SFARI

Spring 2022 Investigator Meeting

Monday - Wednesday, April 11-13

Invitation Only

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Kelsey C. Martin, M.D., Ph.D.
Director,
Simons Foundation Autism Research Initiative
Simons Foundation Neuroscience Collaborations

Dear Investigators,

The SFARI Spring 2022 Investigator Meeting is scheduled for April 11th through the 13th at the Simons Foundation in New York City. I am delighted that you can attend and, as the new SFARI Director, very much look forward to meeting all of you and learning more about your science.

The annual Investigator meeting provides a unique opportunity to bring the SFARI community together to share recent discoveries and advances in autism research and to engage in lively and open discussions. We have organized the meeting to ensure time for individual presentations and for interactive group discussions and encourage your active participation throughout the meeting. We consider that collaborative and interdisciplinary studies, sharing of resources, inclusion of a diversity of perspectives and opinions, and rapid dissemination of discoveries through preprint servers and publications are all critical to achieving our shared mission of advancing the understanding, diagnosis and treatment of autism spectrum disorders. I hope that you will use this meeting to establish new scientific collaborations and to hear about new tools, resources and scientific advances that may enhance your studies.

This year, we hope to continue the momentum from past meetings by sharing unpublished, and sometimes provocative, data, as well as new hypotheses that stimulate each of us to test and thereby advance the fields of brain and autism research. We will consider the event a success if you depart feeling intellectually rejuvenated, with an increased commitment to address the major scientific challenges that must be overcome to better understand brain function and to develop treatments for autism and related neurodevelopmental disorders.

I thank you in advance for sharing your data and contributing your scientific expertise, time and effort to these endeavors. All of us on the SFARI science team will also appreciate your feedback after the meeting. We want to make future meetings as stimulating and useful for you as possible and will welcome your recommendations for changes or improvements after the meeting. You will receive a questionnaire shortly after the meeting that you can use to provide these comments.

Very best regards, Kelsey Martin

VENUE & ACCOMMODATIONS

The James New York – NoMad

22 East 29th Street, New York, NY 10016

Phone: +1 (212) 532-4100

Website: www.jameshotels.com/new-york-nomad

Special Events & Meals

Breakfast, Monday, Tuesday & Wednesday

For all guests, these meals will be held on the 2nd floor promenade at 160 Fifth Avenue and 162 Fifth Avenue.

Lunch

Lunches will be held on the 2nd floor promenade at 160 Fifth Avenue and 162 Fifth Avenue.

Cocktail Reception, Monday

A cocktail reception will be held on Monday from 4:45 PM to 6:15 PM on the 2nd floor promenade at 160 Fifth Avenue.

Monday Dinner

Dinner on Monday will be held from 6:15 PM to 8:00 PM at BLACKBARN Restaurant, which is located at 19 East 26th Street, New York, NY, 10010.

Cocktail Reception, Tuesday

A cocktail reception will be held on Tuesday from 5:30 PM to 7:00 PM on the 2nd floor promenade at 160 Fifth Avenue.

Tuesday Dinner

Dinner on Tuesday will be held from 7:00 PM to 8:45 PM at KYMA, which is located at 15 West 18th Street, New York, NY, 10011.

The James New York – NoMad

WiFi in the guest room is complimentary. WiFi can be accessed with your last name and room number.

Checkout is at 12:00 PM. You will be automatically checked out and a final bill for incidental charges will be sent to the email address you gave at check in.

Transportation. Scheduled transportation will depart from 160 Fifth Avenue following the conclusion of the meeting. Staff will be available on the second floor of 160 Fifth Avenue on Wednesday morning for any questions regarding your travel arrangements.

Contact information For airline questions call Ovation Travel Group at: (917) 408-1555.

For meeting & ground transportation questions call Kanupriya Parasher at (646) 876-5998 or email kparasher@simonsfoundation.org.

Simons Foundation Auditorium at 160 Fifth Avenue and 162 Fifth Avenue

WiFi Internet connection is available on the second floor. You should be automatically connected to the network. If not, the network is: **SimonsGuests** and the password is: **simonsnyc**.

Auditorium A microphone and AC power connection are located at each seat. No food or beverages of any kind is permitted inside the auditorium.

Agenda

Monday, April 11

8:00 – 9:00 am — Breakfast

9:00 – 9:10 am — Welcome and introduction
David Spergel, Ph.D. (Simons Foundation)
Kelsey C. Martin, M.D., Ph.D. (SFARI)

Session 1 **Genetic causes of autism and related neurodevelopmental disorders**

Live from Ingrid Daubechies Auditorium, 162 Fifth Avenue
Streaming from Gerald D. Fischbach Auditorium, 160 Fifth Avenue

9:10 – 9:25 am — Session introduction
Alan Packer, Ph.D. (SFARI)

9:25 – 9:50 am — **Michael Talkowski, Ph.D.** (Massachusetts General Hospital; Broad Institute of MIT and Harvard)
Insights into the allelic architecture of autism spectrum disorder from rare coding variation

9:50 – 10:15 am — **Yufeng Shen, Ph.D.** (Columbia University)
Integrating de novo *and inherited variants in over 42,607 autism cases identifies new risk genes with moderate effect*

10:15 – 10:40 am — **Kavitha Sarma, Ph.D.** (The Wistar Institute)
Elucidating the consequence of R-loop accumulation in autism spectrum disorders

10:40 – 11:10 am — Coffee break

11:10 – 11:35 am — **Elise Robinson, Sc.D.** (Harvard T.H. Chan School of Public Health)
Statistical and functional convergence of common and rare variant risk for neuropsychiatric disease at chromosomes 16p and 22q

11:35 – 12:00 pm — **Beate St Pourcain, Ph.D.** (Max Planck Institute for Psycholinguistics)
Polygenic pleiotropy within ASD and ADHD genetic architectures: Shared risk alleles with discordant polygenic effects

12:00 – 12:30 pm — Panel discussion
Moderator: **Daniel Geschwind, M.D., Ph.D.** (University of California, Los Angeles)

12:30 – 2:00 pm — Lunch and Bridge to Independence fellows networking lunch

Session 2 **Homeostatic plasticity and sleep in neurodevelopmental disorders**

Live from Gerald D. Fischbach Auditorium, 160 Fifth Avenue
Streaming from Ingrid Daubechies Auditorium, 162 Fifth Avenue

2:00 pm	Session introduction **Brigitta Gundersen, Ph.D.** (SFARI)
2:15 – 2:40 pm	**Graeme Davis, Ph.D.** (University of California, San Francisco) *Homeostatic plasticity: A biochemical mechanism of brain resilience relevant to the etiology and treatment of neurodevelopmental and neurological disorders*
2:40 – 3:05 pm	**Graham Diering, Ph.D.** (University of North Carolina at Chapel Hill) *Developmental sleep disruption as a risk factor in autism spectrum disorder*
3:05 – 3:35 pm	Coffee break
3:35 – 4:00 pm	**Shinjae Chung, Ph.D.** (University of Pennsylvania) *Neural mechanisms underlying sleep disturbances in autism spectrum disorder*
4:00 – 4:30 pm	Panel discussion Moderator: **Kevin Bender, Ph.D.** (University of California, San Francisco)
4:30 – 4:45 pm	Closing remarks
4:45 – 5:15 pm	Cocktail reception and clinical and cognitive science social **2nd floor promenade at 160 Fifth Avenue**
5:15 – 5:45 pm	Introduction and highlights from 2021 Human Cognitive and Behavioral Science RFA awardees **Gerald D. Fischbach Auditorium, 160 Fifth Avenue**
5:45 – 6:15 pm	Cocktail reception and clinical and cognitive science social **2nd floor promenade at 160 Fifth Avenue**
6:15 – 8:00 pm	Dinner **Black Barn**

Tuesday, April 12

8:00 – 9:00 am Breakfast

Session 3 **Gene expression, cells and behavior**

Live from Ingrid Daubechies Auditorium, 162 Fifth Avenue
Streaming from Gerald D. Fischbach Auditorium, 160 Fifth Avenue

9:00 – 9:15 am Session introduction
Julia Sommer, Ph.D. (SFARI)

9:15 – 9:40 am **John Rubenstein, M.D., Ph.D.** (University of California, San Francisco)
Sequential functions of ASD risk gene Tbr1 in mouse cortical cell fate specification and synapse formation: Phenotypic rescue by augmenting WNT signaling

9:40 – 10:05 am **Beatriz Rico, Ph.D.** (Kings College London)
Synapse-specific regulation of protein synthesis for cortical wiring

10:05 – 10:35 am Coffee break

10:35 – 11:00 am **Renata Batista-Brito, Ph.D.** (Albert Einstein College of Medicine)
Mef2c-mediated developmental dysfunction of parvalbumin-expressing interneurons

11:00 – 11:25 am **Hirofumi Morishita, M.D., Ph.D.** (Icahn School of Medicine at Mount Sinai)
Role of autism risk genes in frontal-thalamic projections underlying social processing in mice

11:25 am – 12:00 pm Panel discussion
Moderator: **Mriganka Sur, Ph.D.** (Massachusetts Institute of Technology)

12:00 – 1:20 pm Lunch and genomics of ASD networking lunch

Session 4 **Human research studies**

Live from Gerald D. Fischbach Auditorium, 160 Fifth Avenue
Streaming from Ingrid Daubechies Auditorium, 162 Fifth Avenue

1:20 – 1:35 pm Session introduction
Paul Wang, M.D. (Clinical Research Associates)

