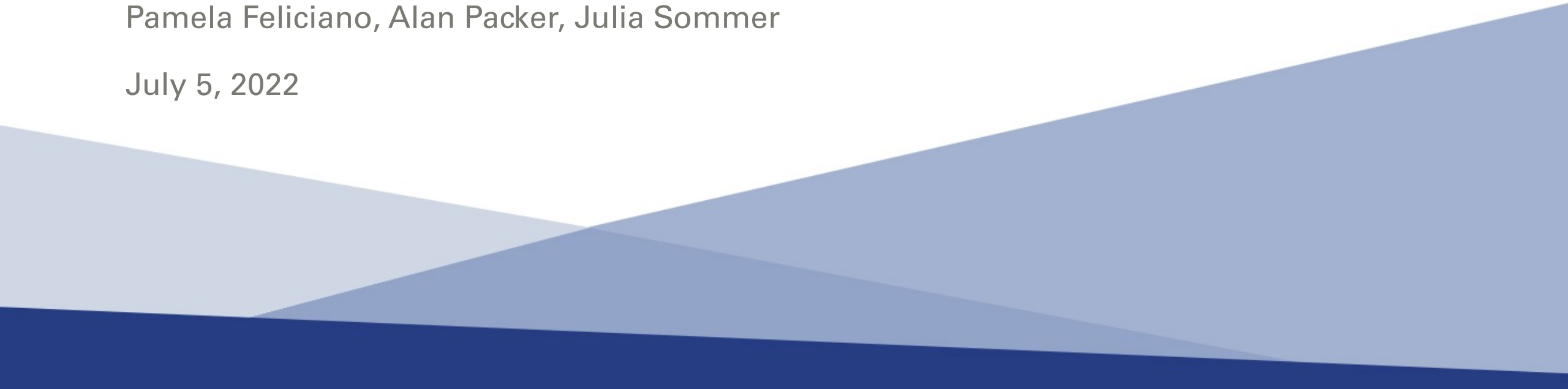


SFARI Informational Event:

Genomics of ASD: Pathways to Biological Convergence and Genetic Therapies RFA

Pamela Feliciano, Alan Packer, Julia Sommer

July 5, 2022



Panelists



Pamela Feliciano, PhD
Scientific Director, SPARK



Julia Sommer, PhD
Senior Scientist, SFARI



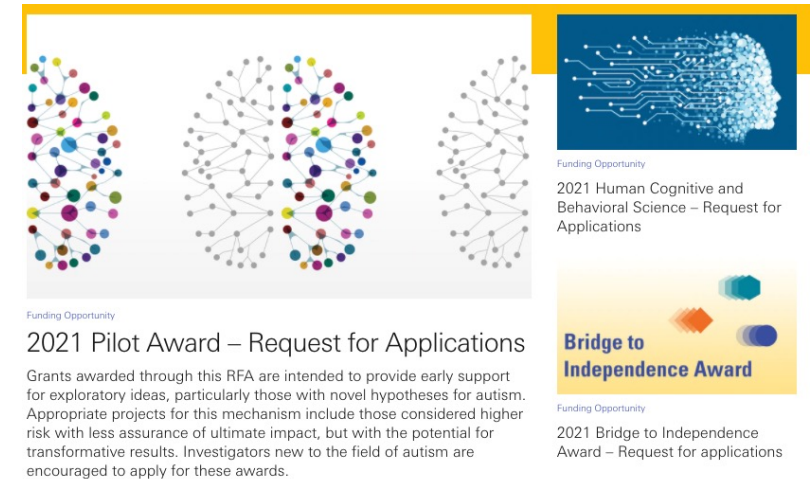
Alan Packer, PhD
Senior Scientist, SFARI

- All audio, except for the presenter's audio, will be muted for the duration of the webinar.
- This webinar is being recorded, and will be available on SFARI.org
- Use the **Q&A** feature to ask **questions for the presenters** throughout the talks.

Please keep your questions brief.

