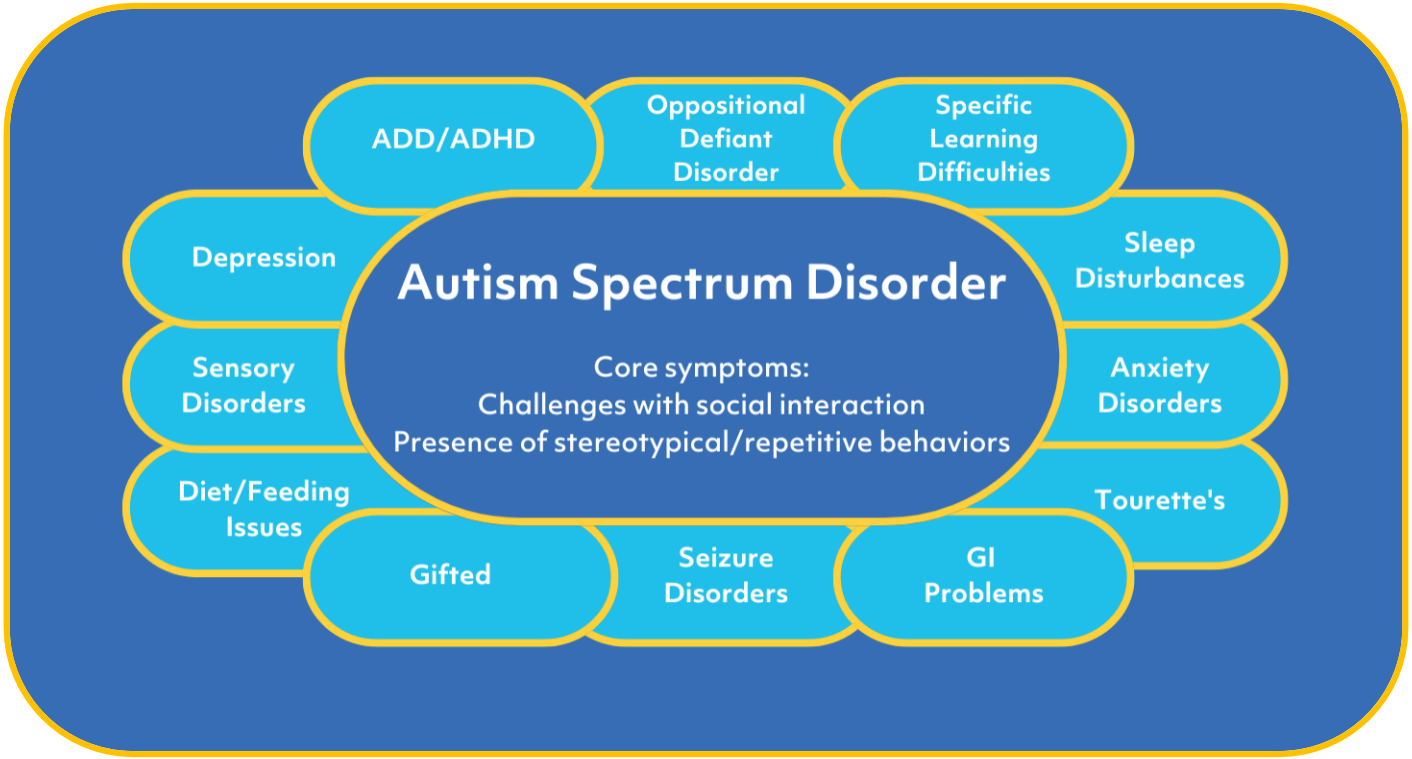
Understanding autism by learning together

Wendy Chung, M.D., Ph.D.
May 4, 2023

SPARK

Autism is complex. It is not a single condition, and many individuals have related challenges.

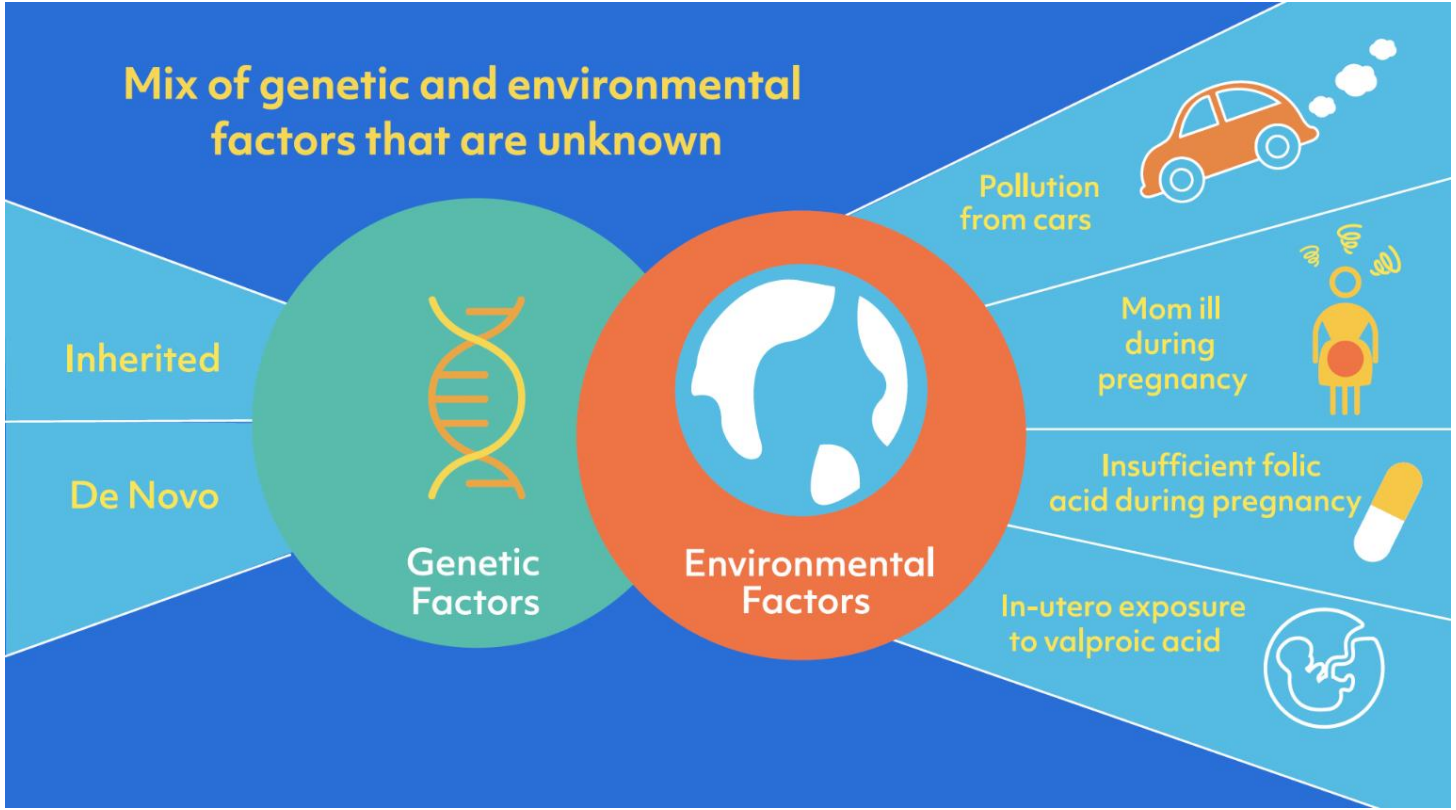


What is “big data” and why is it important?

Big data refers to little bits of data coming from large numbers of people; it’s all of us coming together that makes it **BIG!**

SPARK was launched because we knew that in order to make meaningful progress towards the understanding of autism, we needed a really large dataset from tens of thousands of people with autism. By bringing together tens of thousands of people with autism and their families, we can gain a better understanding of the patterns that may manifest in subsets of individuals to individualize supports.

There are many causes of autism, but for most individuals we do not yet know the cause.



Why SPARK?

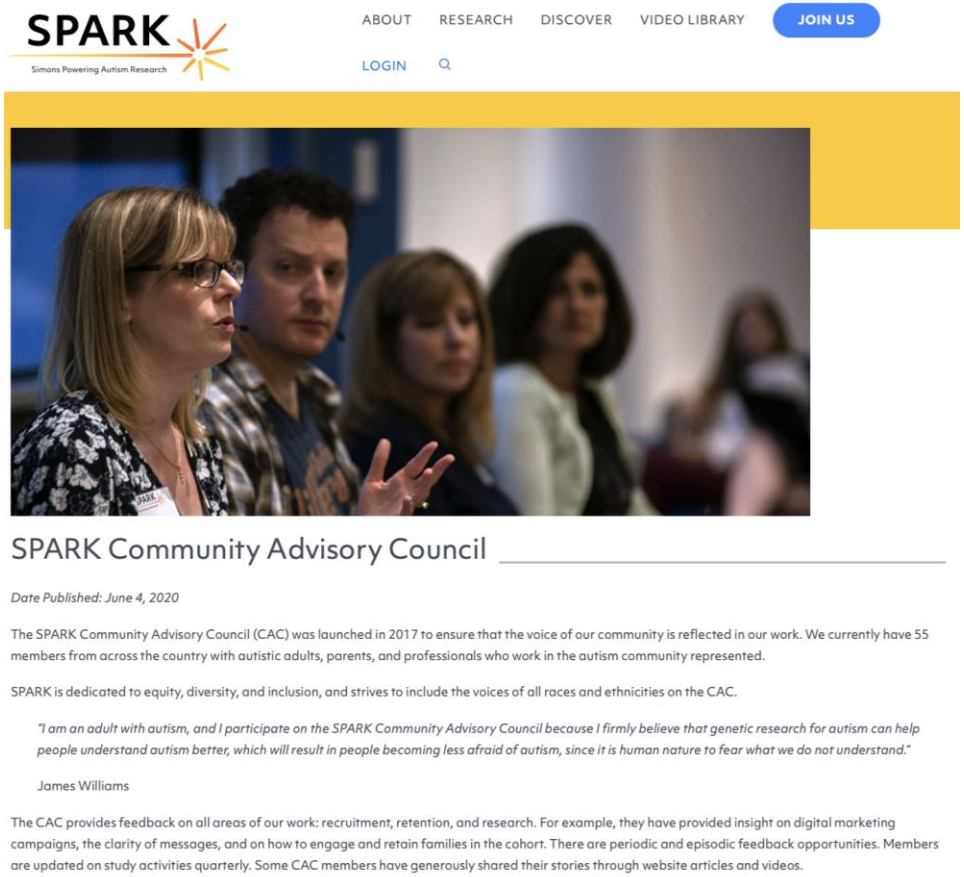
SPARK's goal is to **recruit**, **engage**, and **retain** a community of **individuals with ASD and with their family members** in the United States to:

