Icahn School of Medicine at Mount Sinai
The Mindich Child Health and Development Institute

MCHDI Developmental Outcomes

Fall 2019

Research Advancements: Congenital Disorders

Uncovering the Etiology of Congenital Disorders

What causes congenital disorders? In some cases, inherited mutations in a single gene, or exposure to a single environmental factor, is sufficient to cause a developmental disorder in most or all those affected. For example, recessive mutations in the ß-globin gene result in sickle cell anemia, and in utero exposure to thalidomide caused limb and other deformities in a high percentage of humans exposed during embryogenesis. For many of the most common congenital disorders, however, a single causative factor cannot be identified. It is widely believed that such diseases arise from a complex and ill-defined combination of genetic and environmental influences. Congenital malformations are a major health issue for affected children and their parents, and it is important for researchers and physicians to address the question posed at the start of this essay.

Holoprosencephaly (HPE) is a congenital disorder in midline patterning of the forebrain and midface; i.e., a failure to generate bilateral symmetry of the brain hemispheres, eyes, and/or other facial features. It is remarkably common, occurring about once in 250 conceptions, but with the great majority succumbing in utero. HPE encompasses a spectrum of anomalies that range from a single brain hemisphere and cyclopia (a single, centrally located eye) in its most severe form, to mild mid-facial perturbations, such as a single central incisor (instead of two upper front teeth). The midline of the forebrain and face develop under the influence of the Hedgehog signaling pathway. Mutations in one copy of genes encoding components of the Hedgehog pathway are associated with HPE, but they are not sufficient to cause these malformations (note that in recessive disorders like sickle cell anemia both copies of the relevant gene are mutated, and this is not seen in HPE). There are rare families in which such mutations of HPE genes are inherited. Approximately 30% of family members carrying one mutated copy do not have any clinical manifestation, while others may display anomalies within the full range of HPE severity. These and additional observations have led to the conclusion that the outcomes associated with such mutations are governed by "modifiers", genetic variants and/or environmental exposures that interact to enhance the effects of losing a single copy of a critical gene in the Hedgehog pathway.

While epidemiological studies of HPE are underway, they are difficult to perform. To circumvent this problem, the Krauss lab uses mice as a model organism to study the question of how HPE is caused. We have engineered mice to carry a mutation in the Hedgehog pathway similar to ones found in some patients; these mice have a sub-threshold defect in pathway activity. We have successfully used these animals to identify potential modifiers, both genetic and environmental in nature. Working with pediatric geneticists at the National Institutes of Health, a genetic modifier we identified in mice was then found in some HPE patients. Two environmental modifiers have also been identified. One is fetal alcohol exposure. Strikingly, the critical time-period for alcohol-induced HPE in these mice is equivalent to the third week after conception in humans, a time many women do not yet know they are pregnant. A pilot grant from MCHDI helped us identify THC, the major psychoactive ingredient in marijuana, as another environmental HPE modifier. These studies argue that multiple modifying factors interact with bone fide HPE mutations to grade clinical outcomes. Such modifiers can be genetic or environmental, and they may have either enhancing or protective effects. Despite the complex interplay of HPE risk factors, mouse models have helped establish some clear concepts in HPE etiology. These concepts are likely to be generalizable to additional congenital disorders. A combination of studies with mice and human populations should improve our understanding of this important issue.

"Despite the complex interplay of HPE risk factors, mouse models have helped establish some clear concepts in HPE etiology."

Robert Krauss, PhD
Professor, Cell, Developmental, and Regenerative Biology

Deciphering the Cellular and Molecular Mechanisms of DDX3X Syndrome

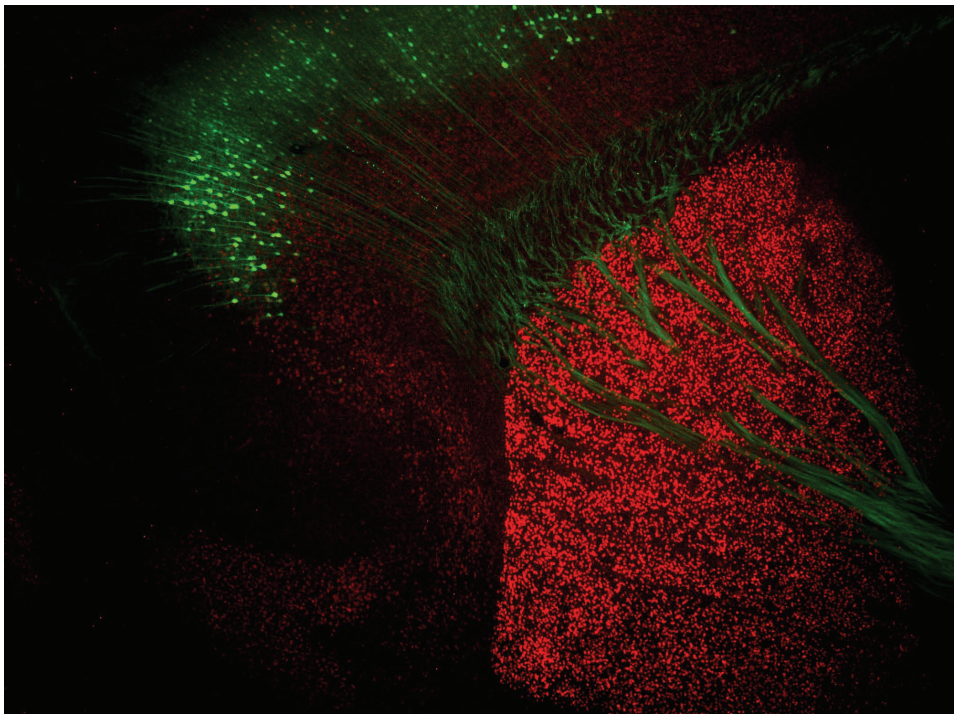
Intellectual disability (ID) is diagnosed in 1 in 40 people worldwide and still has no effective treatment. Early intervention can ameliorate some of the disability, but affected individuals require support throughout their lives. Dozens of genetic disorders associated with ID have recently been discovered. Yet, precision medicine approaches capitalizing on these findings are lagging behind because of the dearth of functional analyses.

DDX3X syndrome is a recently discovered genetic disorder associated ID. In addition, with moderate to severe ID, DDX3X syndrome presents with a constellation of medical comorbidities that further challenge patients and their families. Affected individuals can suffer from failure to thrive, hypotonia, movement disorder, congenital brain malformations, and behavioral problems, including autism spectrum disorder (ASD) and anxiety. The condition is estimated to account for 2% of ID in females, but we expect this figure to continue to rise as awareness increases and clinical sequencing becomes more accessible.

DDX3X syndrome is caused by mutations in the X-linked gene DDX3X. Unlike most genes on the X chromosome, DDX3X escapes X chromosome inactivation across tissues, including the brain. As a result, females express DDX3X at higher levels in their brains compared to males. The DDX3X paralog on the Y chromosome (DDX3Y) does not compensate for the dosage imbalance as it is translated only in spermatocytes. Most individuals diagnosed with DDX3X syndrome are females with DDX3X haploinsufficiency. Only a few male cases have been identified, suggesting that DDX3X mutations in males are often incompatible with life.

Females harboring only one functional DDX3X allele have ID, while males (who are physiologically hemizygous) do not. Why does intact cognition require two functional DDX3X alleles in females but not in males?

Silvia De Rubeis, PhD, and her laboratory aim at answering this fundamental question to decipher mechanisms of sex differences in cognition and understand DDX3X syndrome. To achieve this goal, Dr. De Rubeis' lab uses an integrated approach of genetics, developmental biology and neuroscience, applied to cellular and mouse models.



Zooming in cortical connections. Using a method called retrograde labeling, the De Rubeis lab studies how neurons in the cerebral cortex communicate with other regions of the brain to coordinate cognitive, social and motor function. The picture shows cortical excitatory neurons in green projecting to the pontine nuclei through the striatum (red).

A first line of work, supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), investigates the role of DDX3X at excitatory synapses in the cerebral cortex. Using genetic manipulation of cortical neurons isolated from mouse embryos, the team examines how female and male synapses develop when DDX3X is mutated. Mutations found in girls and boys are both modeled to capture the sex-specific determinants of DDX3X syndrome.

A second line of work, supported by the Beatrice Seaver Foundation, uses a novel mouse model of DDX3X syndrome to identify the behavioral, cellular and molecular drivers of the syndrome. Initial data show that the mouse model has developmental delays and adult behavioral deficits that closely resemble the clinical manifestations of DDX3X syndrome. These behavioral outcomes are accompanied by defects in the cytoarchitecture of the cerebral cortex.

Given the prevalence and sex bias, studying DDX3X syndrome offers an opportunity to take a genetics-first approach to study ID more broadly and explore physiological and pathological neurodevelopment in females, which is a largely understudied area.

Silvia De Rubeis, PhD
Assistant Professor, Psychiatry

Katherine Guttmann, MD, MBE

Katherine Guttmann, MD, MBE is an Assistant Professor at the Icahn School of Medicine and an attending neonatologist in the Mount Sinai Health System. She completed medical school at the University of Pennsylvania followed by residency and fellowship at the Children's Hospital of Philadelphia where she also served as Chief Fellow. Dr. Guttmann conducts research focusing on ethics and communication with families. Past work has investigated parental perspectives on conversations related to diagnosis and prognosis of Cerebral Palsy, success of goals of care discussions in the NICU, parents' experiences of research participation, and telemedicine as a novel means of improving communication with families in the NICU. Additional academic interests include Neonatal Palliative Care and Research Ethics. She holds a Master's degree in Bioethics from the University of Pennsylvania which informs her work. She is committed to understanding and improving the family experience of NICU hospitalization. Current projects include a study investigating patient and physician related factors correlated with low quality communication in the NICU as well as the long term impact of poor communication in the NICU on families. Dr. Guttmann is also working with collaborators at the University of Washington to explore how parents make decisions related to research enrollment in the NICU and how site-specific variation contributes to success of enrollment in a large multi-site Randomized Controlled Trial.

Recent Publications:

Guttmann K, Flibotte J, DeMauro S: **Parental Perspectives on Diagnosis and Prognosis of NICU Graduates with Cerebral Palsy**. *Journal of Pediatrics*. 2018; 203: 156-162.

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Guttmann K, Shouldice M, Levin A. Ethical Issues in Child Abuse Research. New York: *Springer Nature,* 2019.

Katherine Guttmann, MD, MBE
Assistant Professor, Pediatrics

New Extramural Faculty

Maria Curotto de Lafaille, PhD

Maria Curotto de Lafaille, PhD, is an Associate Professor of Pediatrics and member of the Jaffe Food Allergy Institute and the Precision Immunology Institute at Mount Sinai School of Medicine. Dr. Lafaille obtained her PhD degree in Immunology from the University of São Paulo in Brazil and trained as a postdoctoral fellow in Infectious Diseases at Harvard University. Before joining Mount Sinai, Dr. Lafaille held faculty positions at the Agency for Science, Research and Technology in Singapore and at New York University Medical School. Dr. Lafaille has a long-standing interest in allergic diseases, having made important contributions to the understanding of basic mechanisms of mucosal tolerance and allergic sensitization. Among them was the pioneer work on the essential role of outside-thymus induced regulatory T cells in the prevention of allergic inflammation. Studies on the mechanisms of IgE regulation in mice revealed unique aspects of the differentiation of IgE-producing cells that generated new paradigms for the allergy field. Current studies in Dr. Lafaille's laboratory aim to elucidate the mechanisms that maintain the B cell memory of allergic responses in mice and human. In collaboration with colleagues at the Jaffe Food Allergy Institute and the Precision Immunology Institute, her group works to understand how immunological memory shapes the evolution of food allergy towards resolution or persistence of the disease.

Recent Publications:

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Jones LA, Ying S, Ramakrishna L, Srinivasan KG, Yurieva M, Ng WP, Subramaniam S, Hamadee NH, Joseph S, Dolpady J, Atarashi K, Honda K, Zolezzi F, Poidinger M, Lafaille JJ, **Curotto de Lafaille MA**. **A subpopulation of high IL-21-producing CD4+ T cells in Peyer's Patches is induced by the microbiota and regulates germinal centers**. *Sci Rep*. 2016 Aug 8;6:30784.

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Maria Curotto de Lafaille, PhD
Associate Professor, Pediatrics

Magdalena Janecka, PhD

Magdalena Janecka, PhD, is an Assistant Professor in the Department of Psychiatry, and a member of the Seaver Autism Center. Dr. Janecka received her undergraduate degree from the University of St. Andrews, Scotland (double major in Psychology with Biology), and subsequently completed her PhD in Social, Genetic and Developmental Psychiatry at King's College London. After her first postdoctoral position at the University of Oxford, she was awarded the Seaver Foundation Postdoctoral Fellowship, and moved to the Icahn School of Medicine in 2016. Dr. Janecka's research focuses on understanding why certain parental and early-life factors are associated with a higher risk of neurodevelopmental disorders in children. In order to better understand the causal mechanisms underlying this risk, she integrates insights from epidemiology, epigenetics and genetics. The goal of her research is to elucidate how the environments impact long-term developmental outcomes, contributing to identification of modifiable risk factors, prevention and patient stratification.

Recent Publications:

Janecka M, Hansen SN, Modabbernia A, Browne HA, Buxbaum JD, Schendel DE, Reichenberg A, Parner ET, Grice DE. **Parental age and differential risk for neuropsychiatric disorders: findings from the Danish birth cohort**. *J. Am. Acad. Child Adolesc. Psychiatry*. 2019 Jun;58(6):618-627

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Janecka M, Haworth CMA, Ronald A, Krapohl E, Happé F, Mill J, Schalkwyk LC, Fernandes C, Reichenberg A, Rijsdijk F. **Paternal age alters social development in offspring**. *J. Am. Acad. Child Adolesc.* **Psychiatry. 2017 May;56(5):383-390.**

Magdalena Janecka, PhD
Assistant Professor, Psychiatry

Trainee Highlights

TLC Introduces Three New Members and Upcoming Events

The Trainee Leadership Committee (TLC) is in its fourth year of bringing together trainees across multiple disciplines and research areas represented in the MCHDI. Since its start, the TLC has hosted 5 socials, led 9 workshops and continued the MCHDI pilot grant. The fifth social was on September 27th and provided useful feedback on topics of interest for future workshops.

The TLC workshops are part of the Child Health Research Seminar (CHRS) series organized by Dr. Shelley Liu and Dr. Alan Groves. The TLC will be hosting three workshops next year, 2/4, 3/17 and 4/28. The first workshop will be a career panel with diverse fields represented. This will help trainees get a sense of what is available outside of academia. Future workshops will focus on a career panel, the BioMe bank program, and meta-analysis and systematic review.

The flagship TLC accomplishment is the trainee pilot grant, now in its third year. This unique grant offers trainee support for projects independent of their PIs, a crucial step in any trainee's career. Previous winners include the TLC's own Oscar Rodriguez, Michael Breen, PhD, Milo Smith, PhD and Hsi-en Ho, MD. This year's recipients are Conor Gruber and Carolina Cappi, PhD. Carolina is also the newest member of the TLC. Applications for the 2020-2021 academic year will open in March 2020.

The Mindich Child Health and Development Institute is implementing an updated "grant bank" to facilitate both intramural and extramural grant applications. We invite faculty and trainees to share their successful grants as well as other supportive documents. The shared grants will be saved in a repository that can only be accessed by MCHDI faculties and trainees.

Lastly, the TLC would like to thank its members from last year for all their hard work and dedication, Dr. Maya Deyssenroth and Dr. Felix Richter. We would also like to thank Corina Lesseur, PhD for her time and assistance to the TLC. Please help us welcome Oscar Rodriguez, Xueying Zhang, PhD and Carolina Cappi, PhD to the committee! We look forward to another great year ahead.

Jennie Altman
PhD Candidate
Department of Microbiology

Oscar Rodriguez
PhD Candidate
Department of Genetics and Genomic Sciences

Carolina Cappi, PhD
Post-doctoral fellow, Department of Psychiatry

Xueying Zhang, PhD
Postdoctoral Fellow
Department of Environmental Medicine and Public Health

Faculty Grants

James J. Bieker, PhD, and Jeffrey Glassberg, MD, Doris Duke Charitable Foundation, Sickle Cell Disease/Advancing Cures Award, "Quantitative modulation of an erythroid regulator as a novel genetic target for sickle cell disease "

Supinda Bunyavanich, MD, MPH, NIAID, R01, "Gut Microbiome Dynamics in Peanut Allergy"

Jaime Chu, MD, American Association for the Study of Liver Diseases, AASLD Foundation Bridge Award

Silvia De Rubeis, PhD, NICHD, R21, "Investigating DDX3X as a sex-specific translational regulator associated with intellectual disability"

Hirofumi Morishita, MD, PhD, NIMH, R01, "Mechanisms regulating the maturation of prefrontal top-down circuity in control of attentional behavior"

Hirofumi Morishita, MD, PhD, NIMH, R01, "Experience-dependent maturation of prefrontal circuitry in control of social behavior"

Rebecca Trachtman, MD, MS, CARRA, Large Grant, "Procalcitonin and Calprotectin for Differentiation of Infection and Disease Flare in Systemic Juvenile Idiopathic Arthritis"

Faculty Honors/Awards

Supinda Bunyavanich, MD, MPH, Castle Connolly Exceptional Woman in Medicine 2019

Andrew Sharp, PhD, ASHG conference, Plenary session, "PgmNr 95: A survey of epigenetic variation in >23,000 individuals identifies many disease-relevant epimutations and novel CGG expansions"

Trainee Grants/Awards

Carolina Cappi, PhD, Mount Sinai, MCHDI Pilot Grant

Conor Gruber, Mount Sinai, MCHDI Pilot Grant

Anna S. Rommel, PhD, Mount Sinai, Promising Young Investigator (Travel) Award

Publications

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Breen MS, Dobbyn A, Li Q, Roussos P, Hoffman GE, Stahl E, ... **Buxbaum JD**. **Global landscape and genetic regulation of rna editing in cortical samples from individuals with schizophrenia.** *Nat Neurosci*. 2019 Sep;22(9):1402-12.

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Icahn School of Medicine at Mount Sinai

The Mindich Child Health and Development Institute

Website: www.mountsinai.org/mchdi
Email: mchdi@mssm.edu
Facebook: www.facebook.com/mindichchdi
Twitter: @MindichCHDI
Contact: Tel: (212) 824-8938 Fax: (212) 241-3310
Address: 1470 Madison Avenue, 8th Floor
Hess Center for Science and Medicine at Mount Sinai
New York, NY 10029-6542