Simons Foundation Autism Research Initiative (SFARI)

- Largest private funder of autism research in the U.S.
- SFARI issued its first RFA in 2007
- Today, SFARI supports more than 300 investigators worldwide
- 2022 budget: \$100 million overall
 - Cohorts and genetic sequencing (SPARK, Simons Searchlight)
 - Research resources (Autism BrainNet, Data Informatic Tools)
 - RFA grant funding: \$19 million



ASD Genetics, ca. 2020

Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism

F. Kyle Satterstrom,^{1,2,3,37} Jack A. Kosmicki,^{1,2,3,4,5,37} Jiebiao Wang,^{6,37} Michael S. Breen,^{7,8,9} Silvia De Rubeis,^{7,8,9} Joon-Yong An,^{10,11} Minshi Peng,⁶ Ryan Collins,^{5,12} Jakob Grove,^{13,14,15} Lambertus Klei,¹⁶ Christine Stevens,^{1,3,4,5} Jennifer Reichert,^{7,8} Maureen S. Mulhern,^{7,8} Mykyta Artomov,^{1,3,4,5} Sherif Gerges,^{1,3,4,5} Brooke Sheppard,¹⁰ Xinyi Xu,^{7,8} Aparna Bhaduri,^{17,18} Utku Norman,¹⁹ Harrison Brand,⁵ Grace Schwartz,¹⁰ Rachel Nguyen,²⁰ Elizabeth E. Guerrero,²¹

Autism Sequencing Consortium

- Exome sequencing (11,986 ASD)
- 102 genes at an FDR of 0.1

Cell **180**, 1-17 (2020)

Nat Genet **51**, 431-444 (2019)

Identification of common genetic risk variants for autism spectrum disorder

[Jakob Grove](#), [Stephan Ripke](#), ... [Anders D. Børglum](#) 

[+ Show authors](#)



Psychiatric Genomics Consortium

- Genome-wide association study
- ~18,000 genotyped cases, ~28,000 controls
- 5 hits (genome-wide significant)

