or more TFs to co-activate a gene, which allows multiple upstream signals to influence downstream gene expression and provides a way to tune specificity by requiring a defined binding configuration for activation to occur. Why certain TFs need coactivators to function and how that combinatorial regulation evolves is poorly understood. We take advantage of the natural variation in coactivator dependence present in the Phosphate Starvation response network in two yeast species to study the basis for combinatorial regulation. In *S. cerevisiae*, the TF Pho4 (ScPho4) requires the coactivator, Pho2, while in the related *C. glabrata,* Pho4 (CgPho4) is far less dependent on Pho2. Using chimeras of ScPho4 and CgPho4, we found that changes in the DNA binding domain (DBD), the region known to be involved in coactivator binding, and the N-terminal transactivation domain jointly contribute to its activity in the absence of Pho2 and exhibit epistatic interactions. Focusing on the DBD, we tested the hypothesis that CgPho4 DBD binds the shared consensus motif tighter than ScPho4 DBD. We found that CgPho4 binds 3-4 times tighter than ScPho4, confirming our hypothesis. We also tested and found evidence for CgPho4 being more capable of binding nucleosome-occluded DNA *in vivo*. Our results show that coactivator dependence can result from a decreased ability to bind naked and nucleosome -bound DNA, both of which can be strengthened by amino acid substitutions and insertions, which led to reduced coactivator dependence. This work thus provides a basis for studying why transcription factors need coactivators and how they can evolve to no longer require them.

Poster Presentations

29. POLYGENIC SCORES CLARIFY THE RELATIONSHP BETWEEN MENTAL HEALTH AND GENDER DIVERSITY

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Gender diverse individuals are at higher risk for mental health problems. What remains unclear is whether this increased risk is attributable to environmental stressors (e.g., minority stress), innate pleiotropic effects on gender diversity and mental health, or gene-by-environment interactions. Here, we present two studies (N=5,388 and N=696, from the SPARK autism cohort) investigating these questions. First, N=696 independent adults provided thorough information on their gender identities using the Gender Self Report (GSR), a novel assessment for the continuous, multidimensional characterization of gender diversity. We tested 20 behavioral polygenic scores for association with the two GSR dimensions: Binary Gender Diversity (degree of identification with the gender opposite that implied by sex designated at birth) and Nonbinary Gender Diversity (degree of identification with a gender that is neither man/male nor woman/female). We found no evidence of association between gender diversity and polygenic risk for adult-onset psychiatric conditions. Strikingly, we instead found that both gender diversity dimensions were positively associated with the cognitive performance polygenic score (Binary ρ=0.09, p=0.02 and Nonbinary ρ=0.11, p=0.003). We also found Binary Gender Diversity to be positively associated with polygenic scores for autism (ρ=0.08, p=0.045) and non-heterosexual sexual behavior (ρ=0.09, p=0.02). Additionally, we tested for interactions effects and found no association between increasing gender diversity and poorer mental health outcomes in the subsample with low genetic risk for neuropsychiatric conditions. Only in the subsample with high genetic risk for major depression or schizophrenia did we observe a significant relationship between gender diversity and poor mental health outcomes. In the second study (N=5,388), we used self-reported categorical gender identity and found that, in agreement with our first study, transgender and gender nonbinary individuals had significantly higher polygenic scores for cognitive performance (t=3.90, p=0.0001) and non-heterosexual sexual behavior (t=2.0, p=0.04), as well as risky behavior (t=2.10, p=0.04).

30. TRANSCRIPTOMIC ANALYSIS OF THE CEREBELLUM IN THE 16P11.2 DUPLICATION MOUSE MODEL OF SCHIZOPHRENIA

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Schizophrenia is a severe and chronic illness where patients suffer with hallucinations, delusions, and cognitive dysfunction. Medications can reduce hallucinations and delusions, but currently available treatments do not improve cognitive symptoms. Recent work suggests that the cerebellum is involved in cognitive dysfunction in schizophrenia, but the mechanisms underlying this are unknown. To address this, we employ copy number variant (CNV) 16p11.2 duplication mice (16p11.2dup), a genetic mouse model of schizophrenia, to study the use of non-invasive cerebellar stimulation to correct gene expression and brain circuit function. We hypothesized that the cerebellum is an important site of pathology in 16p11.2dup. We first performed a deferential gene expression computational analysis of publicly available RNAseq data from 16p11.2dup mice and saw significant transcriptional dysregulation in the cerebellum between genotype and sex. This led us to generate our own transcriptomic profiles for 16 mice across both sexes and genotypes from the cerebellum using paired-end illumina sequencing. Preliminary analyses of the data suggest that there are strong cerebellar tissue-specific consequences of the CNV. We would like to investigate the neurodevelopmental aspects of 16p11.2dup pathology and will follow up our observations by performing single nucleus RNAseq of the cerebellum at two developmental stages. Overall, our findings shed light on the transcriptional landmark changes occurring in the cerebellum in a valid mouse model and can potentially accelerate the discovery and development of new diagnostic and therapeutic strategies for schizophrenia.

