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NEWS

Research and training in autism spectrum disorder to catalyze the next genomic and neuroscience revolutions

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Autism spectrum disorder (ASD) is a group of neuropsychiatric conditions that manifest in early development and are characterized by deficits in social behavior and communication, along with restricted and repetitive patterns of behavior and interests or atypical response to sensory information. Once considered a rare disorder, recent prevalence estimates of ASD are as high as 1 in 54 [1]. Although the burden of ASD is high for individuals and families, limited progress has been made in understanding etiologies, underlying biological mechanisms, biomarkers, or pharmacological intervention [2].

Key objectives for increasing the impact of ASD research include broadening the involvement of scientists with diverse expertise, as well as expanding research globally. To address these goals, in 2007, Drs. Daniel Geschwind, Sarah Spence, and Pat Levitt initiated a biannual course on ASD at the Banbury Center at Cold Spring Harbor Laboratories (CSHL). The course was designed to draw advanced trainees and junior faculty from around the world and to provide (i) an in-depth and comprehensive overview of the state of ASD science, (ii) an opportunity for basic scientists to learn about the clinical aspects of ASD, (iii) a forum for participants to share and receive feedback on their own research, and (iv) an international network of like-minded researchers to support research progress. The course has continued every 2 years, with the most recent iteration in August of 2019 led by the authors (Fig. 1). Lectures on the topics of clinical presentation, epidemiology, neurobiology, and model systems were provided by field leaders including Fred Volkmar, Helen Tager-Flusberg, Sarah Spence, Daniele Fallin, Daniel Geschwind, Frances Champagne, Nenad Sestan, Carla Shatz, Nicola Allen, Guoping Feng, Cynthia Schumann, Declan Murphy, Mustafa Sahin, Craig Powell, Michael Platt, Connie Kasari, and Alison Singer. In addition to lectures, activities included journal clubs, student research talks, professional development workgroups, group research proposal development, and organized debate. Over the course of the past 12 years of the course, the key themes have evolved substantially.

Understanding ASD risk

Twin and family studies have long implicated genetic risk in ASD, with the most recent work suggesting a nearly 15-fold increase in risk in younger siblings of a child with ASD [3]. When the CSHL course began in 2007, the first copy number variants (CNVs) had recently been described as contributing to ASD risk [4], and there were no high-confidence ASD risk genes. In contrast, we now understand that CNVs contribute to risk in nearly 10% of children with ASD, and more than 100 genes have been implicated by identification of multiple de novo, likely gene-disrupting single-nucleotide variants (SNVs) [5]. Individually, each of these CNVs and SNVs is quite rare, with none accounting for more than 1% of cases, but, collectively, they contribute to risk in 15–20% of affected children.

Environmental risk factors have also emerged over this time period, although at a slower rate corresponding with less powerful methodology. Some of the most robust risk factors, like advanced paternal and maternal age [6], may map, in part, onto risk of mutations or nondisjunction events. Others, like short inter-pregnancy interval and lack of folate supplementation, may fit a deficiency model [7]. Most, however, continue to center around prenatal and

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Fig. 1 The 2019 Banbury Course on Autism Spectrum Disorders at Cold Spring Harbor Laboratory. Students and instructors in the courtyard of the Meyer house on the Banbury campus. Photo credit Constance Brukin.

perinatal factors that may convey general neurodevelopmental risk [8]. While time has increased the confidence and precision of these findings, there is little evidence to indicate broad environmental factors that may contribute to the marked rise in ASD diagnosis.

As genetic risk factors have emerged—and confidence around environmental risk factors has increased—our discussions of risk have shifted from the theoretical to the practical, from the math underlying genetics and epidemiology to the developmental neurobiology that is perturbed by identified risk factors. At the most recent session, speakers highlighted chromatin regulation, synaptic function, and key periods in early brain development as key processes implicated by convergent analyses across genetic or environmental risk factors. These areas of convergence present opportunities for the application of experimental methods in neurobiology.

Asking the right neurobiological questions with the right experimental system

Twelve years ago, when the first course met (and one of us participated as a student), genetic animal models for ASD were just being developed [9]. With a PubMed search now identifying more than 2,300 papers on mouse models of ASD risk, discussions have focused on various levels of phenotyping, from behavior to advanced electrophysiology, as well as the strategies for assessing validity of these models.

In recent years, however, several other experimental systems have been introduced to ask novel neurobiological questions [10]. Primate genetic models are very useful at validating late-stage hypotheses using behavioral phenotyping or testing gene therapies, but they have extremely low throughput. Induced pluripotent stem (hiPS) cells models that use neurons derived from patients in vitro make it now possible to identify functional cellular defects in the context of the complex genetic architectures of ASD. Moreover, tridimensional organoids resembling specific brain regions or assembloids obtained by fusing multiple organoids can be applied to model disease but also to map disease risk onto specific human brain cell types or to build and probe neural circuits in vitro [11]. However, long-term cultures (months to years) are required to capture late stages of human cerebral cortical development, and there are no behavioral measurements for these in vitro models.

Transcriptome and epigenome studies, including at single-cell resolution, have started to uncover the developmental landscape of the human brain and to suggest vulnerability in mid-fetal pyramidal neurons in ASD [12]. It is becoming clear, however, that there are several cell types (including microglia, astrocytes), regions (including cerebellum, striatum), and perturbations of the trajectory of the developing brain that give rise to ASD and that a

combination of experimental models is needed to elucidate the neurobiological mechanisms.

Opportunities and challenges for translation into the clinic

As research on risk factors yields hypotheses to be tested in the laboratory, some bench work is now being tested for translation into the clinic [13]. Discussions of current treatments focus on behavioral approaches that are intensive and make an important impact, but discussions of future treatments focus on interventions that could potentiate synaptic plasticity or learning. Each year, the students' end-of-course projects focus on delivering scientific findings that deliver clinical transformation. We have just now reached the point where such ideas are being properly tested for genetic disorders associated with ASD, from fragile X syndrome to tuberous sclerosis and beyond. With this trajectory of scientific progress, we look forward to the novel insights that will be shared among students of the CSHL course in the coming years.

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Compliance with ethical standards

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