- Understand the biology of ASD
- Accelerate clinical research by providing the autism research community with a clinically and genetically characterized cohort of consented, recontactable participants

Neuron. 2018. PMID 29420931

Advisory Boards

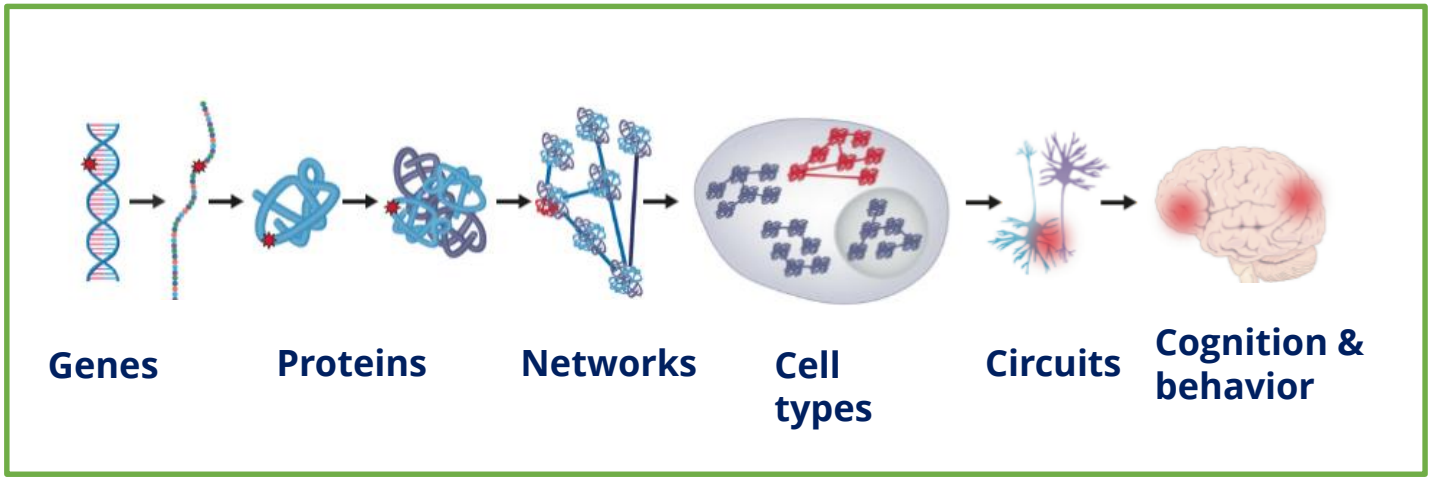
- Science Advisory Board
  - 8 members, including 1 autistic adult & 1 parent
  - Expertise in autism, genetics, epidemiology, online cohorts, & clinical trials
  - Provide input on operational challenges & strategic plans
- Community Advisory Council
  - 55 members, primarily autistic adults & parents
  - Provide input on communication materials, individualized reports, study surveys, etc.



What are SPARK's goals?

- The goal of SPARK is to better understand the causes of autism and to help improve lives.
- It's about uniting the entire autism research community.

The importance of genetics in autism research



- Identifying and understanding new genes is only the first part of SPARK's mission to improve lives.
- Our goal is to connect autism genes to their actions in cells and ultimately to their effects on behavior.
- By understanding the full spectrum of autism genes, we hope to better understand autism and accelerate discoveries to better support all people with the condition.

Adapted from Searles Quick et al., 2020

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

What have we achieved?

Built an unprecedented research community:

- Over 30 clinical sites
- 318,778 participants, including individuals with autism and first-degree family members
- 124,761 research participants with autism
    - 104,107 children 20,490 adults

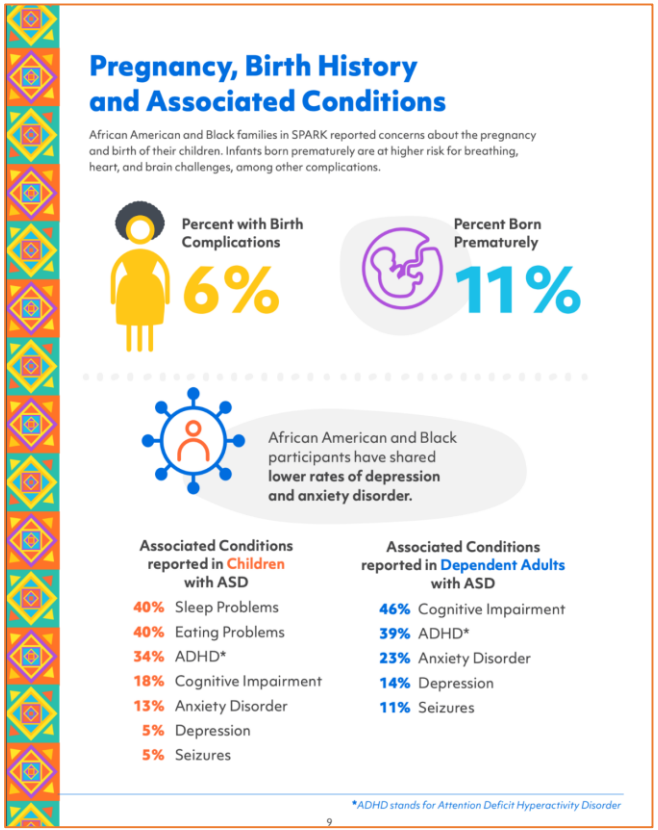
Accelerated research:

- Since launching Research Match in 2017, SPARK has recruited over 52,000 for over 200 research studies
- More than 300 scientists used SPARK data
- 60+ scientific papers including 3 on common and rare genetic variants and 25 from Research Match studies
- Helped researchers discover >100 autism genes
- Advancing understanding of regression, depression, camouflaging, verbal abilities, life in the time of COVID-19, and much more

What has SPARK given back to the community?

- Transformed the community's experiences into scientific knowledge
- 70,000+ personalized reports from online standardized measures
- Notified families and autistic people about a genetic cause (not all have received actual results)
- Invited participants with a genetic diagnosis to join Simons Searchlight as the next step
- 75 webinars with researchers and clinicians
- 170 stories about our participants, treatments and therapies, and other topics important to the community

African American/Black Snapshot



Pregnancy, Birth History and Associated Conditions

African American and Black families in SPARK reported concerns about the pregnancy and birth of their children. Infants born prematurely are at higher risk for breathing, heart, and brain challenges, among other complications.

Percent with Birth Complications

6%

Percent Born Prematurely

11%

African American and Black participants have shared **lower rates of depression and anxiety disorder.**

Associated Conditions reported in Children with ASD

- **40%** Sleep Problems
- **40%** Eating Problems
- **34%** ADHD*
- **18%** Cognitive Impairment
- **13%** Anxiety Disorder
- **5%** Depression
- **5%** Seizures

Associated Conditions reported in Dependent Adults with ASD

- **46%** Cognitive Impairment
- **39%** ADHD*
- **23%** Anxiety Disorder
- **14%** Depression
- **11%** Seizures

*ADHD stands for Attention Deficit Hyperactivity Disorder

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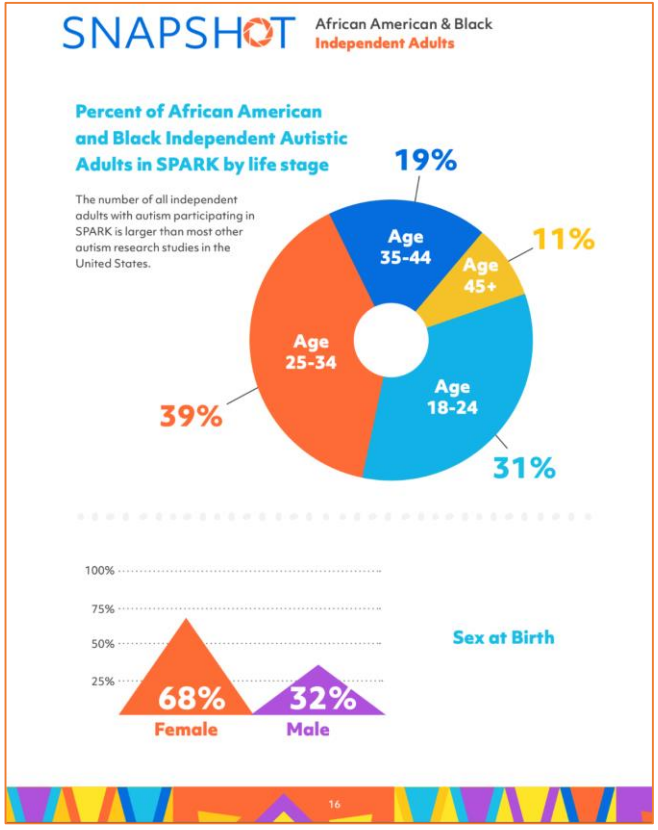


SNAPSHOT African American & Black Independent Adults

Percent of African American and Black Independent Autistic Adults in SPARK by life stage

The number of all independent adults with autism participating in SPARK is larger than most other autism research studies in the United States.