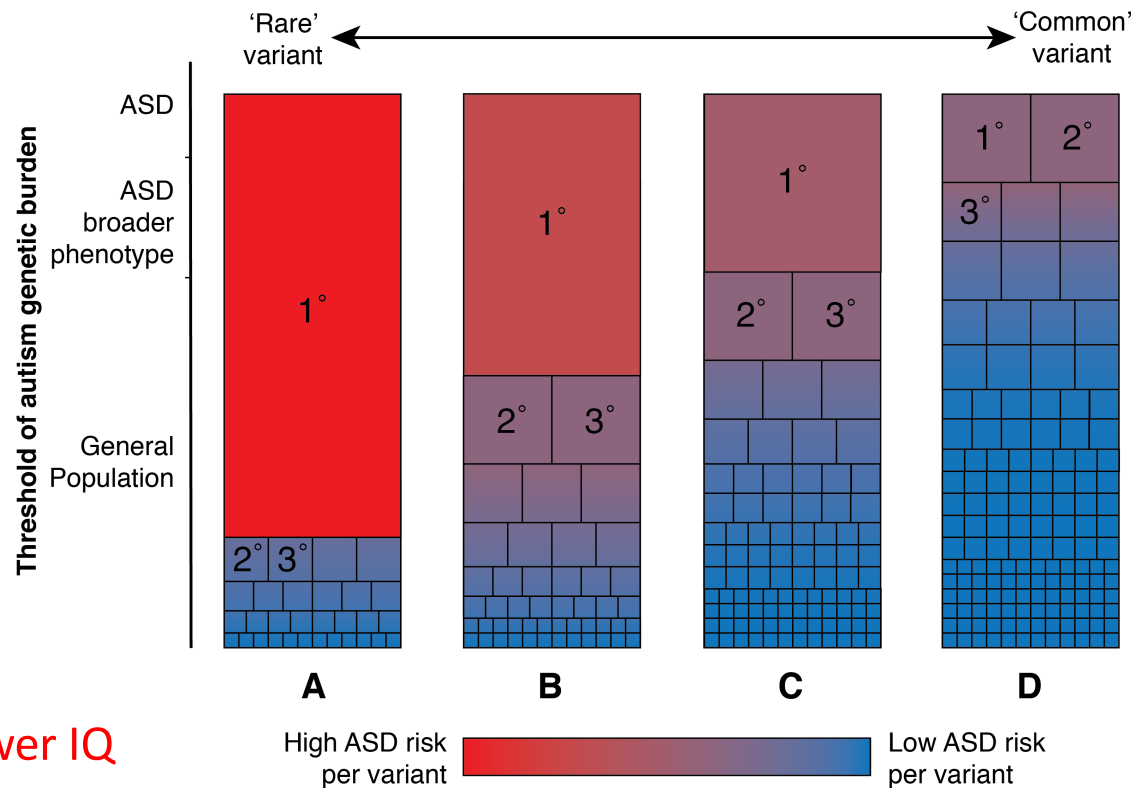
New findings

Corresp. Authors	Citation	ASD Samples & Cohorts	Key Analyses
Talkowski, Sanders, Roeder, Devlin, Daly, Buxbaum (ASC)	<i>medRxiv</i> 21267194 (2021)	20,627 ASD exomes (ASC, SSC, SPARK, DDD, iPSYCH)	Risk gene ID, sex bias, ASD vs. DD, cell-type enrichment.
Chung, Shen (SPARK)	<i>medRxiv</i> 21264256 (2021)	42,607 ASD exomes (SPARK, SSC, ASC, MSSNG)	Risk gene ID, inherited mutations with moderate effect size.
Eichler, Wang	<i>bioRxiv</i> 460398 (2021)	15,560 ASD exomes 31,052 DD exomes (ASC, SSC, SPARK, DDD)	Risk gene ID, sex bias, ASD vs. DD, cell-type enrichment.
Scherer (MSSNG)	<i>medRxiv</i> 22274031 (2022)	5,100 ASD genomes (MSSNG, SSC)	Risk gene ID, rare variants + polygenic risk, genotype-phenotype.
Sebat	PMID 35654974 (2022)	12,270 ASD exomes (SSC, SPARK, REACH)	Risk gene ID, sex bias, rare variants + polygenic risk, genotype-phenotype.
Bourgeron, Rolland	<i>medRxiv</i> 21251621 (2021)	13,901 ASD exomes (SSC, SPARK, iPSYCH)	Odds ratio estimation, sex bias, genotype-phenotype.
Baron-Cohen, Bourgeron, Warrier	PMID 35654973 (2022)	24,420 ASD exomes (SSC, SPARK)	Rare variants + polygenic risk, genotype-phenotype.

In sum

- Rare, dominant *de novo* mutations in 60-600 identified genes contribute to autism risk, with widely varying degrees of estimated effect size (OR from ~2 up to ~200 or higher).
- Most (not all!) *de novo* risk has been identified; most inherited risk has not. Inherited variants may implicate unique biology.
- *De novo* SNVs, indels, and non-recurrent CNVs tend to be paternal in origin, while recurrent CNVs tend to be maternal in origin.
- Burden of common and rare genetic risk is greater in females than in males (female protective effect).
- We call these rare *de novos* 'autism genes', but there is no specificity—most overlap with DD/ID. Some do show a trend for enrichment in ASD vs. ID/DD.
- Risk genes implicate two broad categories of biological function: (1) regulators of gene expression, and (2) synaptic function, and show enrichment in both excitatory and inhibitory neurons.
- *De novo* mutations tend to associate with deficits in IQ, motor coordination, and adaptive behavior, not with core ASD symptoms. Polygenic risk for ASD may be associated with core ASD symptoms and overlaps with polygenic 'risk' for greater educational attainment.
- Phenotypic heterogeneity is driven, in part, by the heterogeneity in genetic architecture.

Genetic architectures of ASD



- Lower IQ
- Lower M:F ratio
- More comorbidities
- Effect on core ASD features may be non-specific or indirect

- Higher IQ (increased 'liability' for higher educational attainment)
- Higher M:F ratio
- Fewer comorbidities
- Effect on core ASD features may be more direct

2022 Genomics of ASD: Pathways to Biological Convergence and Genetic Therapies RFA

Goal: To advance our understanding of the genetic basis of ASD and the molecular and cellular consequences of genetic risk, and to provide a foundation for the development of treatments for select genetically defined forms of the condition.

Applications due: August 18, 2022

Funding decisions: December 21, 2022

Budget has three tracks:

- Explorer: up to \$400,000 over a period of up to two (2) years.
- Expansion: up to \$1,500,000 over a period of up to three (3) years.
- Collaboration: up to \$750,000 per lab over a period of up to three (3) years. Up to four (4) labs may apply as part of a collaboration.

