



IN THIS ISSUE

1 102 AUTISM GENES IDENTIFIED
SEAVER AUTISM CENTER TO ACCELERATE DDX3X RESEARCH THROUGH A GRANT FROM THE CHAN ZUCKERBERG INITIATIVE

2 SEAVER AUTISM CENTER DIRECTOR GAINS ACCOLADES

3 YOUNG FACULTY FROM ACROSS THE CENTER SECURE GRANT FUNDING

CONGRATULATIONS, DR. GRICE!

NEWLY PROMOTED FACULTY

4 NEW FACULTY AND STAFF

5 SEAVER CELEBRATION LUNCHEON

102 Autism Genes Identified

In the largest genetic sequencing study of autism to date, researchers have identified 102 genes associated with risk for autism. The study also shows significant progress towards teasing apart the genes associated with autism from those associated with intellectual disability and developmental delay, conditions which often overlap. The study results are published online January 23 in the journal *Cell*.

For this study, an international team of researchers from more than 50 sites collected and analyzed more than 35,000 participant samples, including nearly 12,000 with autism. Using an enhanced analytic framework to integrate both rare, inherited genetic mutations and those occurring spontaneously when the egg or sperm are formed (de novo mutations), researchers identified the 102 genes associated with autism risk. The larger samples size of this study enabled the research team to increase the number of identified genes associated with autism from 65 in 2015 to 102 today.

Obtaining such a large sample was made possible by the Autism Sequencing Consortium (ASC), an international group of scientists who share autism samples and data. Co-founded by Joseph D. Buxbaum, PhD, Director of the Seaver Autism Center, in 2010 and originally funded by the Beatrice and Samuel A. Seaver Foundation and the Seaver Autism Center, the ASC is now a multiple-Principal Investigator grant funded by the National Institutes of Health.

In addition to identifying subsets of the 102 autism-associated genes that have disruptive de novo variants more often in people with developmental delays or those with autism, the researchers showed that autism genes impact brain development or function and that both types of disruptions can result in autism. They also found that both major classes of nerve cells—excitatory neurons, which trigger a positive and activating change in the downstream neuronal membrane upon firing, and inhibitory neurons, which trigger a negative change upon firing—can be affected in autism.



“Through our genetic analyses, we discovered that it’s not just one major class of cells implicated in autism, but rather that many disruptions in brain development and in subsequent neuronal function can lead to autism. It’s critically important that families of children with and without autism participate in genetic studies because genetic discoveries are the primary means to understanding the molecular, cellular, and systems-level underpinnings of autism,” said Dr. Buxbaum. “We now have specific, powerful tools that help us understand those underpinnings, and new drugs will be developed based on our newfound understanding of the molecular bases of autism.”

Seaver Autism Center to Accelerate DDX3X Research Through a Grant from the Chan Zuckerberg Initiative

The Chan Zuckerberg Initiative (CZI) announced \$450,000 in funding to the DDX3X Foundation, a parent-led organization working to find treatments and a cure for DDX3X syndrome. A rare disorder caused by an alteration of the *DDX3X* gene, the syndrome is linked to autism, intellectual disabilities, seizures, abnormalities of the brain, and slower

physical development. DDX3X syndrome almost always occurs in girls.

The grant is part of CZI’s Rare As One Project, an initiative aimed at supporting the work that patient communities are doing to accelerate research and drive progress in the fight against rare diseases.

The funding will be used to develop and launch collaborative research networks in partnership with the DDX3X Foundation’s chosen research and clinical partners—the Seaver Autism Center and the University of California, San Francisco.

Seaver Autism Center to Accelerate DDX3X Research Through a Grant from the Chan Zuckerberg Initiative CONTINUED

Dorothy Grice, MD, Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai, and a child and adolescent psychiatrist who works on child-onset disorders, will serve as primary clinician for this grant. Dr. Grice works with a team of psychiatrists, psychologists, neurologists, and geneticists at the Seaver Autism Center on preclinical and clinical studies of DDX3X syndrome.

“The Seaver team identified the *DDX3X* gene as a priority in 2016, as mutations in *DDX3X* are one of the most common genetic causes of autism and developmental delays in females. We have worked closely with the DDX3X Foundation to help identify families affected by this syndrome who would like to participate in our research program. We are scheduling two to three DDX3X families

each month for our ongoing clinical research program,” says Dr. Grice.

Through the grant, Dr. Grice will work closely with the DDX3X Foundation and Elliot Sherr, MD, PhD, Professor of Neurology and Pediatrics at the University of California, San Francisco.

Dr. Grice continued, “Together with the DDX3X Foundation, we are honored to have been chosen by CZI. The additional support they are providing will help us all move more rapidly to the translational stage of research so that we can find new therapeutics to improve the lives of those affected by this syndrome.”

The DDX3X Foundation is a nonprofit organization founded in 2015 by Liz Berger, a film publicist in Los Angeles, and Beth

Buccini, a high-end fashion retailer and entrepreneur from the Philadelphia area, who both have daughters afflicted with the disorder.

“We are so honored to be part of CZI’s Rare as One Network and thrilled that we have two highly regarded institutions, Mount Sinai and UCSE, as our partners. We are thankful that the Seaver Autism Center made the *DDX3X* gene a strategic priority in its mission to find a cure and treatment for the disorder. Each and every clinician and researcher has shown incredible compassion and commitment to our children and our cause. We look forward to continuing our partnership with Dr. Grice, Dr. Buxbaum, and their teams,” said Ms. Berger and Ms. Buccini in a statement.

Seaver Autism Center Director Gains Accolades



2019 Honorary Skou Professor Inauguration

Dr. Joseph D. Buxbaum, PhD, was named an INSAR Fellow, the highest honor from the International Society for Autism Research (INSAR). This title recognizes autism researchers who have made a significant international impact on the scientific understanding of autism.

Fellow status is an honor that reflects dedication to the field of autism research and recognition by peers of the substantial impact of the Fellow’s research.

Dr. Buxbaum also was appointed as a 2019-2023 Honorary Skou Professor at Aarhus University in Denmark.

This honor recognizes 50 highly esteemed researchers from around the world and emphasizes the importance of international collaboration.

This initiative hopes to introduce new perspectives to teaching, strengthen relations with leading research units abroad and establish joint research projects and funding applications.

Young Faculty From Across the Center Secure Grant Funding

We have a strong team applying for, and being awarded, grants for critical research projects. These on-going projects will provide additional clarity about idiopathic autism and related genetic disorders that will be the source of future publications and eventual treatments.

Assistant Professor, Hala Harony-Nicolas, PhD has been awarded an R21 Grant to establish a novel, RNA-based approach that will efficiently deliver neuropeptides to the brain. Dr. Harony-Nicolas has also received an R01 Grant to research circuit level understanding of fundamental brain mechanisms underlying social behavior, which is impaired in autism.

Assistant Professor, Silvia De Rubeis, PhD, received an R21 grant to support the study of sex-specific synaptic changes resulting from mutations in the DDX3X gene. Once we know how DDX3X regulates synaptic translation and how sex influences it, mechanism-based precision therapeutics can be developed.

Assistant Professor, Jennifer Foss-Feig, PhD has received an R01 Grant to support a project to develop and validate an innovative new observer report measure for autism that attempts to capture heterogeneity in core symptoms along positive and negative dimensions. This project is similar to those that have been successful in quantifying heterogeneity and facilitating key biological and therapeutic discoveries in schizophrenia.

Dr. Foss-Feig, PhD has also been awarded an Advanced Neuroimaging Research Program (ANRP) Pilot Grant for Junior Investigators. The 3T Imaging of Interactive Social Processes in Autism Spectrum Disorder study will examine a relatively under-studied brain region and looks at dynamic, proactive social behavior, which is rarely emphasized in autism research. The goal of the project is to collect initial pilot data investigating whether the hippocampus is able to effectively track dynamic changes in interpersonal relationships in the context of simulated social interactions. We hope the study will shed new light on the brain basis of social difficulties in autism and hint at novel targets for behavioral interventions.

Congratulations, Dr. Grice!



Seaver Autism Center collaborator, Dorothy Grice, MD, has been named a Distinguished Fellow of the American Academy of Child and Adolescent Psychiatry (AACAP).

The status of Distinguished Fellow is the highest membership honor that AACAP bestows and is a hallmark of excellence.

NEWLY PROMOTED FACULTY

We are pleased to promote two Seaver Fellows to faculty positions to help reinforce the success and growth of the Seaver Autism Center.



MAGDALENA JANECKA, PHD,

joined that Seaver Autism Center in 2016 as a Seaver postdoctoral fellow. After several years of diligent research, she was promoted to Assistant Professor in 2019. In her new role she will be a key contributor to projects in pharmacoepidemiology and functional genomics. These projects consist of the analysis of large, mostly population-based, data sets, using data science approaches, and will involve integration of pharmacological and genetic and epigenetic measures.



MICHAEL BREEN, PHD,

was also promoted to Assistant Professor and will use his support from the Beatrice and Samuel A. Foundation to be a key contributor to current ongoing projects at the Center, while developing novel approaches. Dr. Breen will pioneer cutting-edge genetic and functional genomic technologies and computational biology methods to identify risk factors, biomarkers and mechanisms for neurodevelopmental and neuropsychiatric disorders. The overarching goals of his studies are to improve patient stratification, outcomes and to develop the next-generation treatment approaches.

NEW FACULTY AND STAFF



BARI BRITVAN

Bari joined the Seaver Center in July as a Research Coordinator after graduating Duke University with a major in psychology. She is currently working on a study aimed to better understand the nature and symptoms of autism and Phelan-McDermid Syndrome.



MICHAEL PERUGGIA

Michael graduated from Davidson College in May and joined Dr. Hala Harony-Nicolas' lab in June as a Research Associate. The lab's work investigates oxytocin cells in the hypothalamus, their connections, and their relationship with social behavior in Phelan-McDermid Syndrome.