Sex at Birth

16

Women and Girls Snapshot

Differences in First Concerns

Parents of girls were more likely to report first concerns related to **motor development** such as **late walking**.

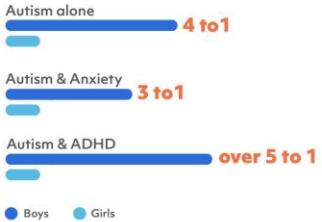
This was different from boys, who more often experienced delayed first words, repetitive behaviors, and loss of speech or other skills.

Sex Ratios

For every 4 boys diagnosed with autism in the US, only 1 girl is diagnosed.

4:1 ratio

SPARK researchers found that sex ratios differed when looking at more specific groups of children.



These data show that when diagnosing autism, anxiety is a more common co-occurring condition in girls, whereas ADHD is a more common co-occurring condition in boys.

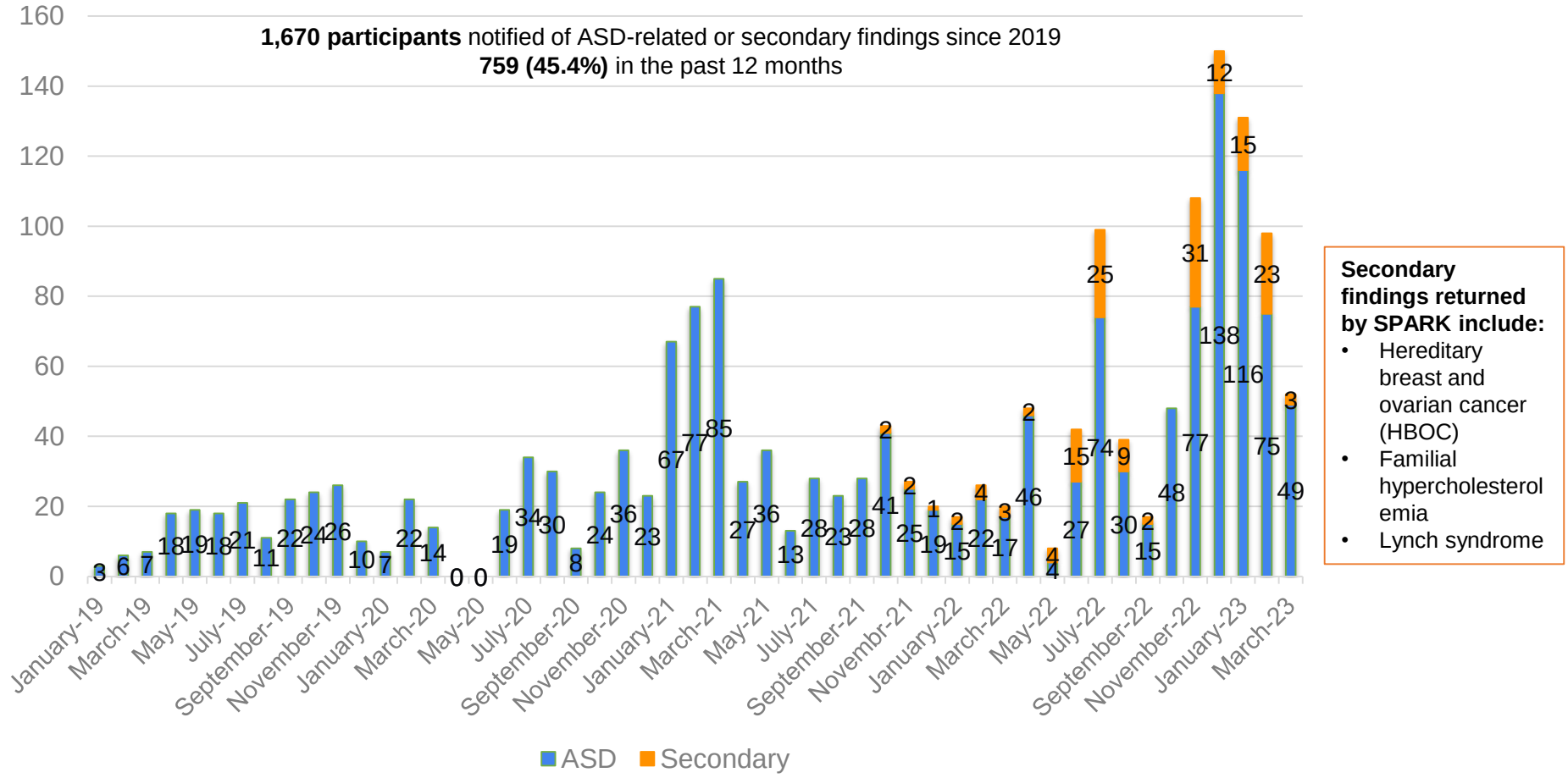
Autism with Anxiety & ADHD

Girls with autism who have **co-occurring anxiety or ADHD** showed more autistic traits, such as repeating phrases or difficulties with eye contact.

Girls with autism who have ADHD had more severe **motor delays**.

Girls with autism who have **co-occurring anxiety *and* ADHD** had more **repetitive behaviors** than autistic females with only one co-occurring condition.

Update on Return of Genetic Results



Secondary findings returned by SPARK include:

- Hereditary breast and ovarian cancer (HBOC)
- Familial hypercholesterolemia
- Lynch syndrome

Using two different methods, confirmation of ASD diagnosis in EMRs was obtained in 98.8% of cases

Categorical variables	N[a]	EMR abstraction N (%)	SPARK participant data N (%)	% agreement
Parents concerned before age 3				
Yes	161	132 (82.0)	147 (91.3)	83.3
Intellectual disability (IQ <70)				
Yes	146	69 (47.3)	57 (39.0)	71.3

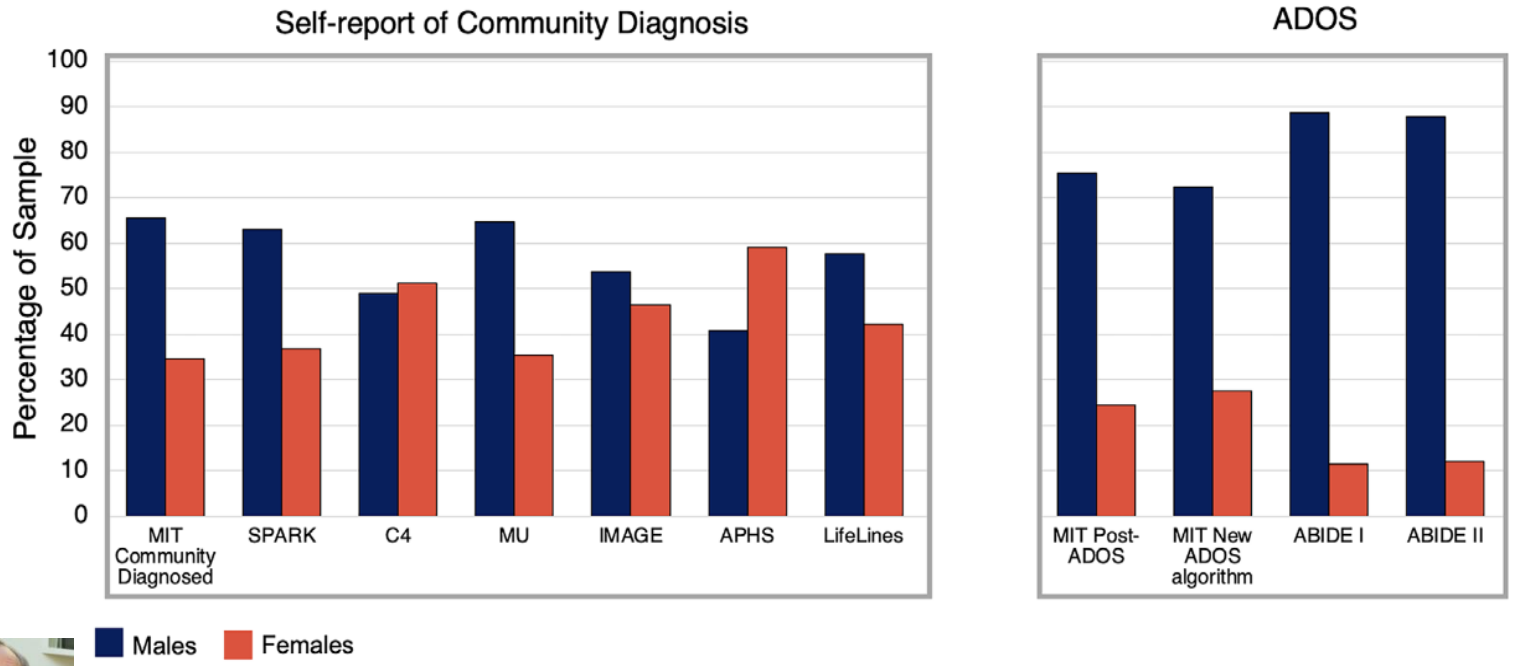
Eric Fombonne

Brian O'Roak

Fombonne et al. (2022). Validation of Autism Diagnosis and Clinical Data in the SPARK Cohort. *Journal of autism and developmental disorders*, *52*(8), 3383–3398. https://doi.org/10.1007/s10803-021-05218-y