Areas of Focus

(1) Systems Biology to Identify Points of Biological Convergence

- Leverage WGS or WES data from SPARK, including 70,487 exomes (34,164 with ASD) and 11,628 genomes (3,100 with ASD), as well as the recent public release of human protein interactome, ENCODE data, and transcription factor binding sites.
- A main goal is to better understand how ASD-associated alleles perturb the regulation of DNA accessibility, transcription factor binding, mRNA splicing and protein-protein interactions, *ultimately leading to convergent changes in signaling pathways in critical cell types at critical developmental stages.*
- Areas of interest that were underrepresented in last year's RFA: (1) the ASD proteome, (2) the contribution of inherited genetic variation to ASD-associated biology, (3) the possible contribution of mitochondrial genetic variation and biology to ASD.

Areas of Focus

(2) Functional Analysis of Associated Variants

- Study the functional effects of any class of variant associated with ASD susceptibility, including but not limited to missense, splicing, and regulatory variants, as well as tandem repeat expansions and contractions. Proposals that are complementary to previous SFARI awards in this area will be of particular interest.

(3) Genetic Therapies

- Accelerate the application of gene-targeting therapeutic approaches (ASOs, RNA-based, vector-based gene-replacement) for treating ASD. Relevant phenotypes to determine efficacy should be identified in molecular, cellular, and/or animal models.
- We encourage collaborative proposals where investigators will apply different technologies to the same gene(s)

Additional Considerations

SFARI Resources

- SFARI resources include genomic and phenotypic data from SSC, SPARK, and Simons Searchlight cohorts, as well as iPS cells, lymphoblastoid cell lines, and fibroblasts

SPARK Gene List

- Applicants are encouraged (but not required) to focus on a subset of 50 genes from the SPARK gene list that SFARI has selected as strong candidates for the development of translational programs

Collaborative Proposals

- Large multidisciplinary projects that assemble the expertise of multiple labs and benefit from resource and data sharing (e.g. focus Area 3: different 'gene targeting' approaches around the same gene, sharing model systems, baseline characterization and data on 'rescue' success)

Scientific Examples (Focus Area 1)

Article | Published: 06 May 2021

Uncovering genetic mechanisms of hypertension through multi-omic analysis of the kidney

James M. Eales, Xiao Jiang, [...]Maciej Tomaszewski 

Nature Genetics **53**, 630–637 (2021) | [Cite this article](#)

Neuron-specific protein network mapping of autism risk genes identifies shared biological mechanisms and disease relevant pathologies

Nadeem Murtaza, Annie A. Cheng, Chad O. Brown, Durga Praveen Meka, Shuai Hong, Jarryll A. Uy, Joelle El-Hajjar, Neta Pipko, Brianna K. Unda, Birgit Schwanke, Sansi Xing, Bhooma Thiruvahindrapuram, Worrawat Engchuan, Brett Trost, Eric Deneault, Froylan Calderon de Anda, Bradley W. Doble, James Ellis, Evdokia Anagnostou,  Gary D. Bader, Stephen W. Scherer, Yu Lu, Karun K. Singh

doi: <https://doi.org/10.1101/2022.01.17.476220>

Nature Genetics **53**, 630-637 (2021)

bioRxiv 476220 (2022)

Nat Commun **11**, 4873 (2020)

AJHG **106**, 885-892 (2020)

Article | [Open Access](#) | Published: 25 September 2020

Integrative genomics identifies a convergent molecular subtype that links epigenomic with transcriptomic differences in autism

Gokul Ramaswami, Hyejung Won, Michael J. Gandal, Jillian Haney, Jerry C. Wang, Chloe C. Y. Wong, Wenjie Sun, Shyam Prabhakar, Jonathan Mill & Daniel H. Geschwind 

Nature Communications **11**, Article number: 4873 (2020) | [Cite this article](#)

Characterizing the Causal Pathway for Genetic Variants Associated with Neurological Phenotypes Using Human Brain-Derived Proteome Data

Nelson K. Kibinge,¹ Caroline L. Relton,¹ Tom R. Gaunt,¹ and Tom G. Richardson^{1,*}

Scientific Examples (Focus Area 2)

ARTICLE



<https://doi.org/10.1038/s41467-020-15943-0>

OPEN

Multi-model functionalization of disease-associated *PTEN* missense mutations identifies multiple molecular mechanisms underlying protein dysfunction