1:35 – 2:00 pm **Amina Abubakar, Ph.D.** (The Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Programme and Aga Khan University)
Challenges and opportunities in carrying out research on neurodevelopmental disorders in Sub-Saharan Africa: Lessons from the Neurodev Study

2:00 – 2:25 pm	**Gaspar Taroncher-Oldenburg, Ph.D.** (Simons Foundation) *Microbiome and other multi-scale associations along the gut-brain axis in autism*
2:25 – 2:50 pm	**Rachel Kelly, Ph.D.** (Harvard Medical School) *Integrative metabolomic endotyping of autism spectrum disorders*
2:50 – 3:10 pm	Coffee break
3:10 – 3:35 pm	**John Murray, Ph.D.** (Yale University) *Mapping brain-behavior relationships in autism*
3:35 – 4:05 pm	Panel discussion Moderator: **TBD**
4:05 – 4:30 pm	Coffee break
4:30 – 5:30 pm	Keynote panel **What's next in ASD research: Perspectives from ASD parent-scientists** Live from Gerald D. Fischbach Auditorium, 160 Fifth Avenue Streaming from Ingrid Daubechies Auditorium, 162 Fifth Ave. Panelists: **Ted Abel, Ph.D.** (University of Iowa) **Michael Boland, Ph.D.** (Columbia University) **Pamela Feliciano, Ph.D.** (SPARK) **Soo-Kyung Lee, Ph.D.** (University at Buffalo) Moderator: **Alice Luo Clayton, Ph.D.** (SFARI)
5:30 – 5:35 pm	Closing remarks
5:35 – 7:00 pm	Cocktail reception with demo and poster session **2nd floor promenade at 160 Fifth Avenue**
7:00 – 8:45 pm	Dinner **KYMA**

Wednesday, April 13

8:00 – 9:00 am	Breakfast

Session 5 **Emerging therapeutic opportunities**

Live from Ingrid Daubechies Auditorium, 162 Fifth Avenue
Streaming from Gerald D. Fischbach Auditorium, 160 Fifth Avenue

9:00 – 9:15 am	Session introduction **John Spiro, Ph.D.** (SFARI)

Agenda

9:15 – 9:40 am	**Arkady Khoutorsky, D.V.M., Ph.D.** (McGill University) *The integrated stress response pathway controls autism-related features in a cell-type-specific manner*
9:40 – 10:05 am	**Allison Bradbury, Ph.D.** (Nationwide Children's Hospital; The Ohio State University) *Optimization and validation of gene therapy using patient specific* in vitro *and* in vivo *models of SLC6A1 related autism disorder*
10:05 – 10:35 am	Coffee break
10:35 – 11:00 am	**Christopher Ahern, Ph.D.** (University of Iowa) *Molecular spell-checking with tRNA to correct stop codon-opathies*
11:00 – 11:25 am	**Richard Huganir, Ph.D.** (Johns Hopkins University) *Regulation of synaptic plasticity by SynGAP*
11:25 – 11:55 am	Panel discussion Moderator: **Joseph Gleeson, M.D.** (University of California, San Diego)
11:55 am – 12:00 pm	Closing remarks **Kelsey C. Martin, M.D., Ph.D.** (SFARI)
12:00 – 1:00 pm	Lunch and departures

Speakers

Genetic causes of autism and related neurodevelopmental disorders

As sample sizes for autism cohorts continue to grow, investigators are identifying an ever-larger number of rare mutations associated with the condition and are conducting well-powered genome-wide association studies to identify relevant common variants. In this session, Michael Talkowski, Yufeng Shen, Kavitha Sarma, Elise Robinson and Beate St Pourcain will provide updates on the genetic and functional contributions of rare mutations to autism. They will also offer intriguing new insights into the nature of polygenic risk in autism and related neurodevelopmental disorders and how rare and common variation might interact across the genome. Their talks will be followed by a panel discussion, during which we anticipate a broader discussion of the genetic underpinnings of autism, how the field can make continued progress toward understanding the totality of genetic susceptibility and how it influences the range and severity of autism-associated phenotypes. The panel discussion will be moderated by Daniel Geschwind.

Michael Talkowski, Ph.D.
Massachusetts General Hospital; Broad Institute of MIT and Harvard

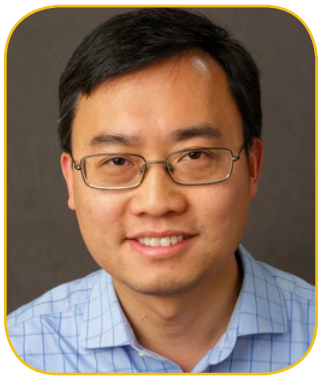
Insights into the allelic architecture of autism spectrum disorder from rare coding variation

Individuals with autism spectrum disorder (ASD) or related neurodevelopmental disorders (NDDs) often carry disruptive mutations in genes that are depleted of functional variation in the broader population. Here, Michael Talkowski and colleagues build upon this observation and exome sequencing from 154,842 individuals to explore the allelic diversity of rare protein-coding variation contributing risk for ASD and related NDDs.

Using an integrative statistical model, Talkowski and collaborators jointly analyzed rare protein-truncating variants (PTVs), damaging missense variants and copy number variants (CNVs) derived from exome sequencing of 63,237 individuals from ASD cohorts, including SPARK and the Simons Simplex Collection (SSC). They discovered 72 genes associated with ASD at a false discovery rate (FDR) ≤ 0.001, a threshold approximately equivalent to exome-wide significance, and 185 genes at FDR ≤ 0.05. Associations were predominantly driven by *de novo* PTVs, damaging missense variants and CNVs, which represented 57.5 percent, 21.1 percent and 8.44 percent of evidence, respectively. Though fewer in number, CNVs conferred greater relative risk than PTVs, and repeat-mediated *de novo* CNVs exhibited strong maternal bias in parent-of-origin (e.g., 95.5 percent of 16p11.2 CNVs), whereas all other CNVs showed a paternal bias. The team further performed CNV discovery in 200,000 exomes from the UK Biobank and used these population-based control data to quantify ASD risk for each of 79 curated genomic disorder loci.

To explore how genes associated with ASD and NDD overlap or differ, Talkowski and his colleagues then analyzed an ASD cohort alongside a developmental delay (DD) cohort from the Deciphering Developmental Disorders study (DDD, n=91,605 samples). The DDD dataset was first reanalyzed using the same models as the ASD cohorts. Joint analyses of both cohorts were then performed, and 373 genes contributing to NDD risk were identified at FDR ≤ 0.001, 54 of which were unique to the joint analyses and not significant in either cohort alone.

These results confirm overlap of most ASD and DD risk genes, although many differ significantly in frequency of mutation. Analyses of single-cell transcriptome datasets showed that genes associated predominantly with DD were strongly enriched for earlier neurodevelopmental cell types, whereas genes displaying stronger evidence for association in ASD cohorts were more enriched for maturing neurons. The ASD risk genes were also enriched for genes associated with schizophrenia from a rare coding variant analysis of 121,570 individuals, emphasizing that these disorders share common pathways to risk.



Yufeng Shen, Ph.D.
Columbia University

Integrating *de novo* and inherited variants in over 42,607 autism cases identifies new risk genes with moderate effect

Despite the known heritable nature of autism spectrum disorder (ASD), studies have primarily identified risk genes with *de novo* variants. To capture the full spectrum of ASD genetic risk, Yufeng Shen and collaborators performed a two-stage analysis of rare *de novo* and inherited coding variants in 42,607 ASD cases, including 35,130 new cases recruited online by SPARK (Zhou *et al., medRxiv,* 2021).

In the first stage, the researchers analyzed 19,843 cases with one or both biological parents and found that known ASD or neurodevelopmental disorder (NDD) risk genes explain nearly 70 percent of the genetic burden conferred by *de novo* variants. In contrast, less than 20 percent of genetic risk conferred by rare inherited loss-of-function (LoF) variants are explained by known ASD/NDD genes.

In the second part of the study, the team selected 404 genes based on the first stage of analysis and performed a meta-analysis with an additional 22,764 cases and 236,000 population controls. 60 genes were identified with exome-wide significance ($p < 2.5e-6$), including five new risk genes (*NAV3*, *ITSN1*, *MARK2*, *SCAF1* and *HNRNPUL2*). The association of *NAV3* with ASD risk is primarily driven by rare inherited LoF variants, with an average relative risk of 4, consistent with moderate effect. ASD individuals with LoF variants in the four moderate risk genes (*NAV3*, *ITSN1*, *SCAF1* and *HNRNPUL2*, $n = 95$) have less cognitive challenges compared to 129 ASD individuals with LoF variants in well-established, highly penetrant ASD risk genes (*CHD8*, *SCN2A*, *ADNP*, *FOXP1*, *SHANK3*) (59 percent versus 88 percent, $p = 1.9e-06$). These findings will guide future gene discovery efforts and suggest that much larger numbers of ASD cases and controls are needed to identify additional genes that confer moderate risk of ASD through rare, inherited variants.

Kavitha Sarma, Ph.D.
The Wistar Institute

Elucidating the consequence of R-loop accumulation in autism spectrum disorders

Numerous proteins function in regulating the cellular levels of R-loops, the three-stranded nucleic acid structures that accumulate on chromatin in neurological diseases and cancers and that contribute to genome instability. Using a proximity-dependent labeling system, Kavitha Sarma and her colleagues uncovered the R-loop proteome and unexpectedly discovered an enrichment of homeodomain-containing proteins (Yan *et al., Nat. Commun.*, 2022).