Sex bias in research participation based on case definition:

Using the ADOS as a confirmatory diagnostic measure resulted in the exclusion of autistic females at a rate over 2.5 times higher than that of autistic males

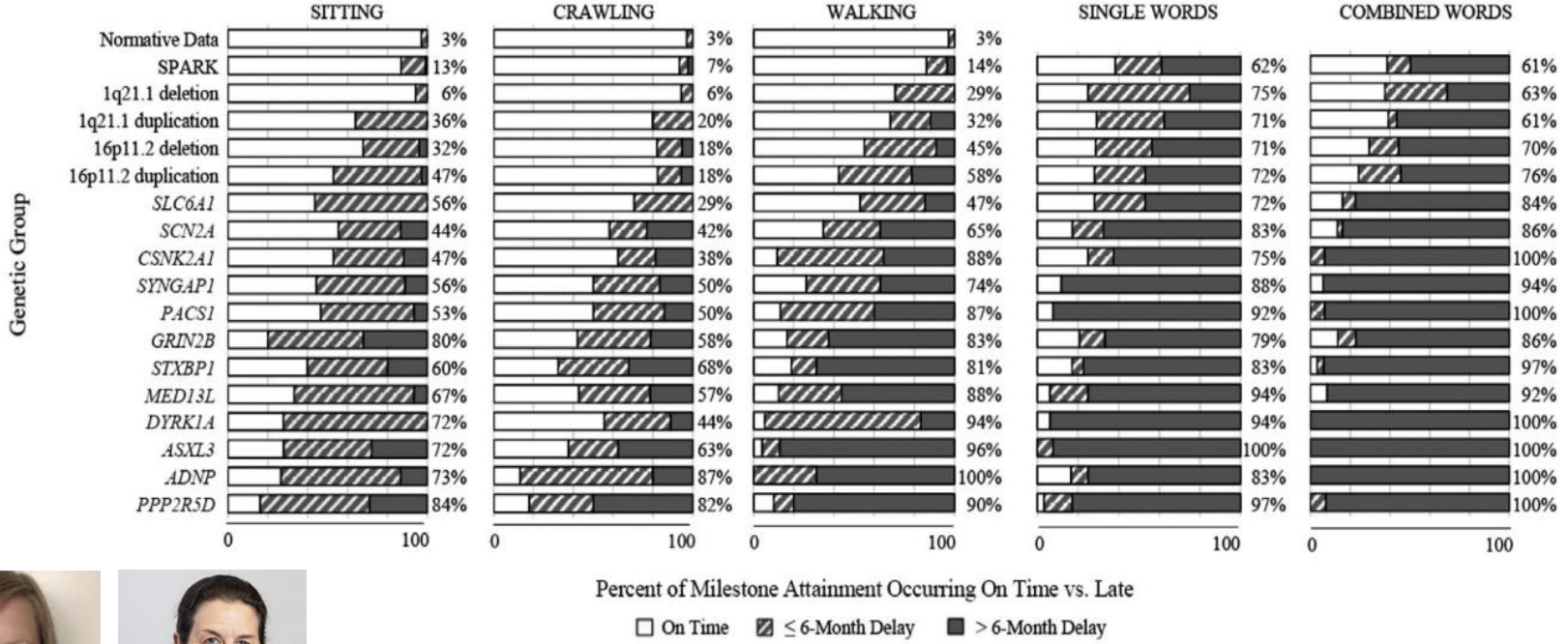


Anila D'Mello

John Gabrieli

D'Mello, A. M., Frosch, I. R., Li, C. E., Cardinaux, A. L., & Gabrieli, J. D. E. (2022). Exclusion of females in autism research: Empirical evidence for a "leaky" recruitment-to-research pipeline. *Autism research : official journal of the International Society for Autism Research*, *15*(10), 1929–1940. https://doi.org/10.1002/aur.2795

Delays in milestone attainment differ between individuals with known genetic causes versus idiopathic ASD

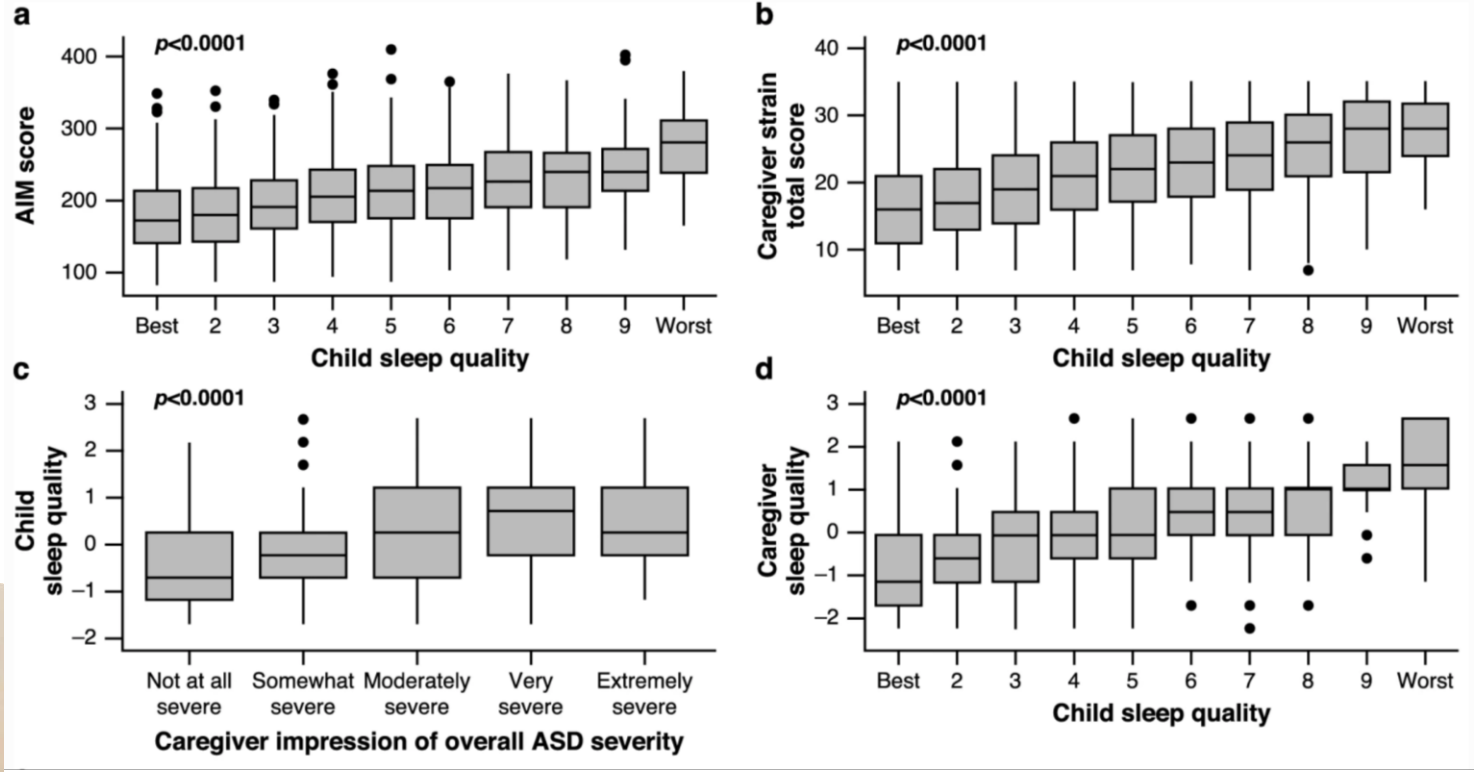


Jordan Wickstrom

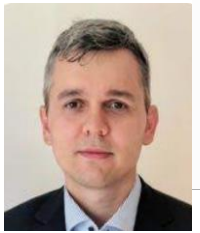
Audrey Thurm

Wickstrom J, et al. Patterns of delay in early gross motor and expressive language milestone attainment in probands with genetic conditions versus idiopathic ASD from SFARI registries. J Child Psychol Psychiatry. 2021 Nov;62(11):1297-1307. doi: 10.1111/jcpp.13492. Epub 2021 Aug 12. PMID: 34382689; PMCID: PMC9939014.