Kathryn L. Post^{1,2,6}, Manuel Belmadani^{3,4,6}, Payel Ganguly^{1,2,6}, Fabian Meili^{1,2,6}, Riki Dingwall^{1,2,6}, Troy A. McDiarmid^{1,5,6}, Warren M. Meyers^{1,2}, Caitlin Herrington², Barry P. Young², Daniel B. Callaghan^{3,4}, Sanja Rogic^{3,4}, Matthew Edwards^{1,2}, Ana Niciforovic^{1,2}, Alessandro Cau^{1,2}, Catharine H. Rankin^{1,5}, Timothy P. O'Connor^{1,2}, Shernaz X. Bamji^{1,2}, Christopher J. R. Loewen², Douglas W. Allan^{1,2}, Paul Pavlidis^{1,3,4,7} & Kurt Haas^{1,2,7}

Resource

Drosophila functional screening of *de novo* variants in autism uncovers damaging variants and facilitates discovery of rare neurodevelopmental diseases

Paul C. Marcogliese^{1,2,37}, Samantha L. Deal^{2,3,37}, Jonathan Andrews^{1,2,37}, J. Michael Harnish^{1,2,37}, V. Hemanjani Bhavana^{1,2}, Hillary K. Graves^{1,2}, Sharayu Jangam^{1,2}, Xi Luo^{1,2,4}, Ning Liu^{1,2,36}, Danqing Bei^{1,2}, Yu-Hsin Chao^{1,2}, Brooke Hull^{1,2}, Pei-Tseng Lee^{1,2}, Hongling Pan^{1,2}, Pradnya Bhadane^{1,2}, Mei-Chu Huang^{1,2}, Colleen M. Longley^{2,3}, Hsiao-Tuan Chao^{1,2,5,6,7,8,9}, Hyung-lok Chung^{1,2,10}, Nele A. Haelterman^{1,2}, Oguz Kanca^{1,2}, Sathya N. Manivannan^{1,2}, Linda Z. Rossetti¹, Ryan J. German^{1,2}, Amanda Gerard^{1,8}, Eva Maria Christina Schwaibold¹¹, Sarah Fehr^{1,2}, Renzo Guerrini^{1,3}, Annalisa Vetro^{1,3}, Eleina England^{1,4}, Chaya N. Murali^{1,8}, Tahsin Stefan Barakat^{1,5}

Nat Commun **11**(1): 2073 (2020).

Cell Rep **38**, 110517 (2022).

Nat Genet **50**, 1032-1040 (2018).

Cell Syst **12**, 353-362 (2021).

nature
genetics

ARTICLES

<https://doi.org/10.1038/s41588-018-0130-z>

An interactome perturbation framework prioritizes damaging missense mutations for developmental disorders

Siwei Chen^{1,2,3,7}, Robert Fragoza^{1,2,3,7}, Lambertus Klei⁴, Yuan Liu^{1,2}, Jiebiao Wang⁵, Kathryn Roeder^{5,6*}, Bernie Devlin^{4*} and Haiyuan Yu^{1,2*}

Report

Tissue-specific enhancer functional networks for associating distal regulatory regions to disease

Xi Chen¹, Jian Zhou^{1,2}, Ran Zhang², Aaron K. Wong¹, Christopher Y. Park¹, Chandra L. Theesfeld², and Olga G. Troyanskaya^{1,2,3,4,*}

¹Center for Computational Biology, Flatiron Institute, Simons Foundation, New York, NY 10010, USA

²Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, NJ 08544, USA

³Department of Computer Science, Princeton University, Princeton, NJ 08544, USA

⁴Lead contact

*Correspondence: ogt@cs.princeton.edu

<https://doi.org/10.1016/j.cels.2021.02.002>

Scientific Examples (Focus Area 3)

LETTER

doi:10.1038/nature13975

Towards a therapy for Angelman syndrome by targeting a long non-coding RNA

Linyan Meng^{1*}, Amanda J. Ward^{2*}, Seung Chun², C. Frank Bennett², Arthur L. Beaudet¹ & Frank Rigo²

Article

Cas9 gene therapy for Angelman syndrome traps *Ube3a-ATS* long non-coding RNA

<https://doi.org/10.1038/s41586-020-2835-2>

Received: 11 October 2019

Justin M. Wolter^{1,2,3,5}, Hanqian Mao^{1,2,3,5}, Giulia Fragola¹, Jeremy M. Simon^{1,2,4}, James L. Krantz¹, Hannah O. Bazick¹, Baris Oztemiz¹, Jason L. Stein^{1,4} & Mark J. Zylka^{1,2,3,5}

Article | Published: 06 January 2021

In vivo base editing rescues Hutchinson–Gilford progeria syndrome in mice

Luke W. Koblan, Michael R. Erdos, Christopher Wilson, Wayne A. Cabral, Jonathan M. Levy, Zheng-Mei Xiong, Urraca L. Tavaréz, Lindsay M. Davison, Yantenew G. Gete, Xiaojing Mao, Gregory A. Newby, Sean P. Doherty, Narisu Narisu, Quanhu Sheng, Chad Krilow, Charles Y. Lin, Leslie B. Gordon, Kan Cao, Francis S. Collins ✉, Jonathan D. Brown ✉ & David R. Liu ✉

Published: 11 October 2017

Radically truncated MeCP2 rescues Rett syndrome-like neurological defects

Rebekah Tillotson, Jim Selfridge, Martha V. Koerner, Kamal K. E. Gadalla, Jacky Guy, Dina De Sousa, Ralph D. Hector, Stuart R. Cobb & Adrian Bird ✉

SFARI iPS cells

- iPSC resource from Simons Searchlight blood biospecimens
- Reprogramming: PBMCs, Sendai virus, extensive QC
- Control iPSCs: gender matched family member control samples will be made

Available	Upcoming	
16p11.2 dup/del	ADNP	PPP2R5D
CSNK2A1	ASXL3	SCN2A
PPP2R5D	DYRK1A	SETBP1
ADNP	GRIN2B	SLC6A
DYRK1A	HIVEP2	STXBP1
GRIN2B	HNRNPH2	SYNGAP1
SCN2A	PACS1	1q21.1 del/dup
SETBP1	CHAMP1	MED13L
SYNGAP1	CLCN4	
STXBP1	CTNNB1	

Summary of SPARK sequencing efforts to date

Available on SFARbase

EXOMES

WES1,2,3,4: 70,487
people & 34,164
with ASD

GENOMES

WGS1,2,3,4: 11,628
people &
3,199 with ASD;
all with parents

1,805 overlapping
samples

In process (2022)

WES5

37,256 people &
12,973 with ASD
(completed
sequencing, in
analysis)

WGS5

~350 ASD trios from
WES1 with no
genetic results;
female probands
with ID and seizures
prioritized

WES6: 9,379
people &
4,399 with
ASD
(Q4 2022)

What is the SPARK gene list?

Updated September 2021

SPARK Gene List

The SPARK gene list contains 167 single genes (blue), 43 copy number variants (orange) and 5 chromosomal differences (green) that are known to be associated with autism. More information about each autism-linked gene or CNV, along with its associated symptoms, is available [here](#).

