2021 SCAND Symposium

Friday, March 5th 9:00 am – 2:30 pm

Virtual Symposium

PROGRAM AGENDA

9:00 - 9:05 **Welcoming and Opening Remarks –**
Rich Steet, PhD, Director of Research, Head of JC Self Research Institute of Human Genetics, Greenwood Genetic Center

9:05 – 9:30 **What is happening at each institution?**
Greenwood Genetic Center
Clemson University
Medical University of South Carolina
University of South Carolina

Session One: Autism
Moderator: Rich Steet, PhD, Director of Research, Head of JC Self Research Institute of Human Genetics, Greenwood Genetic Center

9:30–9:40 **Parent Presentation**
Shannon and Sam Spilker, Parents to four kids, three of whom have Autism, Advocates

9:40–9:50 **Advocacy Presentation**
Lisa Lane, JD and Susan Sachs – co-Founders and co-Executive Directors of Project HOPE

10:00 – 11:00 **Keynote Address: Developmental science meets public health challenge: lessons from autism in infants and toddlers**
Ami Klin, PhD, Director, Marcus Autism Center, Children's Healthcare of Atlanta; Georgia Research Alliance Eminent Scholar Professor, The Bernie Marcus Chair in Autism, and Chief, Division of Autism & Related Disorders, Department of Pediatrics, Emory University School of Medicine; Emory Center for Translational Social Neuroscience.

11:00 – 11:20 **The Carolina Autism Transition Study (CATS)**
Laura Carpenter, PhD, Professor of Pediatrics, Medical University of South Carolina

~~~~~~~~ *Grab your lunch!* ~~~~~~~~~~

12:00 – 1:00 **Networking Lunch with Talks**

- **Breakout 1: The current state and future directions of the autism and neurodevelopmental disorders field**
- **Breakout 2: Training opportunities for undergraduate and graduate students in the autism and neurodevelopmental disorders field**
- **Breakout 3: Early stage investigators: grants, recruitment, and establishing effective collaborations**
~~~~~~~~

Session Two: Neurodevelopmental Disorders

Moderator: Linnea Freeman, PhD, Assistant Professor of Biology and Neuroscience, Furman University

1:00 – 1:20 **Mitochondrial function in the prefrontal cortex is linked with sociability in mice**
Fiona Hollis, PhD, Assistant Professor of Pharmacology, Physiology & Neuroscience, University of South Carolina School of Medicine

1:20 – 1:40 **A TOR of the Developing Brain**
David Feliciano, PhD, Associate Professor of Biological Sciences, Clemson University

1:40 – 2:00 **Phelan-McDermid syndrome: the perfect mix of genetic heterogeneity and clinical variability**
Luigi Boccuto, MD, Faculty Member of the School of Nursing at Clemson University and Research Scientist at Greenwood Genetic Center

2:00 – 2:20 **Humanizing the mouse brain: the role of human genes in brain development, function, and disease**
Ewoud Schmidt, PhD, Assistant Professor of Neuroscience, Medical University of South Carolina

2:20 – 2:30 **Concluding Remarks – Linnea Freeman**

Retreat Planning Committee Members

Linnea Freeman, PhD, Furman University

Jane Roberts, PhD, USC

Rich Steet, PhD, Greenwood Genetic Center

Jeff Twiss, MD, PhD, USC

PRESENTATION ABSTRACTS

Keynote Address

Ami Klin, PhD

Developmental science meets public health challenge: lessons from autism in infants and toddlers.

Abstract: This presentation highlights the critical role of early diagnosis and intervention in attenuating the symptoms and in optimizing outcomes of toddlers with autism. Data will be presented on early diagnostic indicators obtained through eye-tracking-based behavioral assays that quantify the social disabilities in autism. The results of these assays were used to generate "growth charts" of normative social engagement, and the deviations from the norm were taken as early indicators of risk. These methods yielded high sensitivity and specificity for the screening of infants and toddlers. The ultimate goal of this effort is to develop objective and quantitative tools for the detection of autism in infancy and toddlerhood, tools that might be deployed in primary care practices. This work will be contextualized in terms of recent developmental social neuroscience research with toddlers with autism, which implicated developmentally very early emerging, and evolutionarily highly conserved, mechanisms of social adaptation that set the stage for reciprocal social interaction, which in term represent the platform for early social brain development. These mechanisms of socialization are under stringent genetic control, setting the scientific basis for parent-delivered, community-viable, early treatment in which social engagement is “engineered” via daily activities, thus impacting a child’s development during every moment of social interaction.

Effective screening of infants would be unethical without a clinical infrastructure providing access to family support and early intervention for those screened positive. Through a collaboration with Dr. Amy Wetherby, we are now establishing tools and procedures for the full integration of primary care physicians and early intervention providers with the goal of establishing a new system of healthcare delivery for infants & toddlers with autism spectrum disorders. This system deploys “Early Social Interaction” as its modality of parent-delivered treatment.

Laura Carpenter, PhD

The Carolina Autism Transition Study (CATS)

Abstract: The Carolina Autism Transition Study combines epidemiological data from multiple sources to broadly describe service access and negative life experiences of transition-aged youth (ages 17-23) with autism spectrum disorder (ASD) with (n=293) and without (n=316) intellectual disability. Services examined in this study include access to education, medical and dental care, therapeutic interventions, and more. Negative life experiences examined in this study include maltreatment, criminal charges, emergency department admissions, and hospitalizations. Youth with ASD (with and without intellectual disability) are compared to youth with intellectual disability (n=1272) and a population control group (n=2973).

Fiona Hollis, PhD
Mitochondrial function in the prefrontal cortex is linked with sociability in mice

Abstract: Autism Spectrum Disorders (ASD) are a complex group of neurodevelopmental conditions characterized by repetitive behaviors and impaired social interactions. While studies have identified a strong genetic component, the etiology of ASD is complex and attributed to both genetic and environmental factors. Interestingly, metabolic disorders and mitochondrial dysfunction are often reported in ASD patients, suggesting a link between mitochondrial function and ASD. Recent studies in specific brain regions revealed a link between brain mitochondrial function and social competition, suggesting a role for brain mitochondrial function in social behavior. Here we explore the link between mitochondrial function in various brain regions and social ASD-like symptoms both in established ASD mouse models and following environmental manipulation of mitochondrial function. We found reduced mitochondrial respiration in the prefrontal cortex in both environmental and idiopathic ASD mouse models. Interestingly, inhibition of complex I function during the last week of gestation in mice was sufficient to induce both social deficits and a significant reduction in prefrontal cortex mitochondrial function in adult offspring. Our findings suggest an association between mitochondrial dysfunction in the prefrontal cortex and social deficits that may be relevant for ASD disorders.

David Feliciano, PhD
A TOR of the Developing Brain

Abstract: Mutations that effect the Target of Rapamycin (TOR) pathway prevent proper brain development and lead to a spectrum of neurological disorders characterized by seizures, autism, and intellectual delay. TOR is a protein kinase that inhibits catabolic processes and activates anabolic protein translation. The coordination of these processes is required for generating proper brain architecture and for balancing network connectivity. Here, we provide evidence that understanding the basic cell biology of the TOR pathway allows for clinical predictions about disease causing mutations and therapeutic approaches that will help treat a range of neurodevelopmental disorders.

Luigi Boccuto, MD
Phelan-McDermid syndrome: the perfect mix of genetic heterogeneity and clinical variability

Abstract: Phelan-McDermid syndrome (PMS) is a multi-systemic disorder caused rearrangements on chromosome 22q13 or pathogenic variants in the SHANK3 gene. Unlike other microdeletion syndromes, the rearrangements leading to PMS are not characterized by recurrent breakpoint and may vary dramatically in size (from ~60 kb to over 9 Mb) and type (from simple terminal deletions to balanced translocations, del/dup, or ring). Similarly, the variants in the SHANK3 gene seem to be randomly distributed across the gene and lack any correlation with the severity of the phenotype.

PMS is characterized by extreme clinical variability. The most common features are developmental and speech delay, hypotonia (particularly neonatal), and motor impairment, but other neurological traits

have been frequently reported, such as autism, regression, seizures, sleep disorders, problems with regulation of body temperature, and high tolerance to pain. Non-neurological features include gastro-intestinal issues, kidney problems, lack of sweating, and minor dysmorphic traits (long eyelashes, dysplastic nails).

Such combination of genetic heterogeneity and clinical variability poses a serious challenge for the diagnosis, management and prognosis of PMS. For example, the lack of a consistent clinical presentation may delay significantly the diagnosis, and microarrays usually fail to detect certain rearrangements such as balanced translocations, or may classify rings as terminal deletions. Moreover, most of the functional studies on PMS have been focused on SHANK3, even if the majority of patients have lost many other genes, some of which associated with phenotypes compatible with the ones reported in PMS.

We have analyzed the genotype-phenotype correlation in PMS and noted how certain features correlate with the deletion size (i.e. language development) or the type of rearrangement (i.e. cases with ring 22 chromosomes may present with additional traits). The results of our studies highlight the potential contribution of genes proximal to SHANK3 to the clinical variability in PMS and suggest that in cases with small rearrangements multiple modifying factors may play a role in the severity of the phenotype.

Ewoud Schmidt, PhD

Humanizing the mouse brain: the role of human genes in brain development, function, and disease.

Abstract: Human cortical pyramidal neurons (PNs) are characterized by increased synaptic density and prolonged synaptic maturation. These features are thought to be critical for human cognition by increasing neuronal connectivity, including increased feedforward and feedback connectivity. However, we lack insight into how this connectivity emerged and how it contributes to human cognition. We identified a human gene, SRGAP2C, that in mouse cortical PNs induces traits in synaptic development similar to those found in humans. Using a novel implementation of monosynaptic tracing to map inputs from the whole brain onto layer 2/3 PNs in the barrel cortex, we discovered that SRGAP2C selectively increases cortical feedforward and feedback connectivity. In vivo 2-photon Ca2+ imaging in the barrel cortex revealed that SRGAP2C improves sensory coding of layer 2/3 PNs by increasing stimulus response probability, while reducing overall spontaneous activity. We examined whether these structural and functional connectivity changes affect behavior by using a novel two-alternative forced choice texture discrimination task. We tested the ability of humanized SRGAP2C mice to discriminate between two different rough textures using their whiskers and found that SRGAP2C mice display an increased ability to learn this cortex-dependent task. We propose that the emergence of SRGAP2C critically changed cortical circuit connectivity and function and provided a key evolutionary step towards improved cognition. Our current work is focused on understanding how human-specific traits of synaptic development play a role in neurodevelopmental disorders such as autism.