Sarma's team is currently focused on studying *ADNP*, a frequently mutated gene in autism spectrum disorder and one of the most consistently enriched proteins in R-loops. They have recently found that *ADNP* contains R-loop resolution activity *in vitro* that is dependent on its homeodomain. *In vivo*, *ADNP* suppresses R-loops exclusively at its own binding sites. Notably, deletion of the homeodomain, a common occurrence in individuals with *ADNP* syndrome, results in R-loop accumulation at *ADNP* sites and compromises neuronal differentiation. These findings point to a potential new role for homeodomain proteins in R-loop regulation and have important implications for numerous developmental disorders and cancers.

Elise Robinson, Sc.D.
Harvard T.H. Chan School of Public Health

Statistical and functional convergence of common and rare variant risk for neuropsychiatric disease at chromosomes 16p and 22q

Elise Robinson will present results from a series of recent collaborative projects. Using a novel statistical framework applied in an unbiased scan of the genome, Robinson and colleagues identified the 33 Mb p-arm of chromosome 16 (16p) as harboring the greatest excess of common polygenic risk for autism spectrum disorder (ASD). This region includes the recurrent 16p11.2 copy number variant (CNV) — one of the largest single genetic risk factors for ASD and whose pathogenic mechanisms are undefined.

Leveraging RNA-sequencing data from postmortem human brain samples, Robinson and colleagues observed that common polygenic risk for ASD within 16p was associated with decreased average expression of genes in the region. Similarly, using isogenic neuronal cell lines with CRISPR/Cas9-mediated deletion of 16p11.2, they observed that the deletion was associated with decreased average gene expression across 16p. The rare and common variant expression effects were correlated at the level of individual genes. Finally, they observed chromatin contact patterns which they hypothesize explain this transcriptional convergence: elevated contact diffusely within 16p and between 16p11.2 and a distal region on 16p (Mb 0–5.2), which showed the greatest gene expression changes in both the common and rare variant analyses.16p shares its chromatin contact elevation with another region of the genome: the q-arm of chromosome 22 (22q). Consistent with the hypothesis that chromatin contact — or something with which chromatin contact is correlated — is driving the observed 16p effects, 22q manifests similar transcription-level convergence of common and rare variant risk for schizophrenia.

The results demonstrate that elevated 3D chromatin contact may facilitate coordinated genetic and transcriptional disease liability within very large regions of the genome. As applied to ASD and schizophrenia, these analyses highlight the p-arm of chromosome 16 and q-arm of chromosome 22, in full, as important regions of liability for behaviorally defined disorders, ones that can now be studied to understand the mechanisms through which this risk is conferred.

Beate St Pourcain, Ph.D.
Max Planck Institute for Psycholinguistics

Polygenic pleiotropy within ASD and ADHD genetic architectures: Shared risk alleles with discordant polygenic effects

Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) are complex co-occurring neurodevelopmental conditions. Their genetic architectures show striking similarities and are genetically linked but also reveal notable differences, such as strong, discordant polygenic associations with educational attainment (EA).

To better understand the genetic mechanisms that can manifest in such complex association patterns, Beate St Pourcain and colleagues studied the genetic relationships between EA, ASD and ADHD using a multivariable regression (MVR) framework (Verhoef *et al., Nat. Commun.,* 2021). This multivariate analysis technique, adopted from a causal modelling approach, utilizes genome-wide summary statistics, as published for EA, ASD and ADHD by large consortia (N=10,610–766,345). Aggregate polygenic association effects of ASD and ADHD risk with EA were estimated by combining genetic effects across individual risk-related marker alleles, studying sets of single nucleotide polymorphisms (SNPs) selected for association with either ASD or ADHD risk at different thresholds. This association-based approach benefits from controlling for both the genomic position and the direction of the genetic effect at a single variant.

St Pourcain and colleagues showed that EA-related genetic variation is shared across ASD and ADHD architectures, involving identical marker alleles. However, the polygenic association profile with EA, across shared marker alleles, is discordant for ASD versus ADHD risk, indicating independent effects (positive for ASD, negative for ADHD). Findings remained robust when studying SNPs with the same risk increasing allele for both disorders (approximately 80 percent of the original variant sets) and were replicated in a set of independent summary statistics. At the single-variant level, these results suggest either biological pleiotropy or co-localization of different risk variants, implicating microRNA mechanisms. At the polygenic level, they point to a polygenic form of pleiotropy that contributes to the detectable genome-wide correlation between ASD and ADHD and is consistent with effect cancellation across EA-related genomic regions.

Daniel Geschwind, M.D.

University of California, Los Angeles

Panel Moderator

Daniel Geschwind is the Gordon and Virginia MacDonald Distinguished Professor of Neurology, Psychiatry and Human Genetics at the University of California, Los Angeles (UCLA) School of Medicine and the Senior Associate Dean and Associate Vice Chancellor of Precision Medicine in the UCLA Health System and David Geffen School of Medicine. He obtained an A.B. in chemistry and psychology (modified) at Dartmouth College and his M.D.-Ph.D. (neurobiology) at Yale School of Medicine (AOA) prior to completing his internship, residency (neurology) and postdoctoral fellowship at UCLA. He joined the faculty in 1997, founding the neurogenetics program within the department of neurology.

His laboratory has focused primarily on developing a mechanistic understanding of autism and neurodegenerative diseases. The laboratory combines genetic, genomic and bioinformatic approaches with basic neurobiological investigation in model systems and the human brain. These approaches rely heavily on computational and bioinformatic methods in addition to wet laboratory experimentation.

Geschwind has trained over 70 graduate students and postdoctoral research fellows. He is a strong advocate for data sharing, having developed several resources housing genetic and phenotypic data for a number of neurological and neurodevelopmental conditions, including the Autism Genetic Resource Exchange (AGRE) with the Cure Autism Now (CAN) foundation. He has served on several advisory boards, including the National Institutes of Health Council of Councils, the National Institute of Mental Health Council and the Allen Institute. He is also co-chair of the Genetics and Genomics section of the Faculty of 1000 and serves on the editorial boards of *Cell, Neuron, Science* and *Current Opinion in Genetics & Development*. He is an elected member of the National Academy of Medicine and the American Academy of Physicians.

Homeostatic plasticity and sleep in neurodevelopmental disorders

Disruption in sleep is one of the most common clinical features reported in autism spectrum disorder (ASD) and/or related genetic neurodevelopmental disorders (NDD), affecting 40–80 percent of people with ASD (Carmassi *et al., Front. Psychiatry*, 2019; Missig *et al., Neuropsychopharmacology*, 2020). However, it is unclear whether sleep function is a secondary feature of ASD and NDD or whether in fact disruptions in sleep are causal for, or interact with, other aspects of these disorders such as cognition and epilepsy. Studies in experimental systems such as mice may be able to disentangle the causal relationship between sleep and ASD.

Numerous studies have shown that various forms of plasticity occur during sleep. In particular, the synaptic homeostasis hypothesis (SHY) holds that during sleep, synaptic activity is renormalized, after the strengthening that occurs during waking periods, through a process of downscaling (Tononi and Cirelli, *Neuron*, 2014). If sleep is disrupted in ASD and NDD, such homeostatic plasticity processes could be affected as well. Indeed, disruptions of homeostatic plasticity have been described in rodent models with deletions in ASD risk genes (Tatavarty *et al., Neuron*, 2020; Genç *et al., Elife*, 2020).

In this session, Graeme Davis, Graham Diering and Shinjae Chung will present their work on homeostatic plasticity and sleep in animal models for ASD. Their talks will be followed by a panel discussion in which participants will discuss connections amongst their studies as well as the broader implications of this work for understanding ASD. The panel discussion will be moderated by Kevin Bender.

Graeme Davis, Ph.D.
University of California, San Francisco

Homeostatic plasticity: A biochemical mechanism of brain resilience relevant to the etiology and treatment of neurodevelopmental and neurological disorders

Homeostatic plasticity (HP) encompasses a suite of adaptive physiological mechanisms with the power to suppress disease-related perturbations that disrupt neural function, a biochemical basis of brain resilience. HP has garnered particular attention as an adaptive physiological process that might be relevant to the phenotypic penetrance of mutations that confer risk for autism spectrum disorder (ASD). Defining how HP can buffer the adverse effects of altered neural development, injury, age-related cognitive decline and disease without undermining the normal capacity for learning-related (Hebbian) plasticity remains one of the most intriguing and medically relevant topics in neuroscience. Yet we still do not have a complete description of the homeostatic mechanisms that operate within the mammalian brain. Presynaptic homeostatic plasticity (PHP) is an evolutionarily conserved form of HP, classically documented in the peripheral nervous systems of *Drosophila*, mice and humans.

Recently, the laboratory of Graeme Davis demonstrated that PHP is induced in a setting of neurological disease in mice and is neuroprotective, leading to the term homeostatic neuroprotection (Orr *et al., Neuron*, 2020). In parallel, a genome-scale screen in *Drosophila* identified common genetic links between the mechanisms of PHP and mutations that confer risk for ASD and intellectual challenges (Genç *et al., Elife*, 2020).

The Davis laboratory has now translated these fundamental genetic discoveries and placed them within the neural circuitry of the mammalian brain. These new data are among the first to define the phenomenon and molecular mechanisms of PHP in the mammalian brain. Fundamental mechanisms that are necessary for the induction and expression of PHP in the mammalian brain will be presented. Furthermore, data underscoring the relevance of PHP to mouse models of ASD and intellectual challenges will also be presented, translating fundamental genetic discoveries from *Drosophila* to the maintenance and regulation of excitatory and inhibitory synaptic transmission in the mammalian central nervous system. Davis and colleagues propose that new therapeutics designed to promote PHP could be broadly relevant for neurological and neurodevelopmental conditions.