BRETT COLLINS

Brett joined the Seaver Center in September as a Laboratory Manager coming from The Rockefeller University. He will be managing the Center's preclinical laboratories while helping liaise research between the Autism Sequencing Consortium and the Seaver Center's drug discovery and development team.



GAYLE SCHNEIDERMAN

Gayle joined the Seaver Center in August as the Administrative Manager. She received her BA from Vanderbilt University and has been at Mount Sinai since 2013. In her previous role as the Management Analyst for the Division of Pulmonary, Critical Care, and Sleep Medicine she oversaw financial and clinical operations for the Division and Respiratory Institute sites. In her new role, Gayle will manage business operations for the Center and will work with the leadership team to achieve the goals of the Center's strategic plan.



KATE KELLER

Katherine Keller joined the Seaver Center in September as a Research Coordinator after graduating from SUNY Geneseo in May with degrees in psychology and music performance. She will be working on studies investigating biomarkers of idiopathic and rare disease populations, as well as the development of a novel measure for autism.



SOFIA STATHOPOULOS, PHD

Sofia joined the Seaver Center in September as a Postdoctoral Research Fellow. She has a background in autism epigenetics. Her work at the Center will focus on studying the molecular and cellular mechanisms of syndromes related to autism using human neuronal systems.



CHRISTINA LAYTON

Christina joined the Seaver Center in July as the Research Coordinator for studies investigating neural biomarkers of autism using visual evoked potentials as well as neurodevelopmental outcomes in congenital heart disease patients. She graduated from Northwestern University in June with a degree in Theatre on the pre-med track.



SLAYTON UNDERWOOD

Slayton joined the Seaver Center in September as a Data Analytics Manager. He has a background in Epidemiology and Biostatistics and is excited to select, configure, and implement analytics solutions used to leverage unique insights.



TESS LEVY

Tess joined the Seaver Center in October as a senior genetic counselor. Tess graduated with a Master's of Science in Genetic Counseling from McGill University in 2018 and was previously employed at Weill Cornell Medicine's Center for Neurogenetics. She will be focusing on the rare diseases studied at the Seaver Center as well as providing genetic counseling to families of children with idiopathic autism.



HANNAH WALKER

Hannah joined the Seaver Center in July as a Research Coordinator. In addition, she is working towards obtaining her Masters in Clinical Psychology from Teacher College, Columbia University. She will be working on studies involved in characterizing the natural history and symptoms of Phelan-McDermid Syndrome as well as the clinical tools that are used to assess it.

Seaver Celebration Luncheon

In 2019, we continued to recognize our Center's achievements and raise funds to push our research forward by hosting the second annual Seaver Celebration Luncheon.

The celebration was hosted on Thursday, October 31 at the Roosevelt Hotel in Manhattan.

The event brought together 150 members of the Center's families, faculty, staff and supporters to reflect on all we have accomplished together and rally to establish advances for individuals and families affected by autism. The sponsorships and donations in honor of the celebration helped us raise over \$235,000 for the Center.

A special award was presented to the President and CEO of Mount Sinai Health System, Kenneth L. Davis, MD. In 1993, when there was virtually no research happening for the disorder, Dr. Davis readily accepted the challenge to establish what is known today as the Seaver Autism Center. Thanks to the groundwork he laid as the founding director, the Seaver Autism Center continues to expand knowledge and discoveries to develop better treatments for individuals with autism and related rare genetic disorders.

The program included special remarks from the Director of the Seaver Autism Center, Joseph D. Buxbaum, PhD, member of the Beatrice and Samuel A. Seaver Foundation, Myles McGinley, and event co-chairs, Martin Lomazow, Jamie Roitman and Alison Singer.

Two videos, showcasing a day at the Seaver Autism Center from the perspective of our research participants, and past, present and future plans for the Center also premiered at the event.

A special thanks to all of our sponsors and donors, event co-chairs, and our Associates Board and Host Committee who helped contribute to the success of the event.

Please consider making a gift to help us enhance the diagnosis, discover biological causes, and develop and disseminate breakthrough treatments from autism.



Beatrice and Samuel A. Seaver Foundation Trustees, John Cohen and Hirschell Levine present award to honoree, Kenneth L. Davis, MD.



Attendees enjoying the video premier



Dr. Buxbaum thanking attendees for support



Luncheon co-chair and Seaver Autism Center Associates Board Member Martin Lomazow and his family

PLEASE VISIT: giving.mountsinai.org/SeaverCelebration



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- SEAVER IS CONTINUING TO GO GREEN! Please send your email address to seavercentereditor@mssm.edu to receive this newsletter electronically.

COVID-19: Autism and Social Distancing

The Seaver Autism Center for Research and Treatment is wishing you and your families health and safety during this stressful time. We recognize the intense challenge it can be to keep children, adolescents and adults with developmental disabilities at home without their typical routines, social outlets, and professional supports.

For these reasons, our team has compiled resources, including approaches to talk to kids about coronavirus, social stories, behavior management strategies and visual and sensory supports.

To learn more, please visit our Autism and COVID-19 resources webpage: bit.ly/SeaverAutismCOVID19

Follow our social channels for updates and information about our free webinar series that aims to help families affected by autism during this difficult time.