Child sleep quality related to autism severity, caregiver strain, and caregiver sleep quality



Gonzalo Duran-Pacheco



Georg Loss

Durán-Pacheco G. et al. Effect of Children's Autism Spectrum Disorder Severity on Family Strain and Sleep Quality: A Cross-Sectional Online Survey in the U.S. *Journal of Autism & Developmental Disorders* (2022)

Co-occurring psychiatric conditions more frequent in individuals diagnosed with autism as adults

	<21 (N = 2439)		*21+ (N = 2210)*			
	N	**%**	***N***	**%**	**OR**	**CI**
Mood, depression, anxiety, or OCD						
Anxiety disorder (e.g., GAD) except for social anxiety	1212	49.7	1320	59.7	1.907	1.653-2.201
Obsessive-compulsive disorder	567	23.2	559	25.3	1.281	1.092-1.503
Depression or dysthymia	1127	46.2	1336	60.5	1.900	1.652-2.185
Attention and behavior disorders						
ADHD (attention deficit-hyperactivity disorder)	1119	45.9	927	41.9	1.093	0.952-1.254
Oppositional defiant disorder	180	7.4	83	3.8	0.639	0.467-0.875

Nikita Jadav

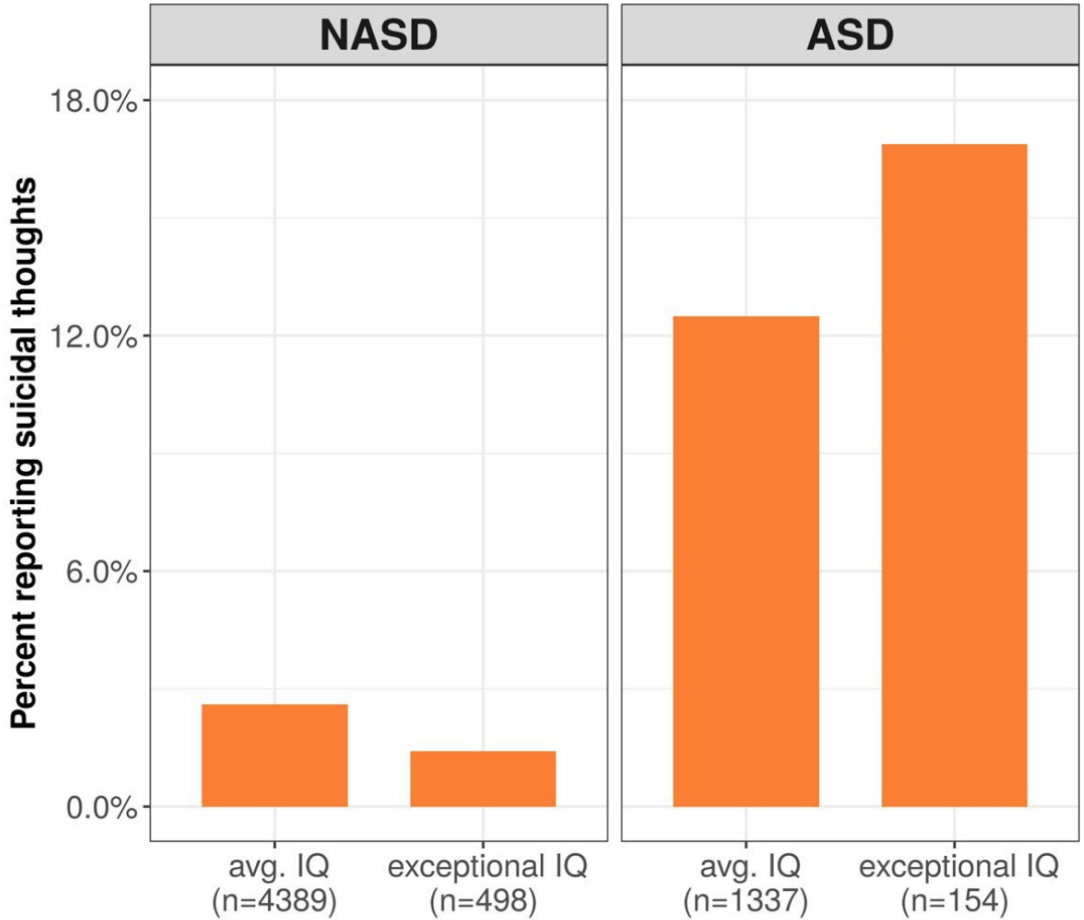
Vanessa Bal

Jadav, N., & Bal, V. H. (2022). Associations between co-occurring conditions and age of autism diagnosis: Implications for mental health training and adult autism research. *Autism research : official journal of the International Society for Autism Research*, *15*(11), 2112–2125. https://doi.org/10.1002/aur.2808

Association between suicidal ideation and high cognitive ability

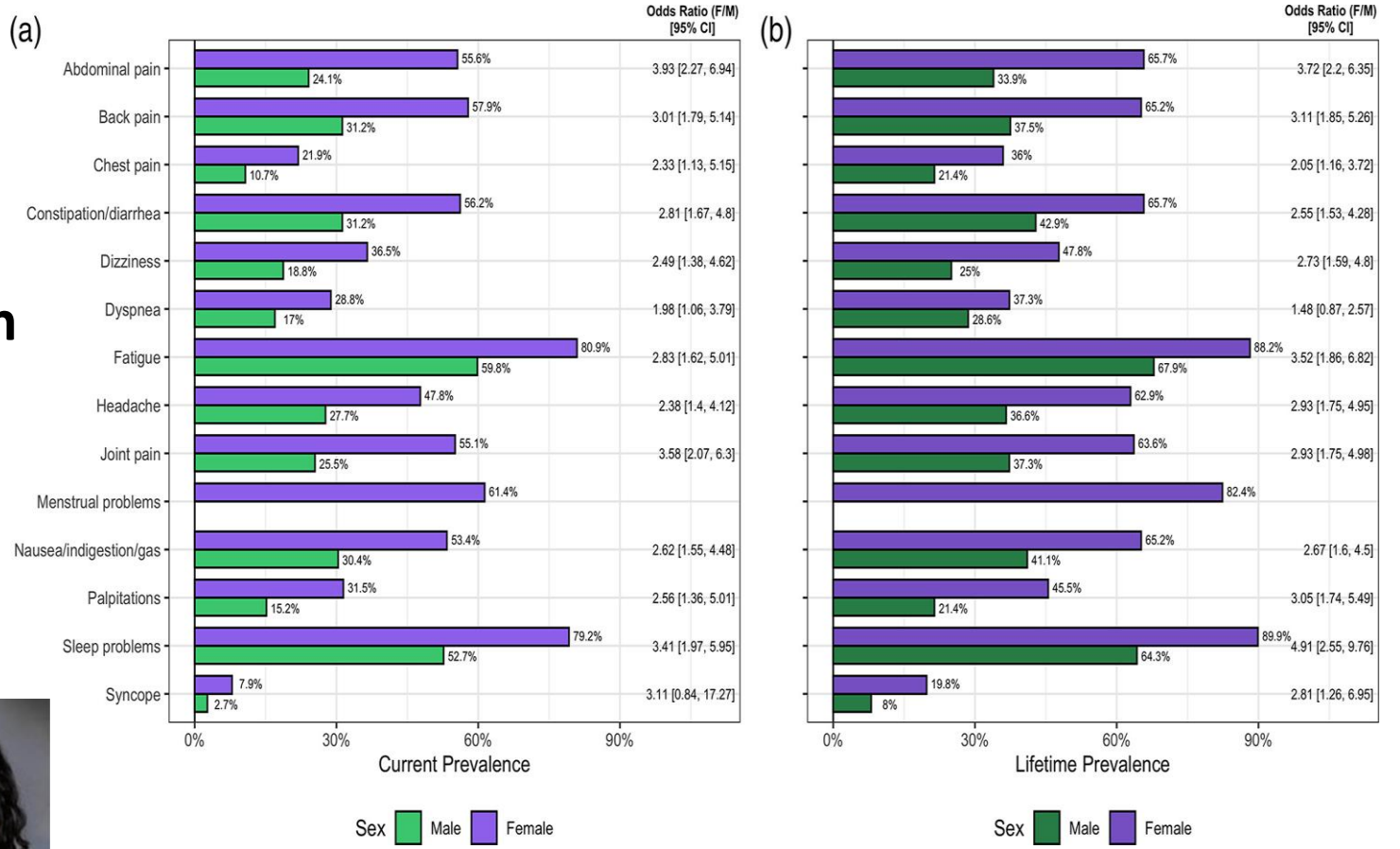
Lucas Casten

Jacob Michaelson



Casten LG et al. The combination of autism and exceptional cognitive ability is associated with suicidal ideation. *Neurobiology of Learning and Memory*. 2023 Jan;197:107698.

Physical health symptoms in autistic adults

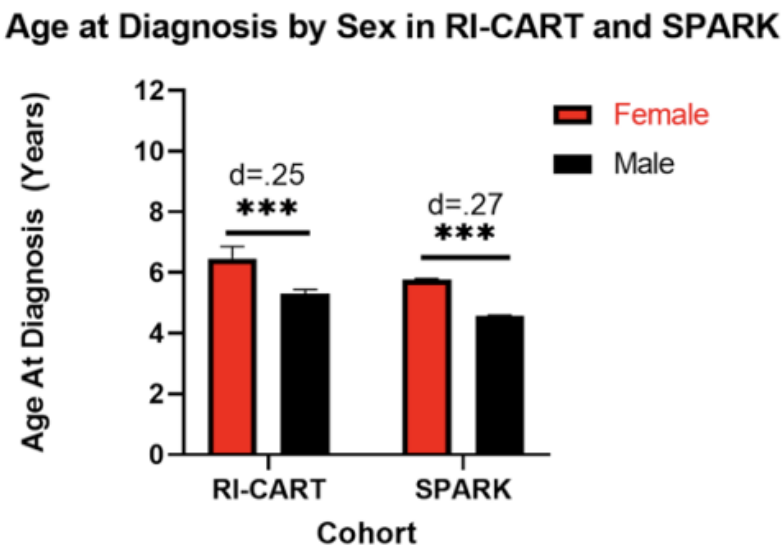


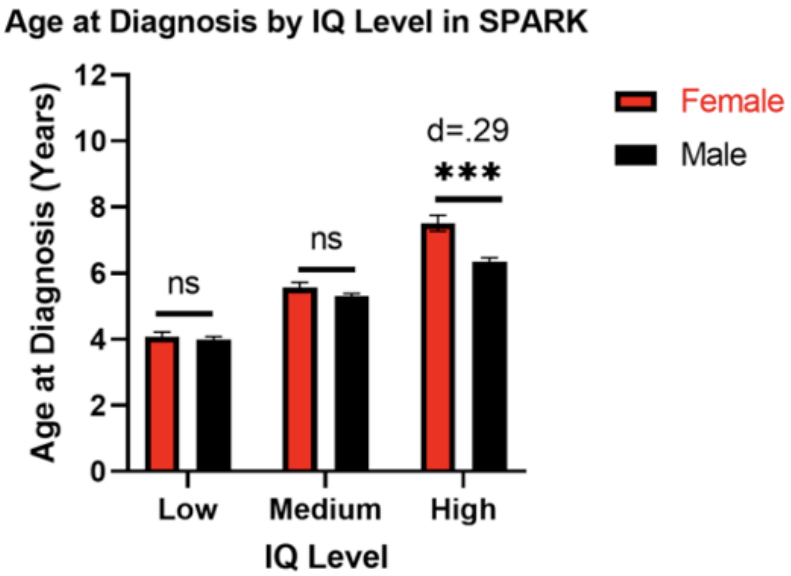
Zach Williams

Kate Gotham

Williams ZJ, Gotham KO. Current and lifetime somatic symptom burden among transition-aged autistic young adults. *Autism Research*. 2022 Apr;15(4):761-770.

Females were first diagnosed with autism 14-months later than males and difference was moderated by a mild or atypical presentation





Brian Kavanaugh

Eric Morrow

Kavanaugh et al. (2023). Moderators of Age of Diagnosis in > 20,000 Females with Autism in Two Large US Studies. *Journal of autism and developmental disorders*, *53*(2), 864–869. https://doi.org/10.1007/s10803-021-05026-4

Culturally sensitive and accessible care is needed to support Black and multiracial children and their families

Table 2 Diagnostic Experience Survey: Open-ended qualitative questions

From: Screening, Diagnosis, and Intervention for Autism: Experiences of Black and Multiracial Families Seeking Care

1) "Do you feel that there were cultural differences between you and the professionals you saw that affected the diagnostic process? If yes, please describe those cultural differences and how you think they impacted the diagnostic process."
2) "Was your child's pediatrician helpful during the diagnostic process? If yes, how were they helpful? If no, what happened?"
3) "Did your child's pediatrician help with follow-up after your child's diagnosis? If no, what happened?"
4) What would have made the diagnostic process easier or less confusing for you and your child? If you selected 'other,' please let us know what else would have made the process easier."
5) "Knowing what you know now, are there behaviors that your child showed before their diagnosis that you did not recognize as autism symptoms, but now know are part of autism? If yes, please describe those behaviors."
6) "If you could go back in time, what (if anything) do you wish you could have known or done differently during the diagnostic process?"

Table 5 Parent selections of a priori processes to improve the diagnostic process

Suggested improvements	n (%)
Receive an evaluation faster	204 (51%)
Have professionals listen to concerns sooner	168 (42%)
Receive more support from family members	147 (36.75%)
Have someone explain what autism is	138 (34.50%)
Have professionals raise concerns sooner	132 (33%)
Receive more support from teachers	61 (15.25%)

Amy Weitlauf

Zach Warren

Weitlauf AS, et al. Screening, Diagnosis, and Intervention for Autism: Experiences of Black and Multiracial Families Seeking Care. *Journal of Autism and Developmental Disorders*. 2023 Jan 10.

Many genomic analyses are being performed on SPARK data

nature genetics

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

Xueya Zhou, Pamela Feliciano, Tianyun Wang, Irina Astrovskaya, Chang Shu, Jacob B. Hall, Joseph U. Obiajulu, Jessica Wright, Shwetha Murali, Simon Xuming Xu, Leo Brueggeman, Taylor R. Thomas, Olena Marchenko, Christopher Fleisch, Sarah D. Barns, LeeAnne Green Snyder, Bing Han, Timothy S. Chang, Tychele N. Turner, William Harvey, Andrew Nishida, Brian J. O'Roak, Daniel H. Geschwind, The SPARK Consortium, Jacob J. Michaelson, Natalia Volfovsky, Evan E. Eichler, Yufeng Shen, Wendy K. Chung

doi: https://doi.org/10.1101/2021.10.08.21264256

Rare coding variation illuminates the allelic architecture, risk genes, cellular expression patterns, and phenotypic context of autism

Jack M. Fu, F. Kyle Satterstrom, Minshi Peng, Harrison Brand, Ryan L. Collins, Shan Dong, Lambertus Klei, Christine R. Stevens, Caroline Cusick, Mehrtash Babadi, Eric Banks, Brett Collins, Sheila Dodge, Stacey B. Gabriel, Laura Gauthier, Samuel K. Lee, Lindsay Liang, Alicia Ljungdahl, Behrang Mahjani, Laura Sloofman, Andrey Smirnov, Mafalda Barbosa, Alfredo Brusco, Brian H.Y. Chung, Michael L. Cuccaro, Enrico Domenici, Giovanni Battista Ferrero, Jay J. Gargus, Gail E. Herman, Irva Hertz-Picciotto, Patricia Maciel, Dara S. Manoach, Maria Rita Passos-Bueno, Antonio M. Persico, Alessandra Renieri, Flora Tassone, Elisabetta Trabetti, Gabriele Campos, Marcus C.Y. Chan, Chiara Fallerini, Elisa Giorgio, Ana Cristina Girard, Emily Hansen-Kiss, So Lun Lee, Carla Lintas, Yunin Ludena, Rachel Nguyen, Lisa Pavinato, Margaret Pericak-Vance, Isaac Pessah, Evelise Riberi, Rebecca Schmidt, Moyra Smith, Claudia I.C. Souza, Slavica Trajkova, Jaqueline Y.T. Wang, Mullin H.C. Yu, The Autism Sequencing Consoritum (ASC), Broad Institute Center for Common Disease Genomics (Broad-CCDG), iPSYCH-BROAD Consortium, David J. Cutler, Silvia De Rubeis, Joseph D. Buxbaum, Mark J. Daly, Bernie Devlin, Kathryn Roeder, Stephan J. Sanders, Michael E. Talkowski

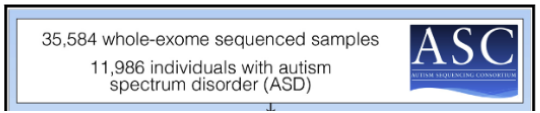
doi: https://doi.org/10.1101/2021.12.20.21267184

Cell

Article

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

Graphical Abstract



Authors

F. Kyle Satterstrom, Jack A. Kosmicki, Jiebiao Wang, ..., Kathryn Roeder, Mark J. Daly, Joseph D. Buxbaum

Correspondence

Article | Published: 26 July 2021

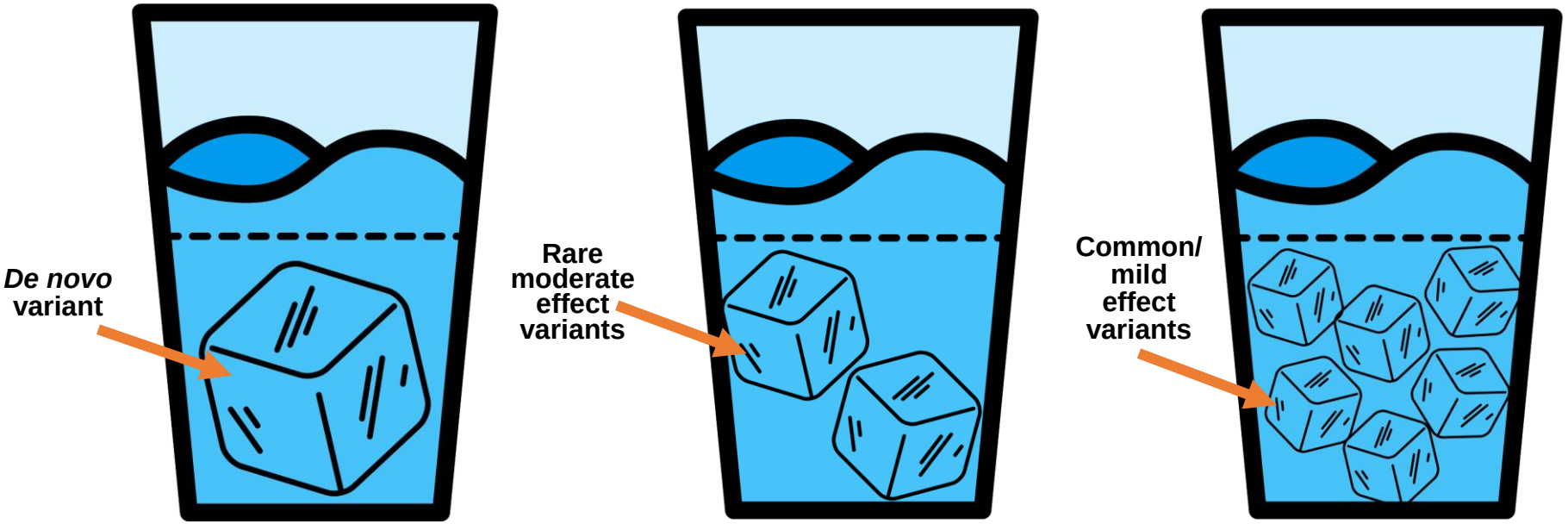
Recent ultra-rare inherited variants implicate new autism candidate risk genes