Graham Diering, Ph.D.
University of North Carolina at Chapel Hill

Developmental sleep disruption as a risk factor in autism spectrum disorder

Sleep disruption is a common comorbidity in autism spectrum disorder (ASD), with more than 80 percent of individuals with ASD affected by it. However, it is not known how sleep disruption, particularly during periods of brain development, contributes to altered brain function and behavior in ASD.

Graham Diering and colleagues have undertaken experiments in mice to establish a causal role for early life sleep disruption (ELSD) in lasting ASD relevant phenotypes and to begin to understand the molecular basis for vulnerability to developmental sleep disruption. *Shank3* is a high-confidence ASD risk gene and heterozygous mutation in *Shank3* is known to cause Phelan-McDermid syndrome, a severe neurodevelopmental condition associated with ASD, intellectual challenges and sleep disruption.

Diering's laboratory examined the effects of ELSD in developing mice bearing *Shank3* C-terminal truncation (deltaC). They found that ELSD interacts with genetic vulnerability in the clinically relevant *Shank3*+/deltaC heterozygotes to drive lasting and sex-specific changes in behavior (Lord *et al., bioRxiv*, 2021). Results from these studies showed that sleep disruption during sensitive periods of postnatal development is causative of lasting changes in behavior in genetically vulnerable individuals, but in a striking sex-specific manner.

To explore the basis for vulnerability to developmental sleep loss, Diering's team examined the behavioral and molecular responses to acute sleep deprivation (SD) in developing and adult wildtype mice. They found that developing mice completely lack the behavioral and transcriptomic response to SD seen in adults. Moreover, using quantitative proteomics, they found that SD has a distinct and profound impact on the developing forebrain synapse proteome. Collectively, these results indicate that developing mice are uniquely vulnerable to the negative effects of sleep disruption and highlight developmental sleep loss as a possible risk factor for ASD.

Shinjae Chung, Ph.D.
University of Pennsylvania

Neural mechanisms underlying sleep disturbances in autism spectrum disorder

Many children with autism spectrum disorder (ASD) suffer from sleep disturbances such as difficulties in falling asleep, staying asleep or waking up early. Sleep disturbances are associated with other ASD core features such as challenges in social skills, hyperactivity and stereotypic behaviors, indicating that sleep problems and the core symptoms of autism may be related. Understanding circuit mechanisms underlying sleep disorders in children with ASD will help to elucidate its etiology.

Using a *Syngap1* mutant mouse model of ASD, Shinjae Chung and her team are examining changes in the activity of sleep neurons in the preoptic area of the hypothalamus and locus coeruleus noradrenergic neurons that underlie sleep disturbances. Recent findings reveal that activating locus coeruleus noradrenergic neurons disrupted the sleep quality and their interactions with hypothalamic sleep neurons orchestrate the sleep microarchitecture. The approach taken by Chung's lab is unique as it involves the use of cutting-edge techniques that enable an unprecedented level of genetic, anatomical and temporal precision to uncover changes in neural circuit mechanisms that causally underlie sleep disturbances in ASD.

Kevin Bender, Ph.D.
University of California, San Francisco

Panel Moderator

Kevin Bender is an associate professor in the Department of Neurology at the University of California, San Francisco (UCSF). His laboratory is interested in understanding how neurons encode information, with a particular focus on cellular mechanisms that mediate and modulate neuronal excitability. They employ a variety of electrophysiological, optical, computational and genetic techniques to probe information processing across neuronal compartments, and test how these processes are altered in neurological disorders, including autism spectrum disorder (ASD).

In collaboration with Stephan Sanders' lab at UCSF, the Bender lab has worked to understand how genetic mutations in *SCN2A* give rise to a range of neurodevelopmental disorders, including seizures of varying severity, developmental delay and ASD. More recently, his laboratory has explored how haploinsufficiency, or the loss of one functional copy, of *Scn2a* affects cellular and network activity in mouse models. Currently, the Bender lab is working with Nadav Ahituv's lab to determine if and when haploinsufficiency in *Scn2a* can be restored to rescue normal neuronal function using CRISPR-activation-based approaches.

Gene expression, cells and behavior

A central goal in autism research is to decipher how rare genetic variants can give rise to the behavioral phenotypes in individuals diagnosed with ASD. Most would agree that the answer lies somewhere along the complex path of neural development and may involve changes in the gene expression and cellular biology of neurons as well as changes in the activity of neurons and the circuits that they are part of. In this session, John Rubenstein, Beatriz Rico and Renata Batista-Brito will speak about their work on different ASD risk genes and their roles in aspects of cortical development. John Rubinstein will speak about the impact of the loss of *TBR1* on gene expression, cell fate of pyramidal neurons and development of synapses in deep layers of the developing mouse neocortex. Beatriz Rico will speak about the role of *TSC2* in the formation of excitatory synapses onto PV+ inhibitory interneurons, through the regulation of translation. Renata Batista-Brito will focus on how the loss of another ASD risk gene, *MEF2C*, affects the maturation and integration of PV+ interneurons into cortical circuits and ultimately results in changes in sensory perception. Lastly, Hirofumi Morishita will present his work on assessing how the loss of different ASD risk genes in mice (*Fmr1*, *Pten* and *Tsc2*) may affect the projections of layer 5/6 projection neurons of the medial prefrontal cortex (mPFC) to the limbic thalamus, a circuit preferentially recruited by social interactions. The talks will be followed by a panel discussion moderated by Mriganka Sur.

John Rubenstein, M.D., Ph.D.
University of California, San Francisco

Sequential functions of ASD risk gene *Tbr1* in mouse cortical cell fate specification and synapse formation: Phenotypic rescue by augmenting WNT signaling

Mutations in the *TBR1* transcription factor gene augment autism spectrum disorder (ASD) risk. Using a conditional mouse model of *Tbr1* deletion, John Rubenstein and colleagues found that *Tbr1* has sequential functions in specifying and maintaining layer 6 pyramidal cortical cell fate, forming connections between the cortex and the thalamus, and dendritic spine maturation followed by formation of excitatory and inhibitory synapses in the neonatal cortex (Darbandi *et al., Neuron,* 2018). Defects in most of these processes are observed in *Tbr1* homozygotes and heterozygotes. In a subset of layer 5 pyramidal neurons in the prefrontal cortex, *Tbr1* also promotes synapse development.

Rubenstein's team has also shown that *Tbr1* promotes expression of a WNT-signaling ligand (Wnt7b). Synaptic defects can be rescued by augmenting WNT-signaling through GSK3A inhibition or with LiCl (Darbandi *et al., Cell Rep.,* 2020). Adult homozygous mutants continue to have reduced cortical synapses and reduced synaptic function — both can be rescued with a single dose of LiCl. A single dose of LiCl rescues spine maturation and synapse formation within 24 hours; the rescue lasts for over two months. Such findings suggest that WNT-signaling agonists may be beneficial for individuals with ASD caused by mutations in *Tbr1*.

Beatriz Rico, Ph.D.
King's College London

Synapse-specific regulation of protein synthesis for cortical wiring

Tuberous sclerosis complex (TSC) is a genetic condition caused by inactivating mutations in *TSC1* or *TSC2* genes, with variable penetrance and severity. The brain is among the most affected organs in individuals with TSC, and the neurological manifestations are often the most devastating, particularly in children carrying mutations in *TSC2*. The proteins encoded by *TSC1* and *TSC2* cooperate to inhibit mTORC1, a protein complex critical for protein synthesis. Consistently, genes encoding proteins involved in regulating translation at the synapse are frequently mutated in autism spectrum disorder (ASD), which has led to the suggestion that altered protein synthesis is a core pathophysiological mechanism of ASD and intellectual challenges. The identification of molecules regulated by local translation, which are crucial for the development of specific neural circuits affected in ASD, remains a major challenge in the field.

Findings from the laboratories of Beatriz Rico and Oscar Marín indicate that synaptic Tsc2 is specifically regulated by the tyrosine kinase receptor ErbB4 in parvalbumin-expressing (PV+) cortical interneurons during the period of synaptogenesis in the mouse (Bernard *et al., bioRxiv*, 2021). These observations suggest that Tsc2 is normally inhibited by ErbB4 signaling during the formation of excitatory synapses onto PV+ interneurons, which implies that the regulation of local translation is important in this process.

Rico and Marín's teams tested this hypothesis and demonstrated that Tsc2 and local translation is important for the formation of excitatory synapses onto cortical PV+ interneurons. Then, by using a RiboTRAP strategy, they identified a set of synaptic proteins regulated by ErbB4. Interestingly, some of these proteins that are dependent on ErbB4-Tsc2 translation are also risk factors for ASD. The synapse-specific molecular program unveiled in this study reinforces the idea that this connection is a sensitive hub for maladaptive network responses in neurodevelopmental disorders.

Renata Batista-Brito, Ph.D.
Albert Einstein College of Medicine

Mef2c-mediated developmental dysfunction of parvalbumin-expressing interneurons

Central to understanding the role of inhibitory neurons in cortical network function is understanding their contributions through a neurodevelopmental lens. To address this, Renata Batista-Brito's laboratory disrupted the expression of a critical regulator of neuronal maturation in interneuron precursors. Myocyte enhancer factor-2C (Mef2c) is a transcription factor linked to neurodevelopmental disorders that regulates the expression of genes involved in the differentiation, migration, survival and synaptic function of excitatory neurons, yet little is known about its role in inhibitory neurons.