Copy Number Variants		Single Genes			
1q21.1 del	16p12.2 del	ACTB	DMPK	MTOR*	SETD2
1q21.1 dup	16p13.11 del	ADNP	DNMT3A	MYT1L	SETD5
2p16.3 del	16p13.3 del	ADSL	DSCAM	NAA15	SHANK2
2q37.3 del	17p11.2 del	AFF2	DYNC1H1	NBEA	SHANK3
3q29 del	17p11.2 dup	AHDC1	DYRK1A	NCKAP1	SHOC2
3q29 dup	17p13.3 del	ALDH5A1	EBF3	NEXMIF	SIN3A
5p- del	17p13.3 dup	ANK2	EHMT1	NF1	SLC6A1
5q35 del	17q11.2 del	ANK3	EIF3F*	NIPBL	SLC9A6
5q35 dup	17q11.2 dup	ANKRD11	EP300	NLGN2	SMARCC2
6q16 del	17q12 del	ARHGEF9	FMR1	NLGN3	SON
7q11.23 del	17q12 dup	ARID1B	FOXG1	NLGN4X	SOS1
7q11.23 distal del	17q21.3 del	ARX	FOXP1	NR4A2	SOS2
7q11.23 dup	17q21.3 dup	ASH1L	GIGYF1	NRAS	SOX5
8p23.1 dup	22q11.2 del	ASXL3	GIGYF2	NRXN1	SPAST
9q34 del	22q11.2 dup	ATRX	GRIN1*	NRXN2	SRCAP
9q34 dup	22q11.2 central del	AUTS2	GRIN2A*	NRXN3	STXBP1
15q11.2q13.1 del	22q11.2 central dup	BAZ2B	GRIN2B	NSD1	SYNGAP1
15q11.2q13.1 dup	22q13.3 del	BCKDK	HIVEP2	PAC51*	TANC2
15q13.3 del	Xq28 dup	BCL11A	HNRNPH2*	PCDH19	TAOK1
15q15 del		BRAF	HNRNPU	PHF21A	TBCK
15q24A_C del		BRSK2	HRAS	PHF3	TBR1
16p11.2 del		CACNA1C	IQSEC2	PHIP	TCF4
16p11.2 distal del		CAPRIN1	IRF2BPL	POGZ	TCF20
16p11.2 dup		CASK	KANSL1	POMGNT1	TLK2
		CASZ1	KCNB1	PPP1CB	TRIO
		CBL	KCNQ3*	PPP2R5D*	TRIP12
		CDKL5	KDM3B	PSMD12	TSC1
		CHAMP1	KDM6B	PTCHD1	TSC2
		CHD2	KMT2A	PTEN	TSHZ3
		CHD3	KMT2C	PTPN11	UBE3A
		CHD7	KMT5B	RAF1	UPF3B
		CHD8	KRAS	RAI1	VPS13B
		CIC	LZTR1	RALGAPB	WAC
		CNOT3	MAGEL2	RELN	WDFY3
		CREBBP	MAP2K1	RERE	YY1*
		CSDE1	MAP2K2	RFX3	ZBTB20
		CTCF	MBD5	RIMS1	ZNF292
		CTNNA1	MBOAT7	RIT1	ZNF462
		CUL3	MECP2	RORB	
		DDX3X	MED13	SCN1A	
		DEAF1*	MED13L	SCN2A	
		DHCR7	MEF2C	SCN8A	
		DLG4	MEIS2	SETBP1	

*Only certain variants in these genes are returned.

- All genes/loci are high-confidence ASD risk genes
- If a consenting SPARK participant has a variant that meets ACMG LP/P criteria in one of these genes/loci, that variant is returned to the participant
- As of 2022, SPARK has collected DNA samples from ~53K participants with ASD and expects to identify LP/P variants in these genes and loci in 8-10% of participants

What is the subset of ~50 prioritized high-confidence ASD genes?

Gene	Reasons for prioritization	Also associated with/known as	Predicted incidence per 100,000 births: total (PTV/missense) see Brain , Lopez-Rivera et al. (2020))	Active family group?	Active Searchlight group?
<i>ADNP</i>	Active family group, intellectual disability	Helsmoortel-Van Der Aa syndrome		TRUE	TRUE
<i>AHDC1</i>	Intellectual disability, active family group	Xia-Gibbs Syndrome, sleep apnea	3.91 (0.45/3.46)	TRUE	FALSE
<i>ANKRD11</i>	Active family group, intellectual disability	KBG syndrome		TRUE	TRUE
<i>ARID1B</i>	Intellectual disability	Coffin-Siris Syndrome 1; hypertrichosis	4.48 (1.62/2.87)	TRUE	TRUE
<i>ASXL3</i>	Active family group, epilepsy & intellectual disability	Bainbridge-Ropers syndrome		TRUE	TRUE
<i>BCKDK</i>	Recessive metabolic condition	Branched-Chain Keto Acid Dehydrogenase Kinase Deficiency (recessive)		FALSE	FALSE
<i>BCL11A</i>	Intellectual disability	Intellectual Developmental Disorder	3.43 (0.26/3.17)		
<i>CASK</i>	Intellectual disability	FG syndrome 4, intellectual disability	2.94 (0.64/2.3)		

- Subset of genes from the SPARK gene list
- Reasons for prioritization include:
 - Recurrent GoF mutations potentially amenable to ASO therapeutics
 - Evidence of clustered mutation spectrum
 - Syndrome associated with severe symptoms
 - Evidence of poison exons
 - Predicted incidence exceeds 5/100K
 - Presence of a well-organized family group
 - Gene encodes protein that is considered druggable
 - Gene encodes a metabolic enzyme, condition is recessive, replacement strategies may be an option

2022 Genomics of ASD: Pathways to Biological Convergence and Genetic Therapies RFA

Contact Info

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Important Dates

Application Available

June 21, 2022

RFA Informational Session

July 5, 2022

Application Deadline

August 18, 2022

Award Notification

December 2022

Award Start Dates

March/April 2023

Questions?