Amy B. Wilfert, Tychele N. Turner, Shwetha C. Murali, PingHsun Hsieh, Arvis Sulovari, Tianyun Wang, Bradley P. Coe, Hui Guo, Kendra Hoekzema, Trygve E. Bakken, Lara H. Winterkorn, Uday S. Evani, Marta Byrska-Bishop, Rachel K. Earl, Raphael A. Bernier, The SPARK Consortium, Michael C. Zody & Evan E. Eichler

Nature Genetics **53**, 1125–1134 (2021) | Cite this article

Different genetic variants, different effects

- Each person with autism has a unique set of environmental and genetic factors that contribute to their condition.
- In some cases, people may have one *de novo* variant of large effect. Other people might have multiple variants of moderate effects.
- You can think of genetic variants associated with autism as ice cubes of varying sizes in a cup of water, with the line representing a threshold for the diagnosis of autism.



A phenotypic spectrum of autism is attributable to the combined effects of rare variants, polygenic risk and sex

- Multiple types of genetic events -- strong effect variants that appear in one person and are very unlikely to be passed down, moderate rare variants that can be transmitted but tend not to be, and common variants that are present throughout the population but may combine to increase the chance that someone has autism – all work together in various ways to lead to autism. They built a prediction score of genetic contribution that considers all these factors.
- Females have more of this genetic contribution than males do, suggesting that it takes more of these genetic factors for autism to present in females.
- When people have more of the common ‘mild’ effect variants they have less of the strong rare ones, and vice versa, supporting that these all work together.

Danny Anataki

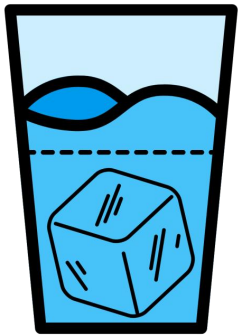
Jonathan Sebat

Antaki, D., Guevara, J., Maihofer, A.X. *et al.* A phenotypic spectrum of autism is attributable to the combined effects of rare variants, polygenic risk and sex. *Nat Genet* **54**, 1284–1292 (2022). https://doi.org/10.1038/s41588-022-01064-5

Rare coding variation illuminates the allelic architecture, genes, cellular expression patterns, and phenotypic context of autism

- Significant overlap with genes found in people with developmental delay/intellectual disability and people with autism. But there are some genes that contribute more to one or the other.

- Autism gene-products are enriched in more mature neurons (appear later in fetal development) whereas genes associated predominantly with intellectual disabilities are active in very early progenitor neuronal cells.

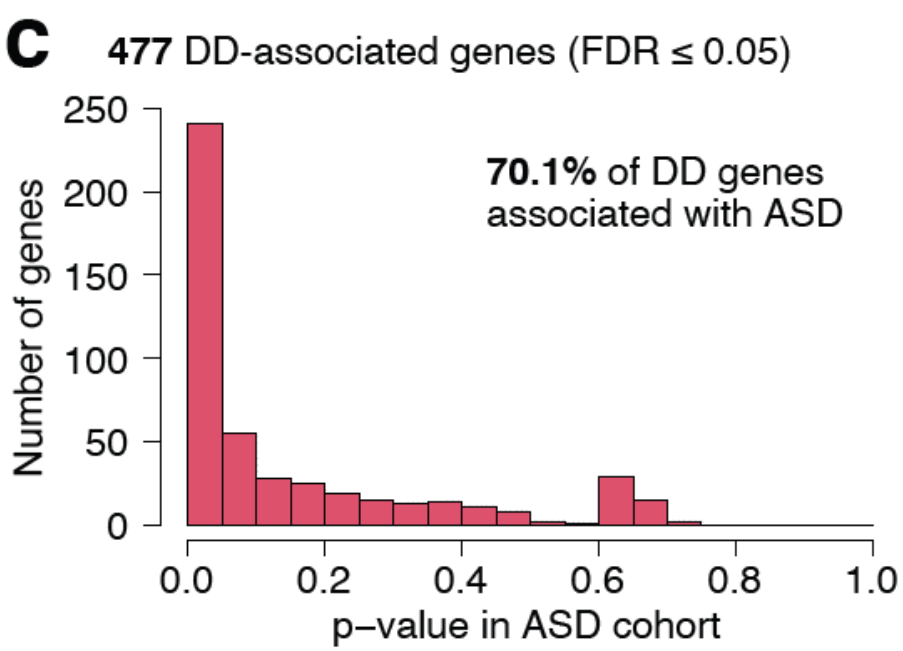


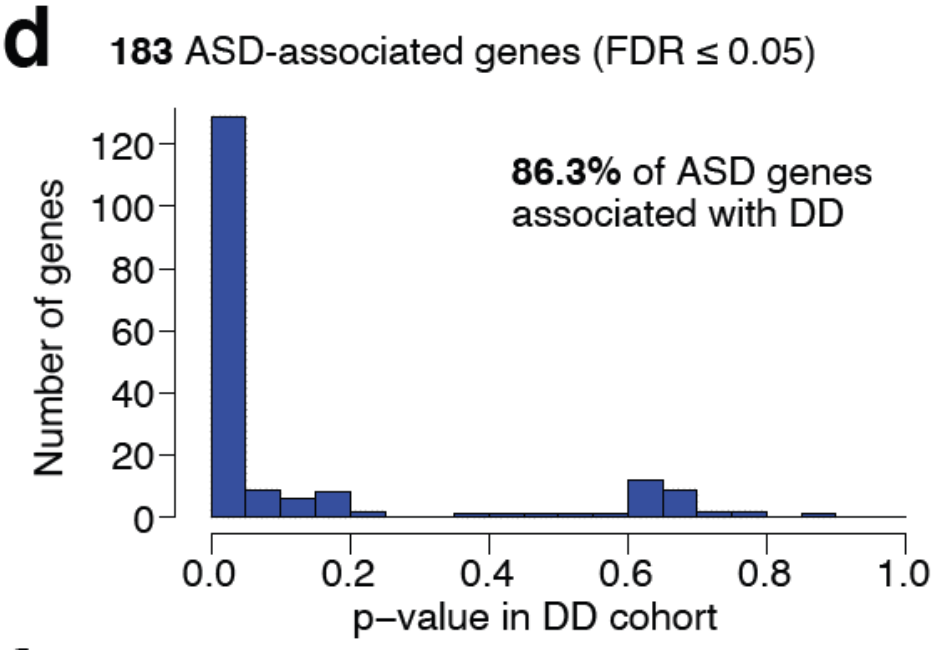
Jack Fu

Mike Talkowski

Fu, J.M., Satterstrom, F.K., Peng, M. *et al.* Rare coding variation provides insight into the genetic architecture and phenotypic context of autism. *Nat Genet* **54**, 1320–1331 (2022). https://doi.org/10.1038/s41588-022-01104-0

Fu et al. integrated their data with data from the UK DDD study (31K trios)





86.3% of autism genes are also developmental delay genes

Fu, J.M., Satterstrom, F.K., Peng, M. *et al.* Rare coding variation provides insight into the genetic architecture and phenotypic context of autism. *Nat Genet* **54**, 1320–1331 (2022). https://doi.org/10.1038/s41588-022-01104-0

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

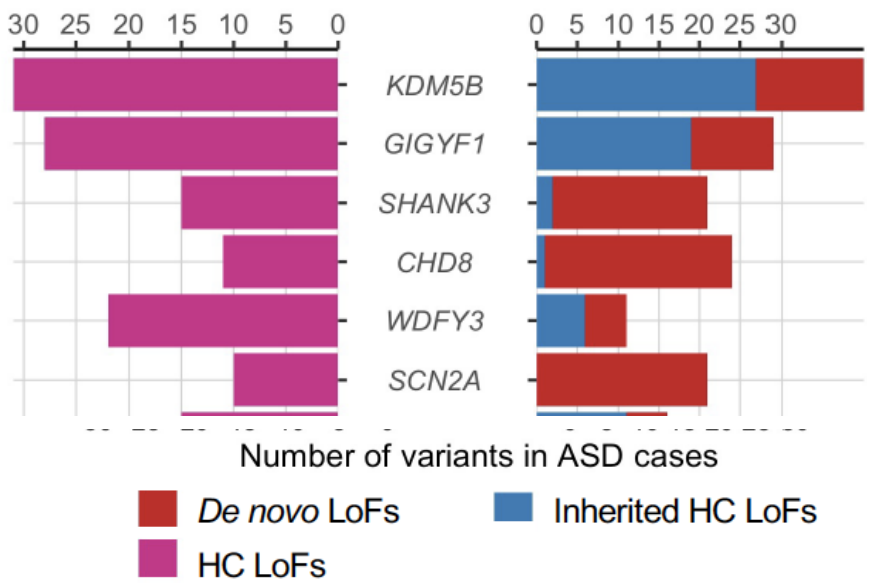
- Most spontaneous, or *de novo* genetic changes linked to autism are in a group of genes mostly already identified.
- Many undiscovered autism-associated genes with genetic variants transmitted from parents
- 5 new genes linked to autism that have moderate effects. (*NAV3*, *ITSN1*, *MARK2*, *SCAF1* and *HNRNPUL2*).
- More genes like these are involved in autism, but even larger numbers of autism participants will be needed to find them.