Among the three major subtypes of cortical inhibitory interneurons, neurons expressing the calcium-binding protein parvalbumin (PV-INs) are highly enriched for Mef2c expression. Embryonic removal of Mef2c in PV-IN precursors leads to signatures of impaired maturation in PV-INs. To understand how PV-IN maturation and integration into cortical circuits are affected by loss of Mef2c, Batista-Brito and her colleagues performed awake extracellular electrophysiology recordings within the primary visual cortex of developing (shortly after eye opening) and adult mice while monitoring behavioral state. They observed that mutant mice showed altered temporal patterns of network activity. In particular, during periods of quiescence, there was increased power between 30–70 Hz. Mutant mice had increased synchronous activity that arose soon after eye opening and worsened in adulthood, and had altered visual responses, including increased noise correlations. To understand the global effects of impaired PV-IN development, the researchers also performed behavioral phenotyping.

Together, findings from these studies show that early removal of Mef2c impacts the development of PV-INs, leading to changes in circuit function and behavior. These studies serve as a foundation for examining the contribution of PV-INs toward early signatures of altered state-dependent network activity and sensory processing.

Hirofumi Morishita, M.D., Ph.D.
Icahn School of Medicine at Mount Sinai

Role of autism risk genes in frontal-thalamic projections underlying social processing in mice

Challenges in social processing are associated with autism spectrum disorder (ASD), yet little is known about the link between mutations in ASD risk genes and neural circuits underlying social processing. Recent genetic and transcriptomic studies have shown that many ASD risk genes are enriched in fetal and infant prefrontal cortical (PFC) layer (L) 5/6 projection neurons.

Hirofumi Morishita's team recently identified the limbic thalamus as the most prominent projection target of medial PFC L5/6 neurons that is preferentially recruited by social interaction (Yamamuro *et al., Nat. Neurosci.,* 2020). His SFARI Pilot Award project aims to examine the impact of different ASD risk genes on medial PFC L5/6 projection neurons to the limbic thalamic pathway and social behavior.

In his talk, Morishita will describe new findings from his ongoing studies using mouse models harboring mutations in multiple ASD risk genes (*Fmr1*, *Pten* and *Tsc2*). Identification of specific PFC circuits that modulate social behavior and whose functions are affected by mutations in ASD risk genes will point toward potential targets that allow circuit-based amelioration of social processing challenges in ASD.

Mriganka Sur, Ph.D.

Massachusetts Institute of Technology

Panel Moderator

Mriganka Sur is a professor of neuroscience and the director of the Simons Center for the Social Brain at the Massachusetts Institute of Technology.

The Sur laboratory studies the development, plasticity and dynamics of cerebral cortical circuits. Using state-of-the-art techniques, the laboratory aims to uncover fundamental mechanisms of brain wiring and processing during development and in adulthood and to understand how such processes go awry in disorders of brain development such as autism and Rett syndrome.

Human research studies

In this session, Amina Abubakar, Rachel Kelly, Gaspar Taroncher-Oldenburg and John Murray will focus on human research studies, with levels of investigation ranging from molecular to microbial to behavioral. Abubakar will describe an ambitious ongoing project to collect deep phenotypic and genotype data from people with ASD in Africa, which provides an important opportunity to expand autism science beyond its historical focus on American and European participants. Kelly will present the first large-scale metabolomic study of biospecimens from the Simons Simplex Collection (SSC) and examine the relationship of metabo-endotypes to clinical and genetic profiles. Taroncher-Oldenberg will present the results of a meta-analysis, using a Bayesian algorithm, of the microbiome in autism and its relationship to metabolomic and other -omic datasets (Morton *et al., bioRxiv*, 2022). Murray will present the results of a novel computational modeling approach that relates brain imaging data to behavioral data in autism spectrum disorder. Their talks will be followed by a moderated panel discussion.

Amina Abubakar, Ph.D.
The Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Programme and Aga Khan University

Challenges and opportunities in carrying out research on neurodevelopmental disorders in Sub-Saharan Africa: Lessons from the Neurodev Study

Little is known of the burden, risk factors and impact of neurodevelopmental disorders (NDDs) among children, families and communities in the African context. Various factors such as a lack of widely accessible standardized diagnostic tools, shortage of expertise, ethical dilemmas and shortage of funding, among others, have been a barrier to a robust research culture around NDDs in sub-Saharan Africa (Bakare *et al., Healthc. Low Resour. Settings,* 2014; Abubakar *et al., Lancet Psychiatry,* 2016).

Amina Abubakar and her colleagues recently set-up a successful collaborative study entitled "The NeuroDev Study: Phenotypic and genetic characterization of neurodevelopmental disorders in Kenya and South Africa" (de Menil *et al., Neuron,* 2019). NeuroDev is a study of the genetics of NDDs, with an emphasis on autism spectrum disorder, intellectual challenges and attention deficit hyperactivity disorder. The study is a collaboration between centres in South Africa, Kenya and the United States. Abubakar and colleagues intend to deeply phenotype and collect genotypic data from approximately 4,800 participants. The study has been running from 2018 to the present.

Based on field experiences and preliminary data, Abubakar will present some of the key lessons learned about carrying out human research studies in sub-Saharan Africa on NDDs.

Gaspar Taroncher-Oldenburg, Ph.D.
Simons Foundation

Microbiome and other multi-scale associations along the gut-brain axis in autism

The gut-brain axis (GBA) facilitates bidirectional communication between the gut and the brain, contributing to brain homeostasis and helping regulate cognitive and emotional functions. Dysregulation of the gut microbiome and the ensuing disruption of the GBA have been implicated in autism and other neurodevelopmental conditions, but the underlying mechanisms and the extent to which the microbiome drives these dynamics are still unknown. Dozens of cross-sectional microbiome and other omic studies have identified autism-specific signatures along the GBA, albeit with little agreement in composition or magnitude.

In collaboration with researchers at the Flatiron Institute, Gaspar Taroncher-Oldenburg has now conducted a comprehensive analysis of existing cross-sectional microbiome and other omic studies to determine a roadmap for advancing our understanding of the role the microbiome plays in autism. To address common pitfalls of previous meta-analyses, such as flawed differential abundance determinations due to the use of absolute feature abundances not supported by the compositional nature of most omic datasets, as well as an information reduction due to traditional cohort averaging approaches, Taroncher-Oldenburg and his collaborators developed an age- and sex-matched Bayesian differential ranking algorithm to estimate the distributions of autism-specific signatures across 11 cross-sectional microbiome datasets and 17 other omic datasets, including dietary patterns, metabolomics, cytokine profiles and human brain expression.

The analysis revealed highly significant multi-scale autism-specific signatures along the GBA. Re-analysis of a longitudinal interventional autism study was consistent with the cross-sectional results and suggested an association between microbiome composition and autism features. The results highlight the complexity of the interplay among multiple omic levels in autism, the shortcomings of existing datasets for addressing questions of causality, as well as provide a framework for advancing our understanding of the role the microbiome plays in autism.

Rachel Kelly, Ph.D.
Harvard Medical School; Brigham and Women's Hospital

Integrative metabolomic endotyping of autism spectrum disorders

Autism spectrum disorder (ASD) is a lifelong complex and heterogenous neurodevelopmental condition, with both genetic and environmental drivers. Rachel Kelly and Jessica Ann Lasky-Su's current study is leveraging a novel approach to link genotype to phenotype while taking the environmental component into account. Metabolomics — the global profiling of all the small modules in a biological system — is the downstream 'ome' closest to phenotype reflecting genetics, environmental influences and the interactions between them.

By classifying ASD cases into subgroups on the basis of their metabolome (metabo-endotypes), one can look at the overall genetic architecture of these subgroups to learn more about their distinct biological mechanisms, as well as their resulting clinical and phenotypic characteristics. Metabolomic profiling was performed at Metabolon Inc. using four ultra-performance liquid chromatography–mass spectrometry platforms on plasma samples from 2,321 probands from the Simons Simplex Collection; samples were split 70:30 into a discovery and replication dataset. Proband similarity networks were built in the discovery population based on the metabolomic data constructed from nodes (ASD cases) connected by edges (metabolomic similarity between two cases) and spectral clustering (an unsupervised machine-learning method) was applied to the networks to identify metabolomic-driven ASD endotypes.

In this talk, Kelly will discuss the findings of these analyses in terms of clinical and epidemiological differences between individuals in the different metabo-endotypes, the most influential metabolites driving the formation of these metabo-endotypes and the role of upstream genetic and environmental factors in metabo-endotypes membership. Crucially, they will demonstrate the validity of these findings by recapitulating the metabo-endotypes in the replication population. The identification of metabo-endotypes has the benefit of improving the understanding of etiology and molecular mechanisms underlying ASD, which can support novel management strategies targeted to specific subgroups.

John Murray, Ph.D.
Yale University

Mapping brain-behavior relationships in autism

A major challenge in psychiatric neuroimaging is to understand individual variation of neural and behavioral features within a diagnostic category, in contrast to a traditional focus on group-level differences between affected and unaffected individuals. Autism spectrum disorder (ASD) is characterized by prominent heterogeneity of phenotypes across individuals, yet how that variation is grounded in neurobiology is poorly understood.