31. IDENTIFICATION OF DISTINCT FUNCTIONAL CNA GROUPS IN NEUROENDOCRINE TUMORS.

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Neuroendocrine tumors (NETs) are a group of malignant cancers that have been reported in 25 different locations throughout the body. NETs often present with metastatic liver disease and incidence has increased 7-fold in the last 30 years, reaching 1/10,000 people worldwide. NETs arise in neuroendocrine cells, which are involved in physiological functions such as digestion in the small bowel and glucose absorption in the pancreas. Ninety percent of NETs originate in the lung, gastrointestinal tract, or pancreas; however, due to similarities in signs/symptoms, tumor size, and accessibility it is often difficult distinguishing pancreatic NETs (pNETs) and small bowel NETs (sbNETs).

Currently, there are 3 NET markers; therefore, available NET biomarkers are lacking and merit further investigation. It is difficult to distinguish between gastrointestinal Copy number alterations (CNAs) are deviations in euploid status observed in somatic cells and are measured using chromosomal microarrays (CMA). CNAs have the potential to affect gene expression, and depending on direction and location, encourage tumor growth and/or metastasis. To identify NET biomarkers that differentiate pNETs and sbNETs while also predicting prognosis, CMA and RNA-sequencing were performed in conjunction on 64 NET patient samples to establish functional CNAs (fCNAs). To validate novel fCNAs, we performed fluorescent *in situ* hybridization using clinically validated probes. Our data show that ***CSFR1*** (Chr5q32), ***MET*** (chr7q31), ***CDKN2A*** (chr9p21.3), ***ERBB2*** (chr17q12), ***SMAD4*** (chr18q21.2), and ***CCNE1*** (chr19q12) tumor status can stratify NETs based on primary tumor site while also predicting prognosis.

32. THE GENETIC AND PHENOTYPIC LANDSCAPES OF *TECTA*-RELATED HEARING LOSS

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Genetic variants in *TECTA* have been implicated in both autosomal dominant and autosomal recessive non-syndromic hearing loss (ADNSHL [DFNA8/12] and ARNSHL [DNFB21], respectively), with missense variants implicated in the former and loss-of-function mutations implicated in the latter. To date, only two missense variants have been reported to be pathogenic for DFNB21 hearing loss, with no evidence as to why. Additionally, the severity of *TECTA*-related hearing loss is variable across the mutational spectrum, but studies of human cohorts have not identified clear genotype-phenotype correlations. To address these knowledge gaps, we studied 125 patients with either DFNA8/12 or DFNB21 hearing loss identified using comprehensive genetic testing (OtoSCOPE^{TM}), classifying genetic variants in the context of clinical and familial data. We present 10 novel missense variants causing *TECTA*-related ARNSHL, and in a comparison of domain location noted that all variants in the zona pellucida domain are associated with ADNSHL while variants in the other domains are implicated in both ADNSHL and ARNSHL. To explore phenotypically driven domain-specificity, we next used mouse mutants to compare hearing and histological phenotypes associated with the zonadhesin domain (*Tecta*$^{C1619S/+}$ mutant mouse) as compared to the zona pellucida domain (*Tecta*$^{C1837G/+}$ mutant mouse). Auditory brainstem response thresholds in *Tecta*$^{C1837G/+}$ mice were higher than in *Tecta*$^{C1619S/+}$ mice, supporting our hypothesis that mutation location impacts *Tecta* phenotypes. Consistent with this finding, light microscopy of organ of Corti cross-sections showed that *Tecta*$^{C1619S/+}$ mice had a slight alteration in tectorial membrane morphology while in *Tecta*$^{C1837G/+}$ mice, the differences were more striking. These results refine our understanding of *TECTA*-related hearing loss and provide insight that will improve the classification of variants in *TECTA*.


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