Xueya Zhou

Pam Feliciano

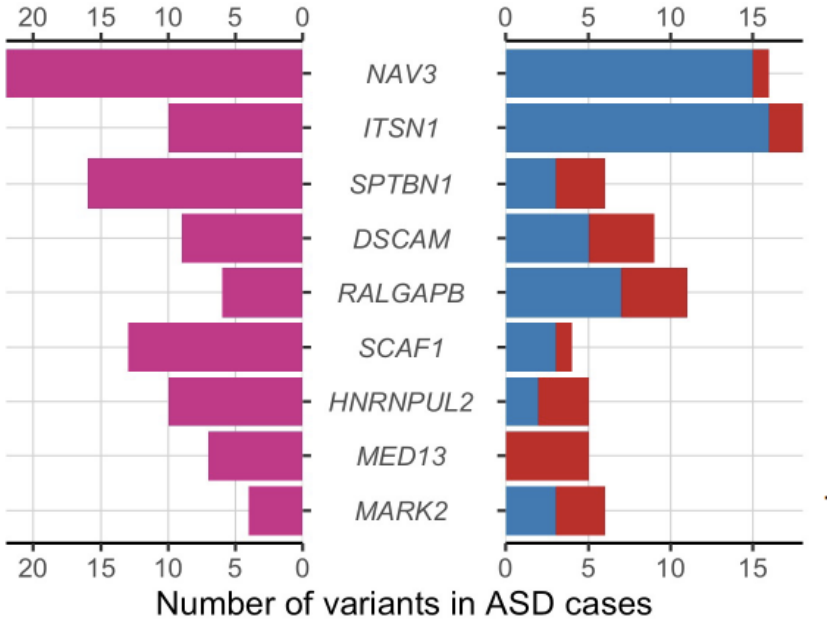
Zhou, X., Feliciano, P., Shu, C. *et al.* Integrating de novo and inherited variants in 42,607 autism cases identifies mutations in new moderate-risk genes. *Nat Genet* **54**, 1305–1319 (2022). https://doi.org/10.1038/s41588-022-01148-2

Genes with transmitted loss of function variants identify new genes with more transmitted variants than *de novo* variants



Known genes

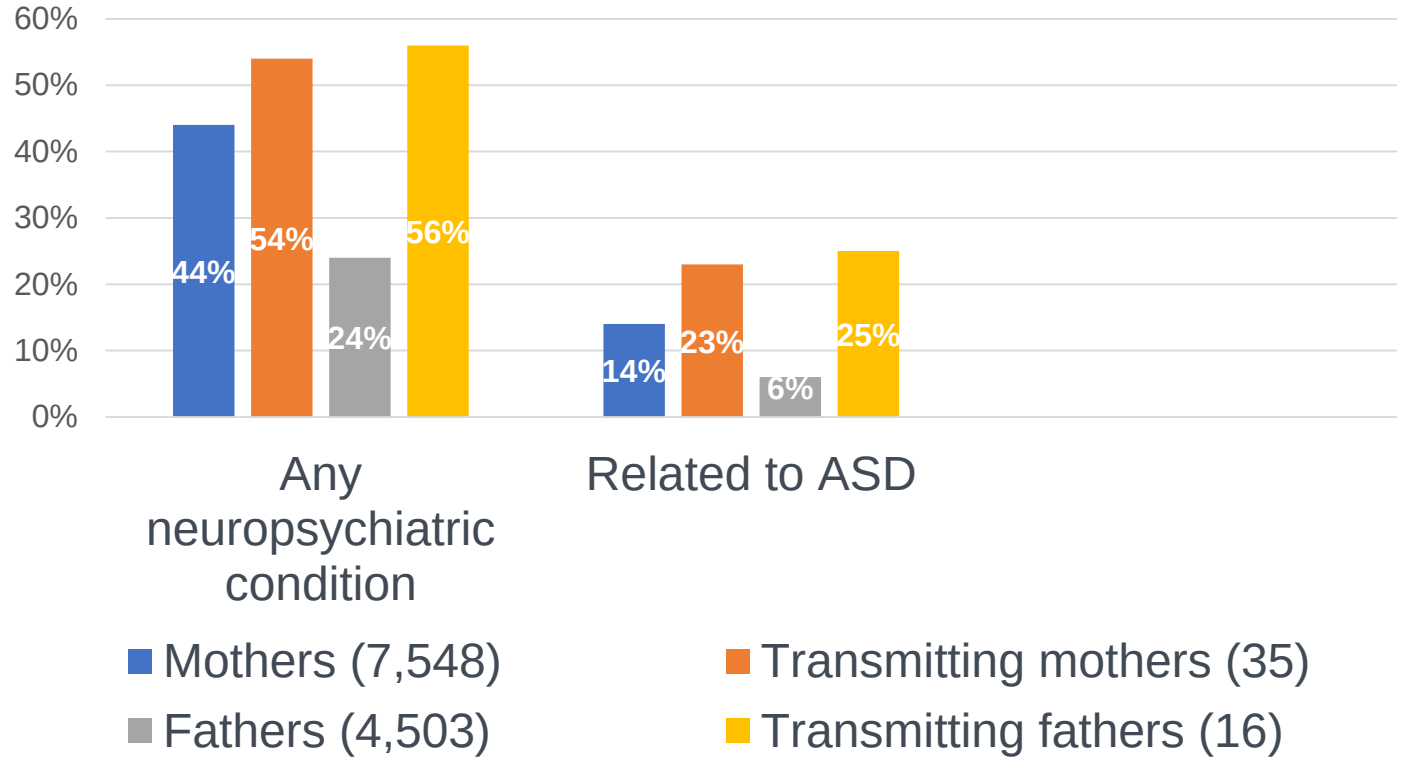
B



New genes

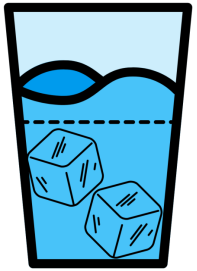
Zhou, X., Feliciano, P., Shu, C. *et al.* Integrating de novo and inherited variants in 42,607 autism cases identifies mutations in new moderate-risk genes. *Nat Genet* **54**, 1305–1319 (2022). https://doi.org/10.1038/s41588-022-01148-2

Percentage of parents with rare LGDs in established ASD genes with mental health phenotypes



ASD related conditions
learning disability, language delay, social anxiety, bipolar disorder, schizophrenia, OCD, personality disorder, cognitive impairment

Any
All of the above plus anxiety, depression, ADHD, sleep disorder



SPARK Research Match

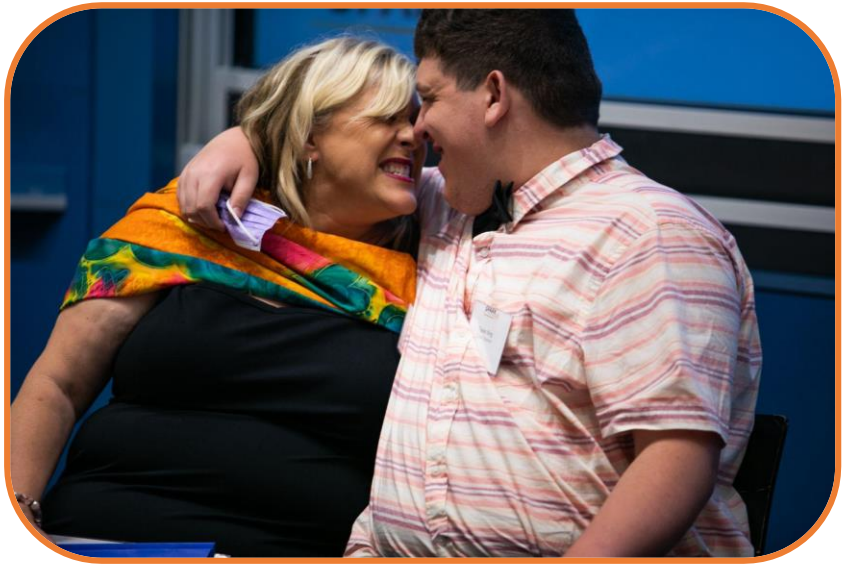
SPARK Research Match invites participants to participate in new research that is not part of the main SPARK study.

Participants can choose to:

- Share their information with the new study team to schedule a visit in-clinic or interview.
- Complete surveys online.

After the research team analyzes their data, they help SPARK communicate the results back to participants and the SPARK community.

What does the future hold?



- ***Continue recruiting!*** We need a larger sample size to capture the diversity of individuals' experiences
- Increase diversity through initiatives including SPARK in Spanish and inclusion efforts
- Follow people over time. Learn about the life course of people with autism and their families
- Retain participants after they turn 18
- Short and quick research surveys
- Continue accelerating all types of research through Research Match
- Gather data using wearable devices
- Discover more about autism genetics and subtypes to fuel evidence-based "precision" treatments and therapies
- SPARK will let participants know if we find genetic variants related to autism and related to certain serious medical conditions