In this talk, John Murray will discuss multiple computational approaches to mapping brain-behavior relationships using neuroimaging with application to ASD, including multivariate statistical approaches and biophysically grounded models of brain dynamics. A key neural feature of interest is the topographic organization of signals across cortex, which can be related to hierarchical function and linked to large-scale gradients of microcircuit specialization reflected in gene expression mapping. A critical issue in brain-behavior mapping is the stability of findings when faced with high-dimensional feature spaces, which affects many studies. Finally, Murray will discuss implications for these investigations for the future of large multi-site neuroimaging consortium projects to better map brain-behavior relationships in ASD.

What's next in ASD research: Perspectives from ASD parent-scientists

In previous SFARI Investigator Meetings, SFARI has hosted speakers that have direct insight into the human condition of autism. This panel will highlight four researchers in the autism research community who are also parents of individuals with autism. We will discuss their perspective of autism, autism research and autism treatments with important questions such as:

- What should the research community know about autism?
- What should the ultimate goals of research be?
- How can basic research goals be balanced with the needs of the autism community today?
- What would meaningful treatments look like to you?

Ted Abel, Ph.D.

University of Iowa

Panel Speaker

Ted Abel is the director of the Iowa Neuroscience Institute, Roy J. Carver Chair in Neuroscience, and chair of the Department of Neuroscience and Pharmacology at the University of Iowa. He is a member of the National Academy of Medicine and a fellow of the American Association for the Advancement of Science. His research focuses on the molecular mechanisms of memory storage and the molecular basis of neurodevelopmental and psychiatric disorders. He has been a pioneer in the use of molecular and genetic approaches to define how neural circuits mediate behavior. Until 2017, Abel was the Brush Family Professor of Biology at the University of Pennsylvania where he was co-director of the Biological Basis of Behavior Program and directed a National Institute of Mental Health (NIMH)-funded predoctoral training program in behavioral and cognitive neuroscience.

A week after the birth of their son, Seamus, Abel and his wife, Noreen, found themselves in the neonatal intensive care unit at Children's Hospital of Philadelphia. Brain imaging revealed low-grade ventricular bleeding and, at age three, Seamus was diagnosed with autism spectrum disorder. He did not see a typical classroom until the fourth grade. Although Seamus, now 22, is now a sophomore at the University of Iowa where he is studying German, he still encounters daily challenges. The experience as a parent of a individual on the autism spectrum led Abel to expand his research focus to examine the molecular basis of neurodevelopmental conditions. He is actively involved in a number of advisory boards to help set priorities for autism research, and he is currently a member of the National Advisory Mental Health Council. Abel is the founding co-director of the National Institute of Child Health and Development (NICHD)-funded Hawkeye Intellectual and Developmental Disabilities Research Center, launched in 2021 at the University of Iowa, which focuses on the diagnosis, prevention, and treatment of intellectual and developmental disabilities.

Michael Boland, Ph.D.
Columbia University

Panel Speaker

Michael Boland is an assistant professor in the Institute for Genomic Medicine and Department of Neurology at Columbia University. His group studies the etiology of monogenic neurodevelopmental diseases (NDDs) with an emphasis on pediatric epileptic encephalopathy, autism spectrum disorder and cortical malformations of development. Because no single model system accurately reflects human neurological disease, Boland takes a cross-species approach to disease modeling that combines genetic mouse models and monolayer (2D) and organoid (3D) models from human pluripotent stem cells. He and his team have developed patient-specific pluripotent stem cell models of fragile X syndrome, and organoid models of cortical malformations of development attributed to *MAP1B* and *FLNA* mutations, as well as studied NDDs that result from mutations in *GRIN2A*, *KCNT1*, *GNB1* and *HNRNPU*, and disorders of glycosylation/deglycosylation (*PMM2*, *DPAGT1*, *NGLY1*, *SLC35A2* and *ALG13*).

In 2018, Boland's newborn son exhibited seizure-like activity the day after birth. This prompted a barrage of clinical tests that ruled out brain malformations, viral infections and metabolic disorders. A targeted epilepsy panel identified a genetic cause for his seizures – a frameshift in *STXBP1*. He and colleagues quickly pivoted research priories to develop a cross-species modeling paradigm that includes a genetic mouse model and human induced pluripotent stem cell (iPSC)-derived cortical organoid models of *STXBP1* haploinsufficiency. Their integrated, multi-modal approach utilizes whole cell patch-clamp electrophysiology, calcium imaging and multielectrode arrays to study cell-type-specific functional effects of *STXBP1* haploinsufficiency, and single-cell transcriptomics and systems biology approaches to identify disrupted pathways responsible for, or contributing to, aberrant phenotypes. Together, they use these models as screening tools to identify and test drugs/small molecules and genetic therapies for their ability to correct disease relevant phenotypes.

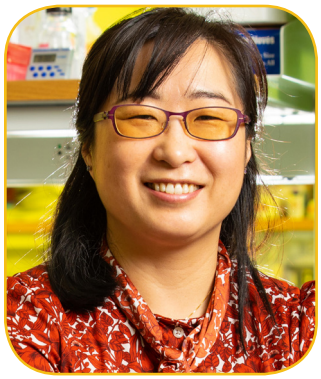
Pamela Feliciano, Ph.D.

Simons Foundation Autism Research Initiative (SFARI)

Panel Speaker

As scientific director of SPARK, Pamela Feliciano helps lead the effort to build the largest autism research cohort in the United States, which has enrolled over 100,000 individuals with autism spectrum disorder to date. Feliciano works with a consortium of researchers that are analyzing genomic data from tens of thousands of SPARK participants. Feliciano also manages a unique aspect of SPARK—returning genetic results related to autism to individual participants.

Feliciano is also a senior scientist at SFARI, the largest private funder of autism research in the United States. At SFARI, she has been involved in efforts to fund the development of objective outcome measures for autism clinical trials. Prior to joining SFARI, Feliciano was a senior editor at *Nature Genetics*, where she was responsible for managing the peer review and decision process of research publications in all areas of genetics. Feliciano has a B.S. from Cornell University and a Ph.D. from Stanford University. Feliciano is also the mother of a teenager with autism.



Soo-Kyung Lee, Ph.D.
University at Buffalo

Panel Speaker

Soo-Kyung Lee has been studying the role of transcriptional regulators in the central nervous system (CNS). Her primary goals are, first, to dissect gene regulatory events that generate cellular diversity and functional circuit formation in the CNS. Second, she wants to apply this knowledge to understand the genetic and mechanistic basis of neurodevelopmental conditions. Lastly, through her study, she wants to provide insights into developing therapies to treat neurodevelopmental disorders.

Over the past two decades, studies in Lee's laboratory have identified transcription factor codes and chromatin regulatory factors that direct neuronal fate specification in the CNS. Her lab's findings have significantly contributed to understanding gene regulatory networks in CNS development. For the first time, there is a mammalian chromatin modifier complex containing histone H3-lysine 4- methyltransferases, *Kmt2c* and *Kmt2d*, and histone H3-lysine 27-demethylase *Kdm6a*. Lee has pioneered biochemical and molecular approaches in mouse and chick embryos to unravel the fundamental principles controlling gene expression in the CNS. This led to a series of seminal discoveries into the gene regulatory network required for neuronal fate specification, including the role of the LIM complexes, micro RNAs and epigenetic regulators in motor neuron generation.

Intriguingly, but not surprisingly, many of the factors Lee studies are implicated in human neurodevelopmental conditions, including autism spectrum disorder (ASD). One of these examples is *FOXG1* syndrome, which results from the mutations in the *FOXG1* gene. The location and type of variants in the *FOXG1* gene produce a spectrum of symptoms from severe developmental challenges to relatively milder cases with behaviors associated with ASD. Her lab is establishing animal models covering the range of *FOXG1* syndrome symptoms and exploring the therapeutic options for *FOXG1* syndrome.

Alice Luo Clayton, Ph.D.

Simons Foundation Autism Research Initiative (SFARI)

Panel Moderator

Alice Luo Clayton joined the Simons Foundation in 2011. Her role involves managing programs related to neural circuits and behavior in animal models and human cohorts. She contributes to the development and availability of rodent models of autism, as well as overseeing preclinical projects. In addition, she developed and manages SFARI's early career grant program, the Bridge to Independence Awards.

Luo Clayton earned her Ph.D. in systems neuroscience at the University of Pennsylvania, in the laboratory of Gary Aston-Jones, and did postdoctoral work at the National Institute on Drug Abuse Intramural Research Program, with Roy Wise and Carl Lupica. Luo Clayton is broadly interested in brain connectivity and how information processing within neural networks translates into behavior. Her postdoctoral research focused on the ventral tegmental area (VTA), a major source of midbrain dopamine neurons, which modulates reward-associated behaviors and has been implicated in a number of psychiatric disorders, including drug addiction and schizophrenia; she identified and characterized afferent VTA circuits using primarily electrophysiological and neuroanatomical techniques.

Luo Clayton was a 2009–2011 AAAS Science and Technology Policy Fellow in the Division of Developmental Translational Research at the National Institute of Mental Health. The division focuses on understanding the mechanisms and developmental trajectories of child- and adolescent-onset psychiatric disorders, including autism, attention deficit hyperactivity disorder and mood and anxiety disorders. Her experience there involved managing grant portfolios, conducting workshops and site visits, organizing scientific review panels and developing research initiatives.

Emerging therapeutic opportunities

In this session, Arkady Khoutorsky, Allison Bradbury, Christopher Ahern and Richard Huganir will present work highlighting several different approaches taken to develop therapies for severe neurodevelopmental disorders.

Khoutorsky will discuss work describing how dysregulation of the integrated stress response (ISR), which is the main intracellular signaling pathway controlling general protein synthesis, could underlie fragile X syndrome and other neurodevelopmental disorders, and how a better understanding of this pathway suggests therapeutic targets.

Bradbury will present results using gene replacement strategies with adeno-associated viruses to treat the loss of one copy of the *Slc6a1* gene (which encodes the GABA transporter GAT-1) in mice; in humans, loss of *SLC6A1* results in epileptic encephalopathy, intellectual challenges and autism spectrum disorder.

Ahern will discuss a strategy that uses laboratory edited transfer RNA (tRNA) to repair premature termination codons — an approach that may be applicable to many neuronal genes; here, he will highlight work in repairing the sodium channel *SCN2A* in patient iPS cells and mouse models.

Huganir will present how a detailed understanding of SynGAP — an abundant synaptic GTPase-activating protein (GAP) that is critical for synaptic plasticity, learning, memory and cognition — informs therapeutic strategies for treatment (using antisense oligonucleotides to alter splicing) of *SYNGAP1*-related neurodevelopmental disorders.

Talks will be followed by a panel discussion moderated by Joseph Gleeson.

Arkady Khoutorsky, D.V.M., Ph.D.
McGill University

The integrated stress response pathway controls autism-related features in a cell-type-specific manner

Dysregulation of protein synthesis is thought to underlie autism phenotypes in fragile X syndrome (FXS) and several other neurodevelopmental disorders. Increased general protein synthesis in FXS has been reported in animal models and humans; however, the role of the main signaling pathway controlling general protein synthesis, the integrated stress response (ISR), in mediating features linked to autism is unclear.

The ISR is a highly conserved cellular mechanism that suppresses general protein synthesis during stress via phosphorylation of the α-subunit of eukaryotic translation initiation factor 2 (p-eIF2α). Conversely, a decrease in p-eIF2α stimulates general protein synthesis. The *Fmr1* knockout (KO) mouse model recapitulates many phenotypes observed in individuals with FXS, including challenges in social interaction and repetitive behaviors. *Fmr1* KO mice also display increased global mRNA translation, which is thought to contribute to the pathophysiology observed in this mouse model.

Arkady Khoutorsky's lab is examining the hypothesis that dysregulation of the ISR pathway contributes to the increased general translation and altered behavioral phenotypes in *Fmr1* KO mice. They are also studying cell-type-specific changes in the activity of the ISR and investigating the crosstalk between the mTORC1 and the ISR in the regulation of mRNA translation and autism-related features.

Allison Bradbury, Ph.D.
Nationwide Children's Hospital; The Ohio State University

Optimization and validation of gene therapy using patient specific *in vitro* and *in vivo* models of *SLC6A1* related autism disorder

SLC6A1 encodes the GABA transporter, GAT-1, which is responsible for the reuptake of the inhibitory neurotransmitter GABA from the synapse. A mutation in one copy of the *SLC6A1* gene results in epileptic encephalopathy, intellectual challenges and autism spectrum disorder. The genetic variants result in loss-of-function, which makes gene replacement strategies a viable therapeutic approach. Efficient cellular targeting of disease-relevant cell types is critical for the success of this gene therapy.

As a GABA transporter, *SLC6A1* is primarily expressed in the brain, specifically in inhibitory, GABAergic neurons and astrocytes. Adeno-associated virus serotype 9 (AAV9) has a natural neuronal and astrocytic tropism; however, expression level and cell-type-specific transduction can be further regulated by using different promoters to drive transgene expression. Allison Bradbury and colleagues aimed to assess whether increased expression of *SLC6A1* would have toxic effects in mice. They also wanted to quantify expression levels in various tissues and assess cell-specific transduction of various promoters.

To do this, they first performed intracerebroventricular (ICV) injections of five different AAV constructs expressing wildtype *Slc6a1* in neonatal wildtype mice. Wildtype mice treated with AAV-*Slc6a1* targeting neurons and astrocytes had the highest expression in the brain and spinal cord. Subsequently, neonatal S295L, generated to model an *Slc6a1* patient mutation, were treated by ICV injection with each of the five AAV constructs. To date, the mice have been followed for more than six months. S295L mice treated with the AAV9 construct targeting both neurons and astrocytes have outperformed the other cohorts and uninjected animals on behavioral tests including cage hanging and elevated plus maze. In addition, this cohort of treated animals showed normalized weight gain and the treatment has corrected the clasping defect which is very pronounced in untreated S295L mice. Dose ranging studies with the lead construct will now be completed and mice will be evaluated by additional clinically-relevant readouts, including seizure monitoring and electrophysiological testing.

Christopher Ahern, Ph.D.
University of Iowa

Molecular spell-checking with tRNA to correct stop codon-opathies

The *SCN2A* gene encodes the alpha subunit of the neuronal voltage-gated sodium channel $Na_V1.2$ that regulates the balance of excitatory activity in the human brain. Spontaneous and inherited changes in the coding sequence of the *SCN2A* gene are associated with autism spectrum disorder (ASD) and intellectual challenges. *SCN2A* was one of the earliest genes associated with ASD and up to half of individuals with *SCN2A* syndrome are also diagnosed with autism. DNA changes in the *SCN2A* gene can put in the wrong type of amino acid, resulting in a non- or mis-functioning sodium channel protein, or they can put in a 'stop' signal that introduces an abnormal premature termination codon (PTC) within the channel's reading frame, much like a misplaced period or truncated word within a sentence. For a complex sodium channel protein, making less than the entire protein (due to the 'stop' signal) has essentially the same functional consequence as making no protein at all, resulting in widespread and aberrant excitatory brain activity. Similarly, such inherited or (more often) spontaneous PTCs in as many as 400 other neuronal genes (including *CDLK5*, *FOXG1*, *SCN1A* and *SYNGAP1*) can result in individually rare neuronal disorders with a common genetic cause of the PTC.

The labs of Christopher Ahern and Aislinn Williams are developing a strategy that utilizes a laboratory-edited transfer RNA (tRNA) to repair PTCs in neuronal ion channels. This method corrects the PTC during peptide synthesis, efficiently encodes the correct amino acid and spares native stop codons. The application of this approach to correct PTCs in patient-derived induced pluripotent stem cells and mouse models of *SCN2A* channelopathies will be discussed.

Richard L. Huganir, Ph.D.
Johns Hopkins University

Regulation of synaptic plasticity by SynGAP

SynGAP is an abundant synaptic GTPase-activating protein (GAP) that is critical for synaptic plasticity, learning, memory and cognition. Deleterious mutations in *SYNGAP1* in humans result in intellectual challenges, autism-related behaviors and epilepsy. Heterozygous *Syngap1* knockout mice display deficits in synaptic plasticity, learning and memory and exhibit seizures. SynGAP negatively regulates small G-protein signaling at excitatory synapses but also forms liquid condensates with the major synaptic scaffolding protein PSD-95 (Zeng *et al., Cell,* 2016), suggesting it may dynamically regulate synapse structure. Interestingly, alternative splicing of SynGAP regulates its ability to form liquid condensates with PSD-95.

To examine whether SynGAP imparts unique structural properties to synapses independent from its GAP activity, Richard Huganir's lab has examined the ability of various splice isoforms and GAP domain mutations to regulate synaptic structure and plasticity (Araki *et al., eLife,* 2020). Their data reveal a structural role for SynGAP in synaptic plasticity that is independent of its GAP activity and thus informs therapeutic strategies for the treatment of *SYNGAP1*-related neurodevelopmental disorders.

Joseph Gleeson, M.D.

University of California, San Diego

Panel Moderator

Joseph Gleeson graduated from the University of Chicago Pritzker School of Medicine with honors, then trained in pediatrics and neurology, with a chief residency year at Boston Children's Hospital and Harvard Medical School. He performed postdoctoral research training at Harvard Medical School and was a faculty member at University of California, San Diego (UCSD) and an attending physician at Rady Children's Hospital San Diego. From 2014 to 2015, he was the Leon Hess Professor and head of the Laboratory for Pediatric Brain Disease at the Rockefeller University and director of Mendelian sequencing at the New York Genome Center. He relocated to San Diego in 2015 with the Rady Children's Hospital Auxiliary Endowed Professorship of Neuroscience at UCSD and directorship of neuroscience research at the Rady Children's Institute for Genomic Medicine.

Gleeson has directed research that has led to the identification of over 50 genetic causes of pediatric brain disease, including those involved in lissencephaly syndrome, Joubert syndrome and autism. He is a Howard Hughes Medical Institute Investigator and an elected member of the National Academy of Medicine.

Demo & Poster Sessions

Ivan Iossifov, Ph.D.
Cold Spring Harbor Laboratory

GPF: An open-source platform for genotype and phenotype data managing and analysis

The Genotypes and Phenotypes in Families (GPF) tool was developed by SFARI Investigator Ivan Iossifov and his collaborators. In this demo, Iossifov will demonstrate the open source GPF system that has been deployed to manage the large genotypic and phenotypic data sets supported by SFARI. These include data from the Simons Simplex Collection, SPARK and Simons Searchlight, and comprise phenotypic data from more than 50,000 individuals with autism and unaffected family members, and genotypic data from 50,000 whole-exomes and 15,000 whole-genomes.

Monkol Lek, Ph.D.
Yale University

SFARI genomics browser

The SFARI genomics web portal uses the successful gnomAD framework and codebase to represent the summary variant data from exomes and genomes from the Simons Simplex Collection (SSC) and SPARK cohorts. The gene page includes allele counts (total and affected), Variant Effect Predictor (VEP) annotation and gnomAD allele frequency of each variant discovered in the SPARK/SSC data sets. The variant page includes the allele counts of variant across the cohort data sets, population ancestry and sex along with VEP annotation and pathogenicity predictions. Users can assess the quality of the variant by visualizing representative read data evidence from heterozygous and homozygous calls along with depth, genotype quality and allele balance metrics. In addition, *de novo* variants that were discovered are represented on the gene and variant pages. Lastly, the familiar features and navigation in common with the gnomAD browser makes this resource easy to use.

Poster Session

Tuesday evening

1. Hiroki Asari, Ph.D.
   European Molecular Biology Laboratory
   Role of the cortical feedback on the neuronal representation of contextual visual information in the superior colliculus of an autistic mouse model

2. Kristina Denisova, Ph.D.
   City University of New York
   Sensorimotor signatures in infancy are dissociable in ASD-positive toddlers with and without genetic risk for autism

3. Kirsten A. Donald, MBChB, Ph.D.
   University of Cape Town
   Validity of the SNAP-IV for ADHD assessment in South African children with neurodevelopmental disorders

4. Evan Elliott, Ph.D.
   Bar Ilan University
   Autism-associated gene CHD8 regulates gut epithelial cell function and affects autism-related behaviors through the gut-brain axis

5. Jennifer Foss-Feig, Ph.D.
   Icahn School of Medicine at Mount Sinai
   Neurocomputational mechanisms of impaired social decision-making in autism spectrum disorder

6. Alfred R. George Jr., M.D.
   Northwestern University
   High-throughput functional evaluation of ASD-associated missense SCN2A variants

7. Jay Gibson, Ph.D.
   University of Texas Southwestern Medical Center
   Cell-type-specific functional studies of FOXP1 in striatal development and circuitry

8. Paul Jenkins, Ph.D.
   University of Michigan
   Physical and functional convergence of the autism risk genes Scn2a and Ank2 in neocortical pyramidal cell dendrites

9. Sung Eun (Samuel) Kwon, Ph.D.
   University of Michigan
   The role of SynGAP1 in inhibitory cortical circuit

10. Eirene Markenscoff-Papadimitriou, Ph.D.
    University of California, San Francisco
    Interrogating the neurodevelopmental functions of POGZ

11. Pierre Mattar, Ph.D.
    Ottawa Hospital Research Institute
    Genetic and systems analysis of NuRD and ChAHP chromatin remodelling complexes in neocortical development

12. Jacob Michaelson, Ph.D.
    University of Iowa
    Digital phenotyping in 1,800 SPARK participants to identify genetic factors in language ability

13. Jonathan Mill, Ph.D.
    University of Exeter
    Developmental trajectories of DNA methylation across human brain development

14. Marino Pagan, Ph.D.
    Princeton University
    High-throughput characterization of cognitive flexibility in rat models of autism

15. Stefano Panzeri, Ph.D.
    Istituto Italiano di Tecnologia
    Model-based analysis tools to infer neural changes in ASD from the EEG

16. Anna-Sophie Rommel, Ph.D.
    Icahn School of Medicine at Mount Sinai
    The impact of prenatal COVID-19 vaccination on delivery and neonatal outcomes: Results from an ongoing cohort study investigating the effects of SARS-CoV-2 infection, inflammation and COVID-19 vaccination

17. Tychele Turner, Ph.D.
    Washington University in St. Louis
    Germline mosaicism of a missense variant in KCNC2 in a multiplex family with autism and epilepsy characterized by long-read sequencing

18. Dmitry Velmeshev, Ph.D.
    Duke University School of Medicine
    Analysis of convergent cell type-specific gene expression changes in dup15q syndrome and idiopathic autism

19. Jason Wester, Ph.D.
    The Ohio State University
    The development of excitatory and inhibitory neocortical circuits in a mouse model of Arid1b haploinsufficiency

20. Zhuzhu Zhang, Ph.D.
    Salk Institute for Biological Studies
    Single-cell studies of epigenomic regulations in brain circuitry and disorders

SFARI Resources

SFARI Resources

Simons Simplex Collection

The Simons Simplex Collection (SSC) contains genetic and phenotypic data from nearly 3,000 families with a child affected by autism.

Simons Searchlight

Simons Searchlight is studying individuals with recurrent genetic variants associated with autism and related neurodevelopmental conditions.

SPARK

SPARK is an online research initiative that aims to recruit 50,000 individuals with autism and their family members living in the U.S.

Autism Inpatient Collection

Autism Inpatient Collection (AIC) is a study designed to produce a collection of phenotypic and genetic data from children with a clinical diagnosis of autism who have been admitted to one of six specialized inpatient child psychiatry units in the United States.

Autism BrainNet

Autism BrainNet is a collaborative network of academic sites that collects, stores and distributes brain tissue for autism research.

Therapeutics

Clinical Research Associates (CRA) is evaluating new potential treatments for autism, including R-baclofen.

SFARI Base

SFARI Base provides approved researchers with access to data and biospecimens from the SSC, Simons Searchlight, SPARK and Autism Inpatient Collection. Autism BrainNet postmortem brain tissue can now be requested through SFARI Base.

SFARI Gene

SFARI Gene is an evolving database for the autism research community that is centered on genes implicated in autism susceptibility.

Data analysis tools

Visualization and analysis tools are available to explore genetic and phenotypic data from the SSC, Simons Searchlight and SPARK, including the Genotypes and Phenotypes in Families tool.

Mouse models

Mouse models to study autism spectrum disorders are available from The Jackson Laboratory.

Rat models

Rat models to study autism spectrum disorders are available from the Medical College of Wisconsin. These models are being maintained in the outbred Long-Evans background strain and being behaviorally phenotyped through a partnership with the Simons Initiative for the Developing Brain.

Zebrafish models

SFARI is now curating zebrafish lines with mutations in zebrafish paralogs of several autism risk genes in which gene loss-of-function is validated by directly measuring mRNA or protein levels (where antibodies are available) rather than by assessing phenotype.

iPS cell models

Human induced pluripotent stem cells (iPSCs) created from individuals who participated in the Simons Simplex Collection (SSC) and Simons Searchlight are available for distribution to approved researchers.

Other Initiatives

Spectrum

Spectrum is an editorially independent publication funded by SFARI.

SFARI Funding Opportunities

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2022 Human Cognitive and Behavioral Science — Request for Applications

Grants awarded through this RFA are intended to produce foundational knowledge about the neurobehavioral differences associated with ASD. Many of these projects are expected to inform or relate to the development or refinement of tools needed for translational efforts, such as biomarkers and outcome measures. Special emphasis is placed on objective, quantitative measures that may be used in conjunction with standardized clinical measures and genomic information to better triangulate phenotypic and neurobiological variability within and across individuals with ASD.

Two tracks are offered within this RFA solicitation: Explorer and Expansion. The Explorer track is appropriate for early-stage projects where establishing feasibility and proof-of-concept are the most relevant outcomes of the grant period. The total budget is $500,000 or less, inclusive of 20 percent indirect costs, over a period of up to two (2) years. The Expansion track is appropriate for more mature projects with evidence of feasibility and preliminary validity, for which goals such as scalability, generalizability and/or ecological validity are now the most relevant translational outcomes. The total budget is $900,000 or less, inclusive of 20 percent indirect costs, over a period of up to three (3) years.

Application deadline: April 25, 2022

Genomics of ASD and Targeted Molecular Therapies — Request for Applications

Similar to the 2021 Genomics of ASD: Pathways to Genetic Therapies RFA, SFARI is planning to launch an RFA broadly covering the areas of autism genetics (including inherited genetic risk as well as mitochondrial genetics), integrative analysis of multi-omic autism data sets, functional analysis of autism associated genetic variants, and development of genetic therapies. We intend for this RFA to also cover projects that propose to make use of SFARI's induced pluripotent stem cell (iPSC) resource at a large scale — in particular, projects seeking to generate multi-omic data sets from the iPSC resource that are suited to provide insight into the developmental, cellular and molecular origins of autism.

RFA opens: Late spring 2022
Application deadline: Summer 2022

SFARI Supplement to Enhance Equity and Diversity (SEED) — Request for Applications

Funds awarded through this program are intended to provide supplements to existing grants for the recruitment of new lab members from American underrepresented minority groups at the postdoctoral level. For the purposes of this supplement, eligible groups include the following: African American/Black; Latin American/Hispanic; Native American/Alaskan Native; Native Hawaiian/other Pacific Islander (including Filipino).

The goal of this award is to increase diversity and fight inequity. SFARI Principal Investigators are encouraged to recruit candidates for this supplement not only at their home institution, but also at historically Black colleges and universities and other institutions with high minority enrollment.

The budget is up to $100,000 per year for up to three years.

SPARK Research Match Diversity, Equity and Inclusivity – Request for Applications

The Diversity, Equity and Inclusivity request for applications from SPARK Research Match aims to address historic disparities in research participation by Black or African American individuals by soliciting studies on autism that recruit Black or African American participants. Funding will provide per-person participant incentive (e-gift cards) for participation in projects that utilize SPARK Research Match to recruit participants into new research studies.

The maximum budget is $20,000 in per-person incentive funding per study.

Next quarterly application deadline: June 30, 2022

For more information about SFARI's 2022 RFAs, please read our blog post "Updates to SFARI's 2022 requests for grant applications."

SFARI-Funded Publications

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Publications and preprints generated with SFARI support can be found here. The list includes papers from SFARI-funded investigators as well as from researchers who used genetic/phenotypic data or biospecimens from the Simons Simplex Collection, Simons Searchlight, SPARK, the Autism Inpatient Collection or Autism BrainNet.

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE