

# SPARK and the Future of Autism Research

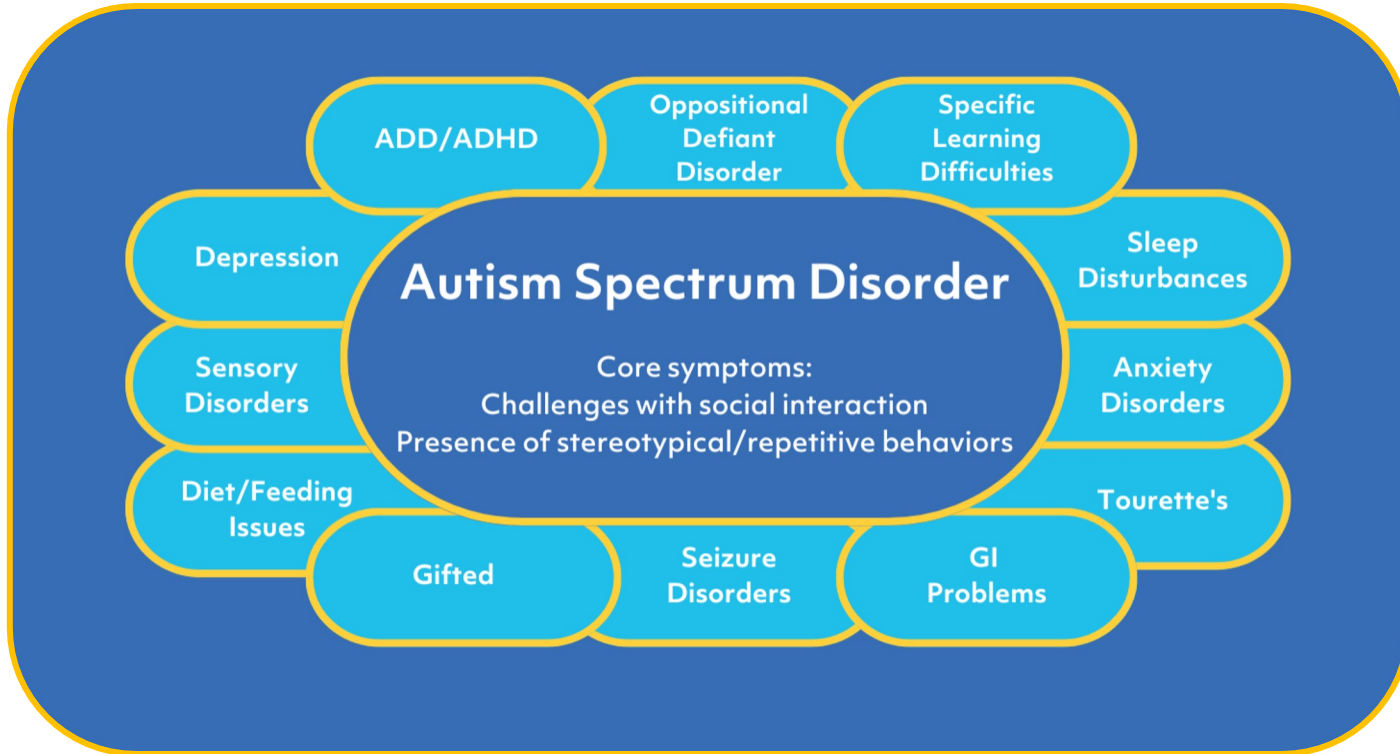
Wendy Chung, M.D., Ph.D.  
April 25, 2023



# Understanding the Spectrum of Autism:

*What's going on in the world of autism research?*

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



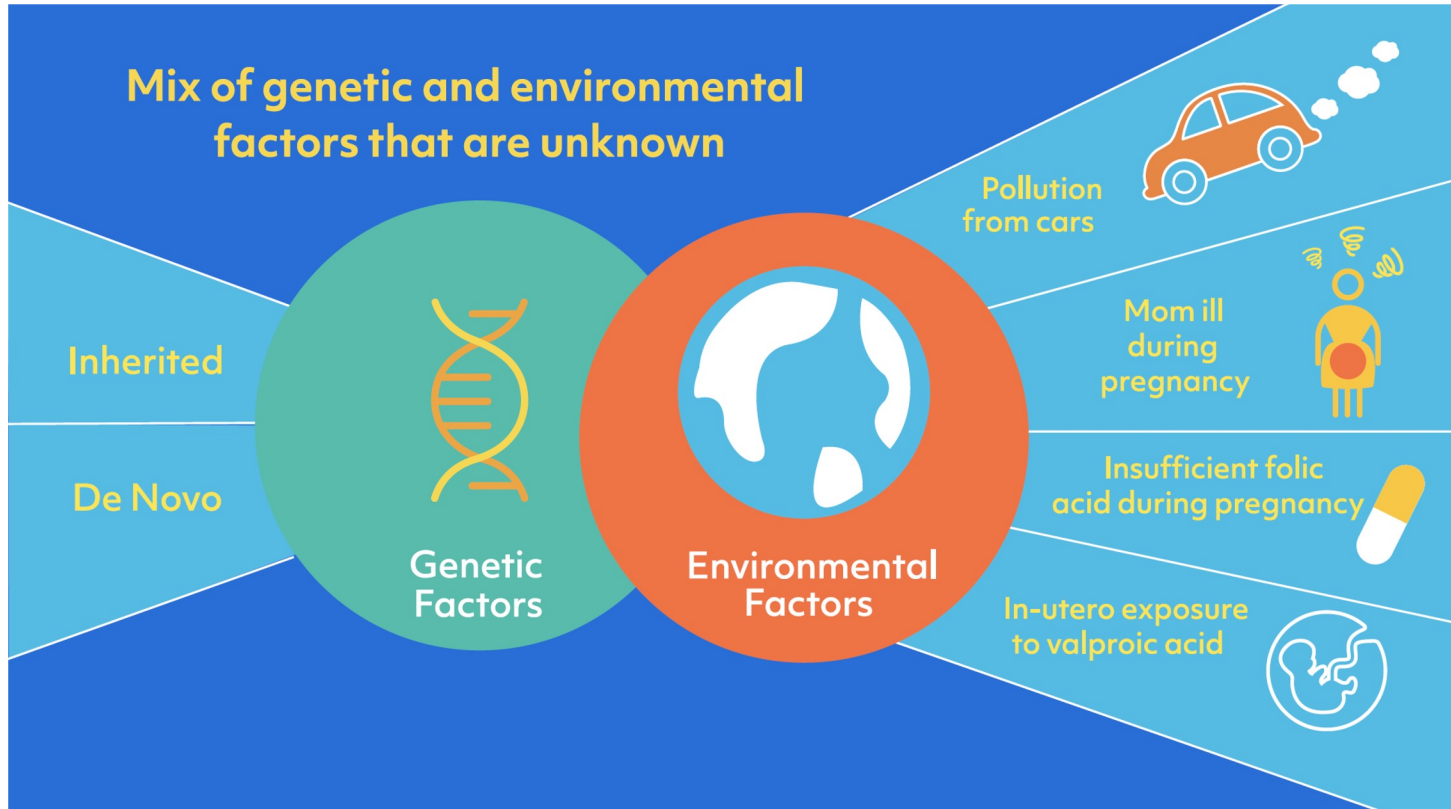
# What is “big data” and why is it important?

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.**



# What are SPARK's goals?

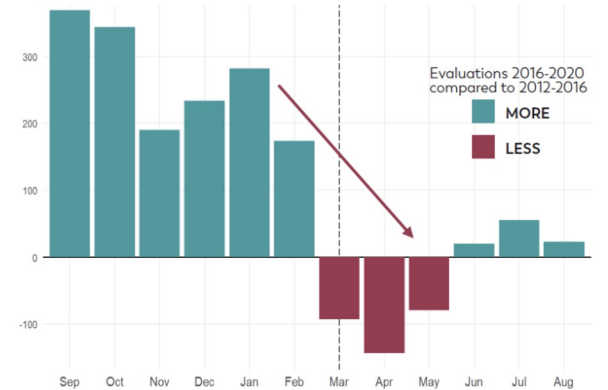


- The goal of SPARK is to better understand the causes of autism and to help improve lives.
- It's about uniting the entire autism research community.

# Autism prevalence

- According to 2020 data from the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network, the prevalence of autism has increased to **about 1 in 36 8-year-old children**.
  - The increase in diagnosis could be largely related to improved access to care, not a significant increase in the actual numbers.
  - Parents are more aware, and more children are being diagnosed → children are going to receive services and treatments earlier, which may increase likelihood of better outcomes.
- Reported to occur in all racial, ethnic, and socio-economic groups.
- 4 times more common among boys than girls.
- The COVID-19 pandemic impacted early ASD-identification.

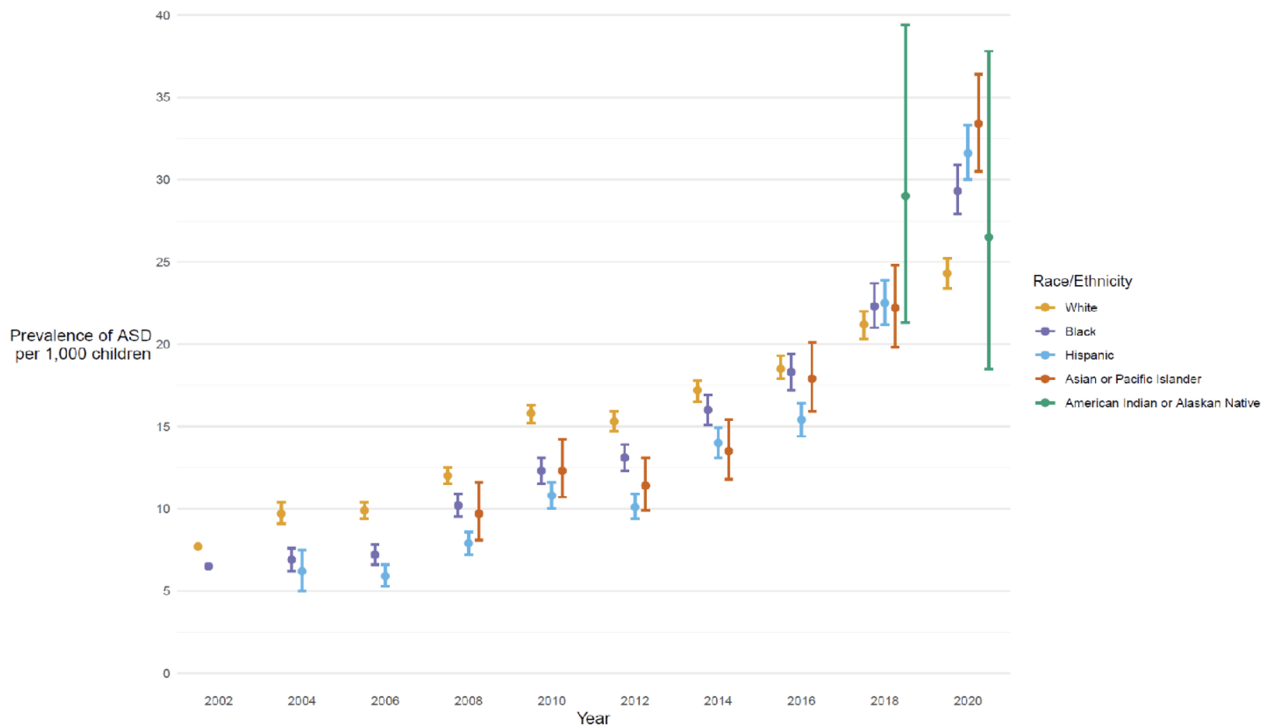
From 2016 to the beginning of 2020, **4-year-old children** had more evaluations and identifications than children aged **8-years** (when they were 4) had from 2012 through 2016.



Displayed as 6 months prior and 6 months post-pandemic

# Autism prevalence by race or ethnicity

Supplementary Figure 1. Reported autism spectrum disorder (ASD) prevalence by race or ethnicity, ADDM Network 2002-2020.





# 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

# How many samples have been sequenced and how many are processing?

- **40,269** families sequenced and analyzed
- **5,932** families sequenced and currently being analyzed
- **4,856** families in process for sequencing
- **1,662** results returned



## Genetic diagnoses in 8-10% of families

### Result characteristics

	Total	Female	Male
	(N=1738)	(N=556)	(N=1182)
Result type			
SNV_INDEL	1060 (61.0%)	369 (66.4%)	691 (58.5%)
CNV	627 (36.1%)	178 (32.0%)	449 (38.0%)
Chromosomal Abnormality	51 (2.9%)	9 (1.6%)	42 (3.6%)

# What has SPARK given back to the community?

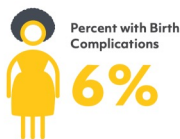


- Transformed the community's experiences into scientific knowledge
- 70,000+ personalized reports from online standardized measures
- Notified families and autistic people about a genetic cause (not all have received actual results)
- Invited participants with a genetic diagnosis to join Simons Searchlight 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.



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

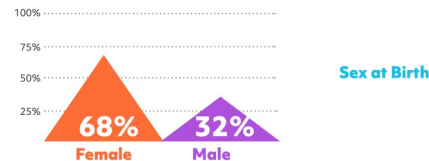
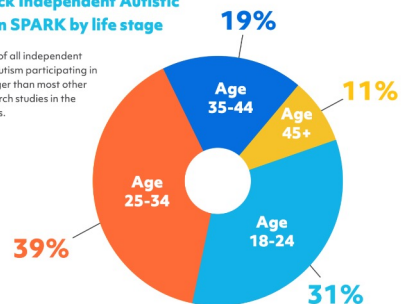
- 46%** Cognitive Impairment
- 39%** ADHD\*
- 23%** Anxiety Disorder
- 14%** Depression
- 11%** Seizures

\*ADHD stands for Attention Deficit Hyperactivity Disorder

## 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.



# 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.



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



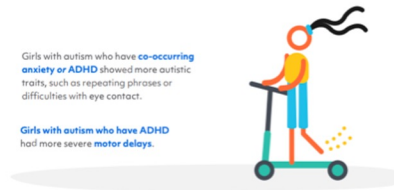
● Boys ● Girls

*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**.

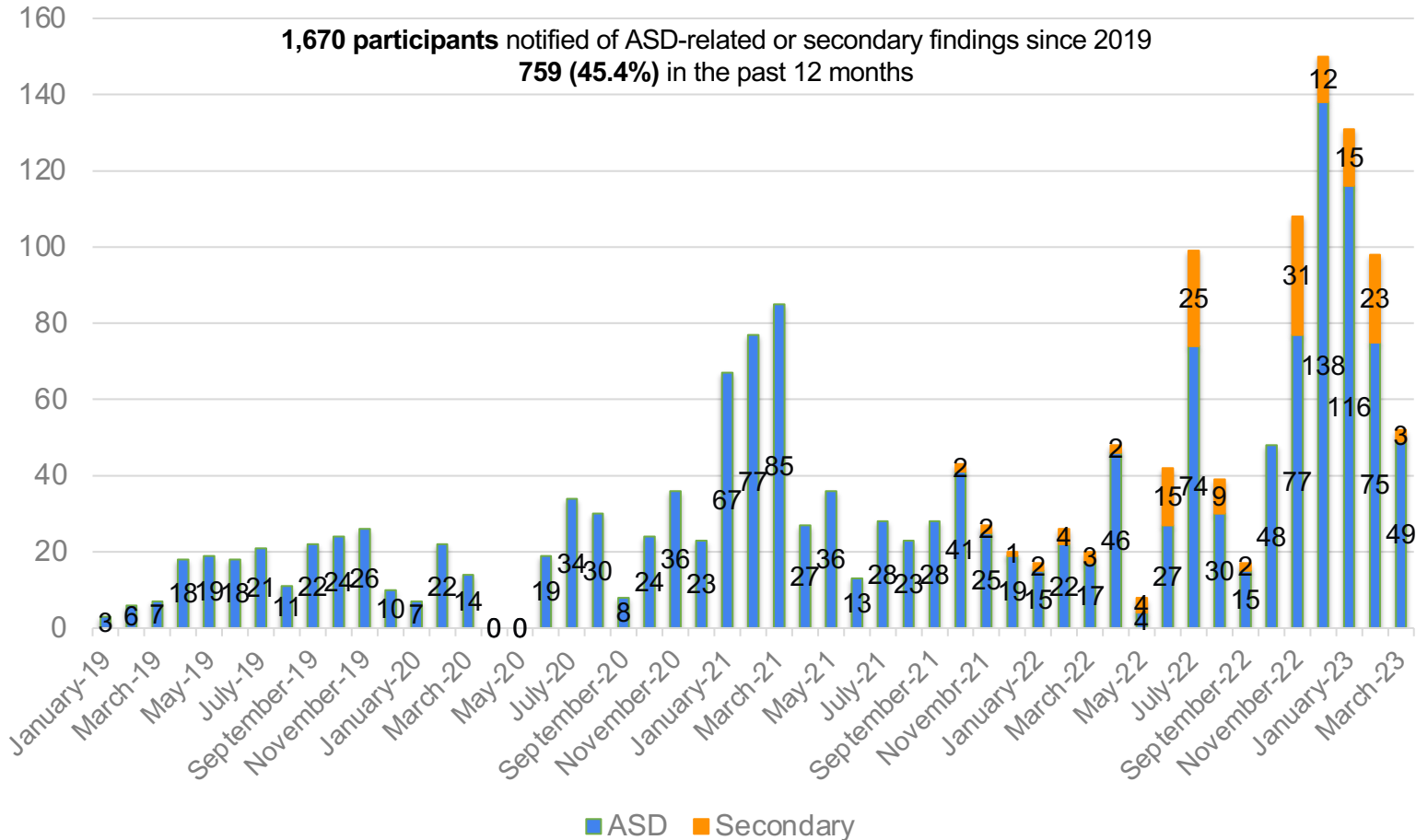


Girls with autism who have **co-occurring anxiety and ADHD** had more **repetitive behaviors** than autistic females with only one co-occurring condition.



# Update on Return of Genetic Results

**1,670 participants** notified of ASD-related or secondary findings since 2019  
**759 (45.4%)** in the past 12 months



**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



E. Fombonne



B. O'Roak

**Table 3** Comparison of EMR abstracted data with SPARK participant data

Categorical variables	N <sup>a</sup>	EMR abstraction N (%)	SPARK participant data N (%)	% agreement	Kappa
Parents concerned before age 3					
Yes	161	132 (82.0)	147 (91.3)	83.3	0.289
No		29 (18.0)	14 (8.7)		
Evidence of language delay					
Yes	226	178 (78.8)	166 (73.5)	75.2	0.321
No		48 (21.2)	60 (26.5)		
Evidence of regression (language and/or other skill)					
Yes	156	36 (23.1)	74 (47.4)	70.5	0.394
No		120 (76.9)	82 (52.6)		
Evidence of motor delay					
Yes	218	51 (23.4)	34 (15.6)	81.2	0.407
No		167 (76.6)	184 (84.4)		
Evidence of prematurity					
Yes	233	43 (18.5)	30 (12.9)	92.7	0.725
No		190 (82.5)	203 (87.1)		
History of seizure (febrile or otherwise)					
Yes	254	44 (17.3)	13 (5.1)	87.8	0.409
No		210 (82.7)	241 (94.9)		
Twin birth					
Yes	181	11 (6.1)	12 (6.6)	98.3	0.861
No		170 (93.9)	169 (93.4)		
Intellectual disability (IQ < 70)					
Yes	146	69 (47.3)	57 (39.0)	71.3	0.418
No		77 (52.7)	89 (61.0)		
Continuous variables	N <sup>a</sup>	EMR abstraction X (SD)	SPARK participant data X (SD)	Correlation <sup>b</sup>	ICC
Age at diagnosis in years, median (IQR)	224	4.0 (2.92–6.98)	3.58 (2.67–5.98)	0.836***	0.947***

ICC intraclass correlation coefficient, IQR interquartile range, IQ intellectual quotient, EMR electronic medical record

<sup>a</sup>This column provides the actual denominator of the sample available for the EMR SPARK comparison (after excluding participants with missing data in one or both datasets)

<sup>b</sup>Spearman correlation coefficient

\*\*\*p < 0.001

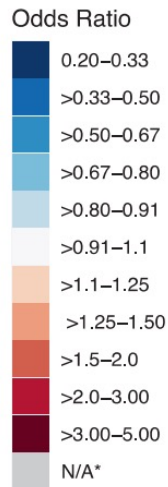
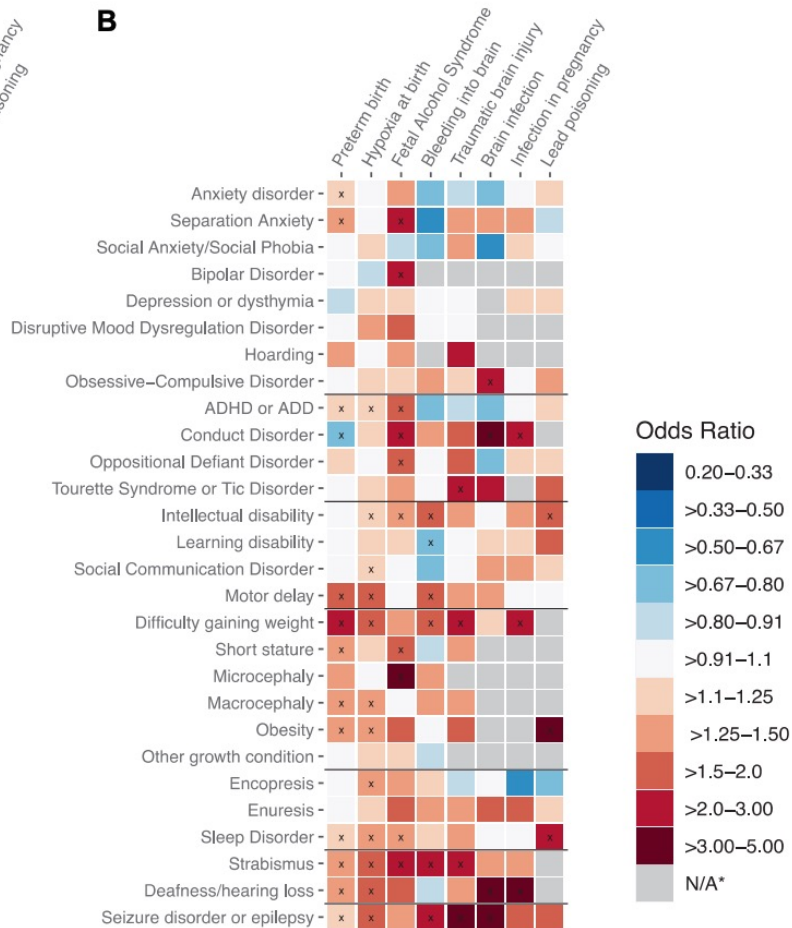
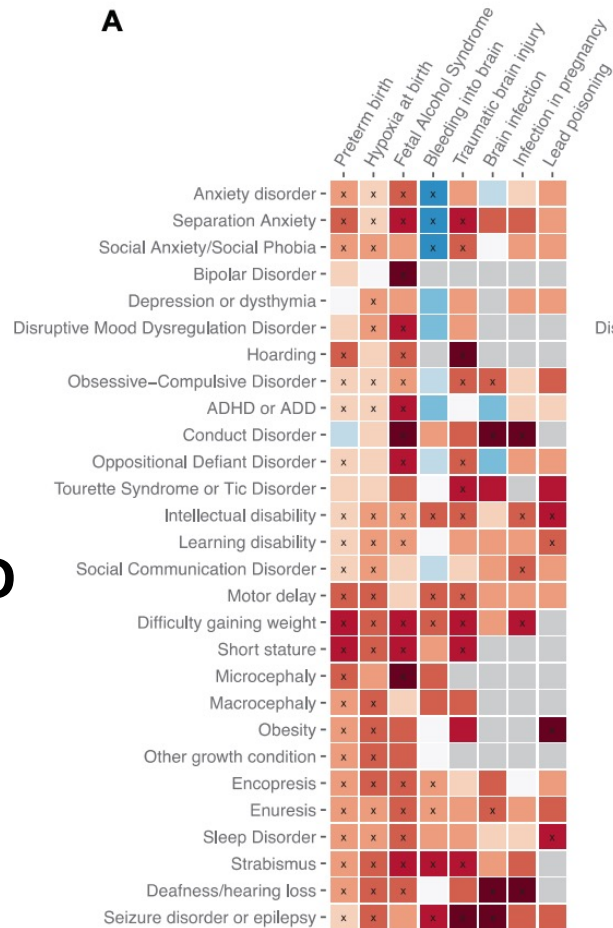
# The association between pre- and postnatal exposures and co-occurring conditions in ASD



V. Khachadourian



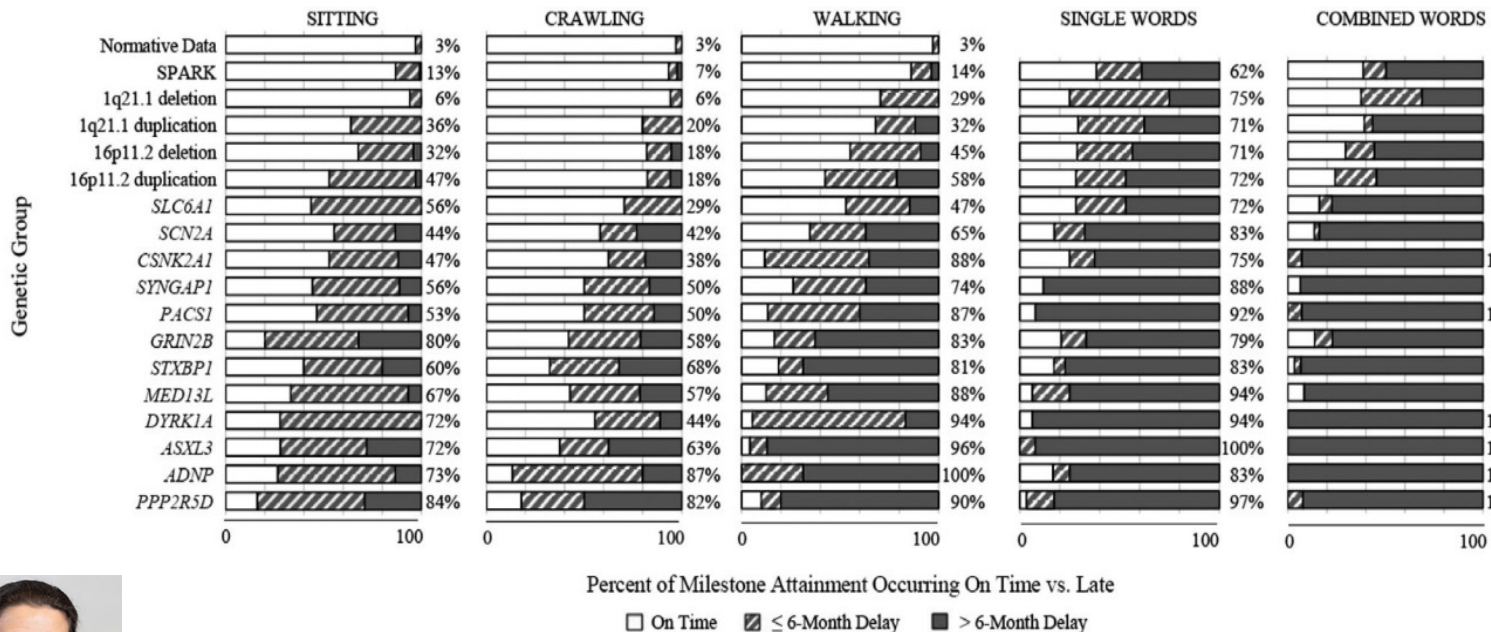
M. Janecka



Khachadourian, V., Mahjani, B., Sandin, S., Kolevzon, A., Buxbaum, J. D., Reichenberg, A., & Janecka, M. (2023). Comorbidities in autism spectrum disorder and their etiologies. *Translational psychiatry*, 13(1), 71. <https://doi.org/10.1038/s41398-023-02374-w>



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



J. Wickstrom



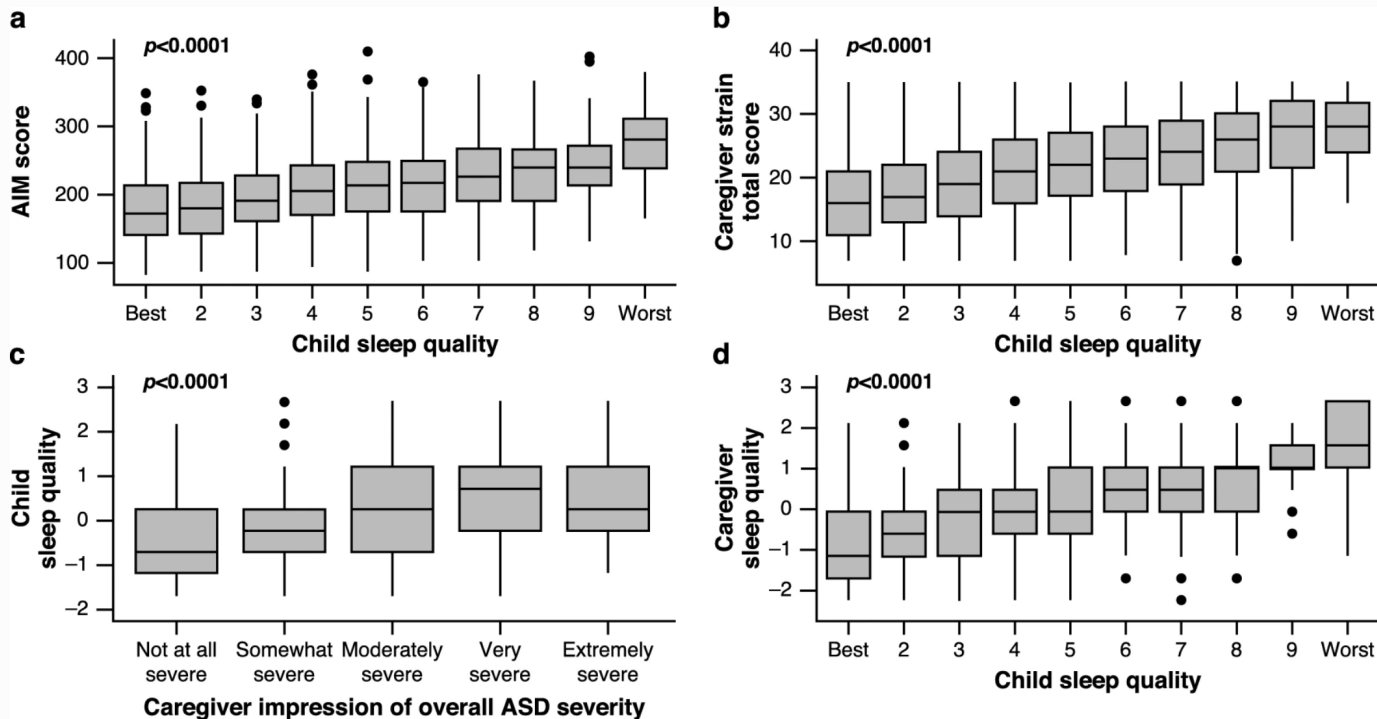
A. Thurm

**Figure 1.**

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

From: [Effect of Children's Autism Spectrum Disorder Severity on Family Strain and Sleep Quality: A Cross-Sectional Online Survey in the U.S.](#)



G. Durán-Pacheco

G. 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 increase likelihood of early ASD diagnosis



N. Jadav



V. Bal

**TABLE 5** Logistic regressions for psychiatric conditions by age of ASD diagnosis (<21 and 21+)

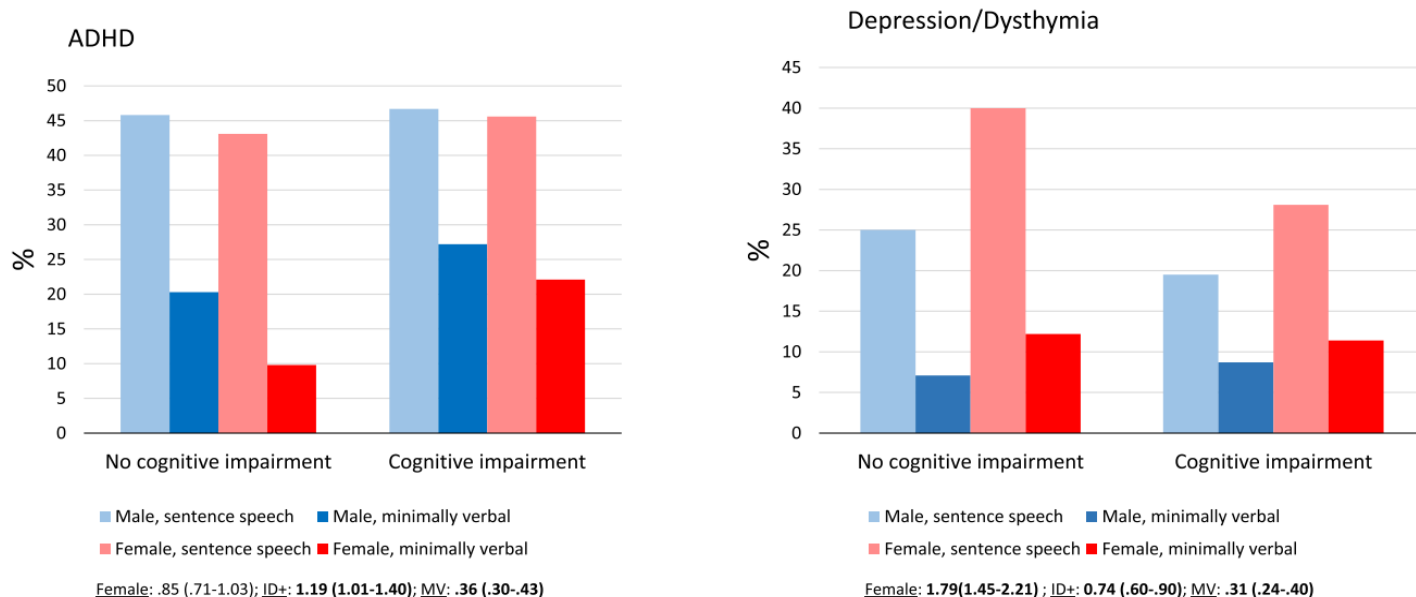
	<21 (N = 2439)		21+ (N = 2210)		OR	CI
	N	%	N	%		
<b>Mood, depression, anxiety or OCD</b>						
Anxiety disorder (e.g., GAD) except for social anxiety	1212	49.7	1320	59.7	<b>1.907</b>	1.653–2.201
Social anxiety disorder/social phobia	803	32.9	894	40.5	<b>1.472</b>	1.277–1.696
Separation anxiety	290	11.9	237	10.7	0.868	0.701–1.075
Obsessive-compulsive disorder	567	23.2	559	25.3	<b>1.281</b>	1.092–1.503
Hoarding	117	4.8	122	5.5	0.824	0.609–1.115
Depression or dysthymia	1127	46.2	1336	60.5	<b>1.900</b>	1.652–2.185
Bipolar (manic-depressive) disorder	391	16.0	362	16.4	1.153	0.959–1.387
Any anxiety disorders (first 3)	1459	59.8	1581	71.5	<b>2.196</b>	1.886–2.557
Any affective disorder (last 3)	1271	52.1	1445	65.4	<b>1.905</b>	1.652–2.197
Any emotional/affective disorder (any of the above eight disorders)	1731	71.0	1820	82.4	<b>2.386</b>	2.011–2.831
<b>Attention and behavior disorders</b>						
ADHD (attention deficit-hyperactivity disorder) or ADD	1119	45.9	927	41.9	1.093	0.952–1.254
Conduct disorder	50	2.1	38	1.7	0.769	0.462–1.280
Oppositional defiant disorder	180	7.4	83	3.8	<b>0.639</b>	0.467–0.875
Intermittent explosive disorder	57	2.3	50	2.3	0.938	0.595–1.479
Any disruptive disorder (any of the above 4)	1156	47.4	958	43.3	1.090	0.950–1.250
Schizophrenia, other psychosis or schizoaffective disorder	121	5.0	90	4.1	0.878	0.630–1.224
Tourette's or tic disorder	116	4.8	75	3.4	0.849	0.596–1.210
Other psychiatric condition	235	9.6	292	13.2	1.299	1.049–1.607
<b>Overall psychiatric morbidity</b>						
Any lifetime disorder (excluding other psychiatric condition)	1960	80.4	1928	87.2	<b>2.315</b>	1.908–2.809
Any lifetime disorder	2023	82.9	1981	89.6	<b>2.583</b>	2.097–3.182
Personality disorder	248	10.2	327	14.8	<b>1.361</b>	1.108–1.673
Eating disorder	231	9.5	270	12.2	1.360	1.093–1.691
Any lifetime disorder (including personality and eating)	2032	83.3	2002	90.6	<b>2.707</b>	2.185–3.354

Note: Bolded reflects  $p \leq 0.005$ . OR controlling for age at reporting, intellectual disability, and sex at birth.

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>

# Over two-thirds of independent adults in SPARK diagnosed with at least one mental health condition

Effects of sex, cognitive and language levels on lifetime prevalence



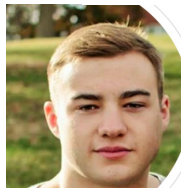
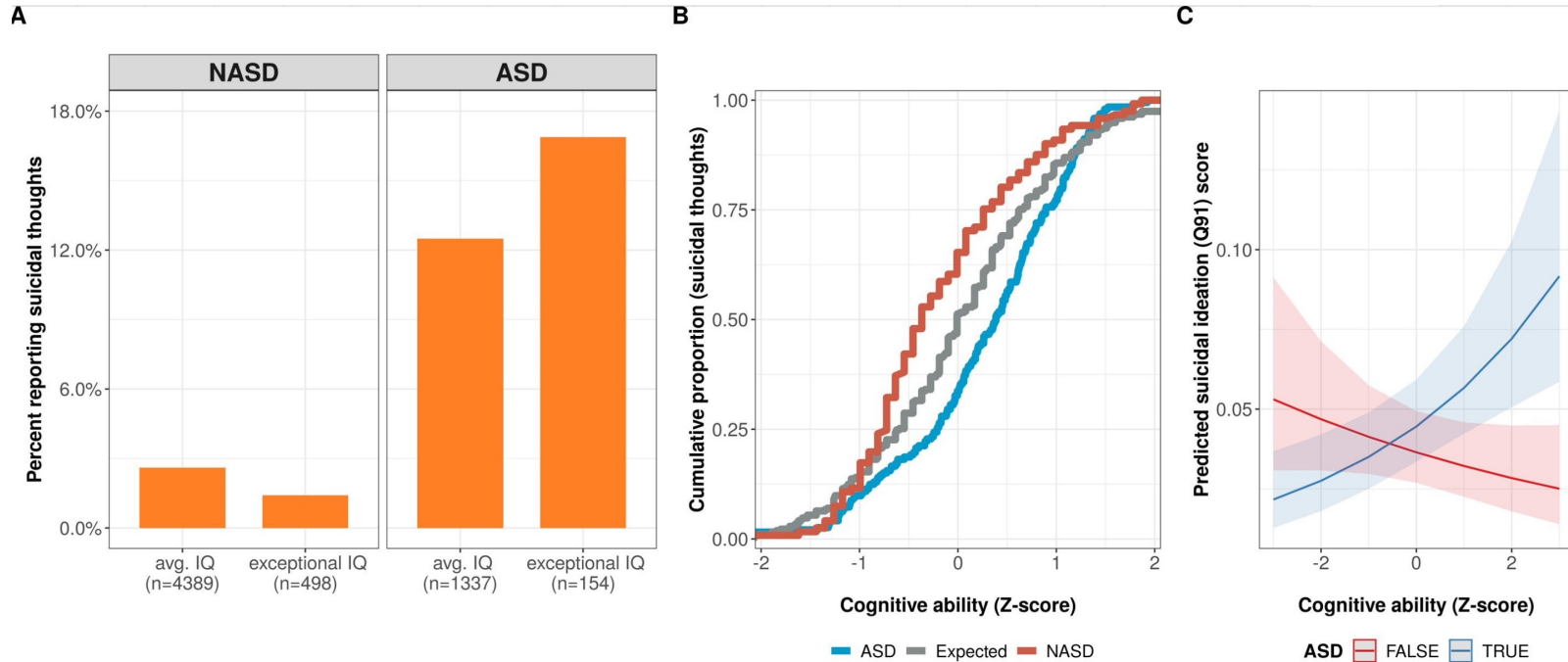
Age-adjusted multiple logistic regression models

**Fig. 2** Effects of sex, cognitive and language levels on lifetime prevalence. Note: Odd-ratios (95% CI) indicate the age-adjusted effect on prevalence to be from female sex, to have co-occurring ID (ID+) or to be non- or minimally verbal (MV)



E. Fombonne

# Association between suicidal ideation and high cognitive ability



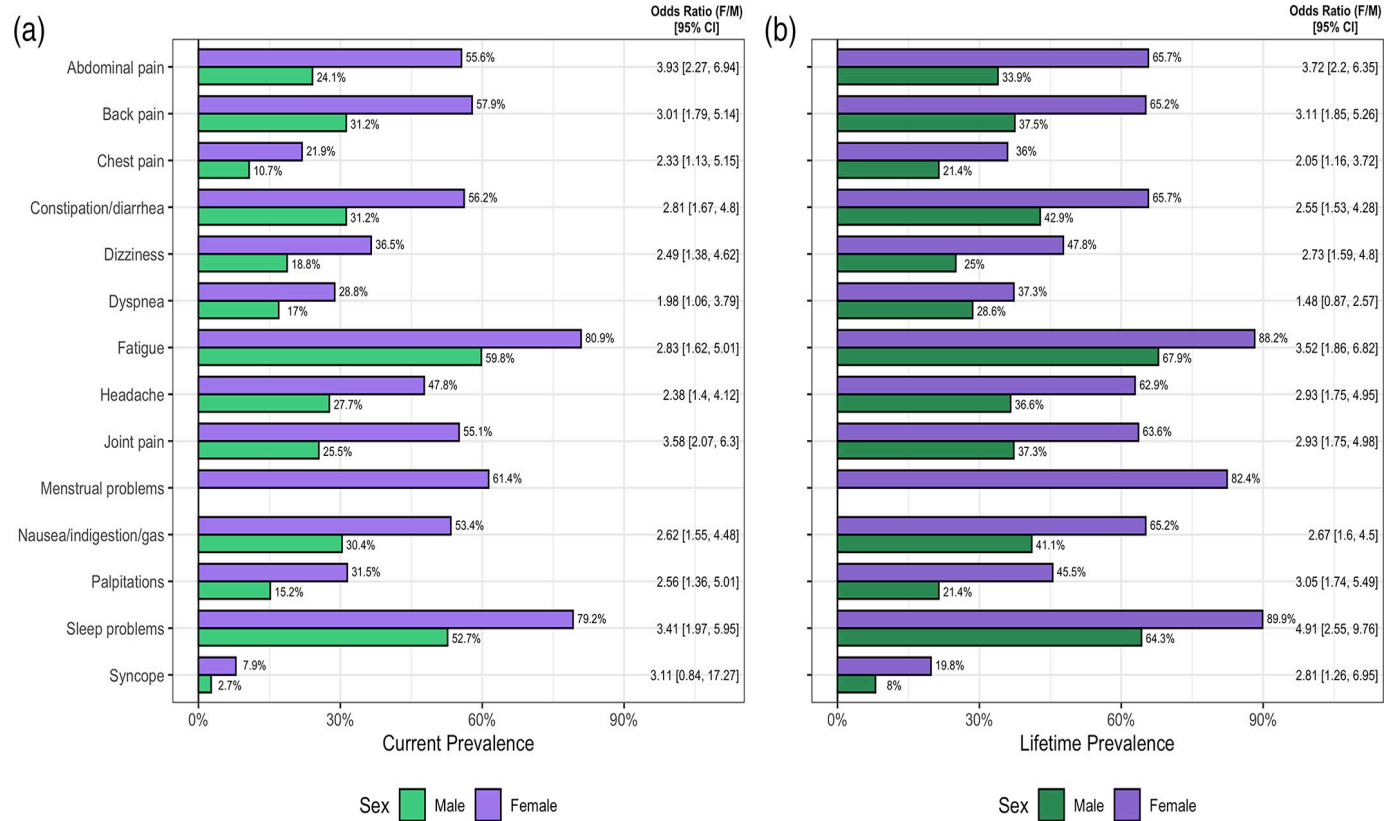
L. Casten



J. 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



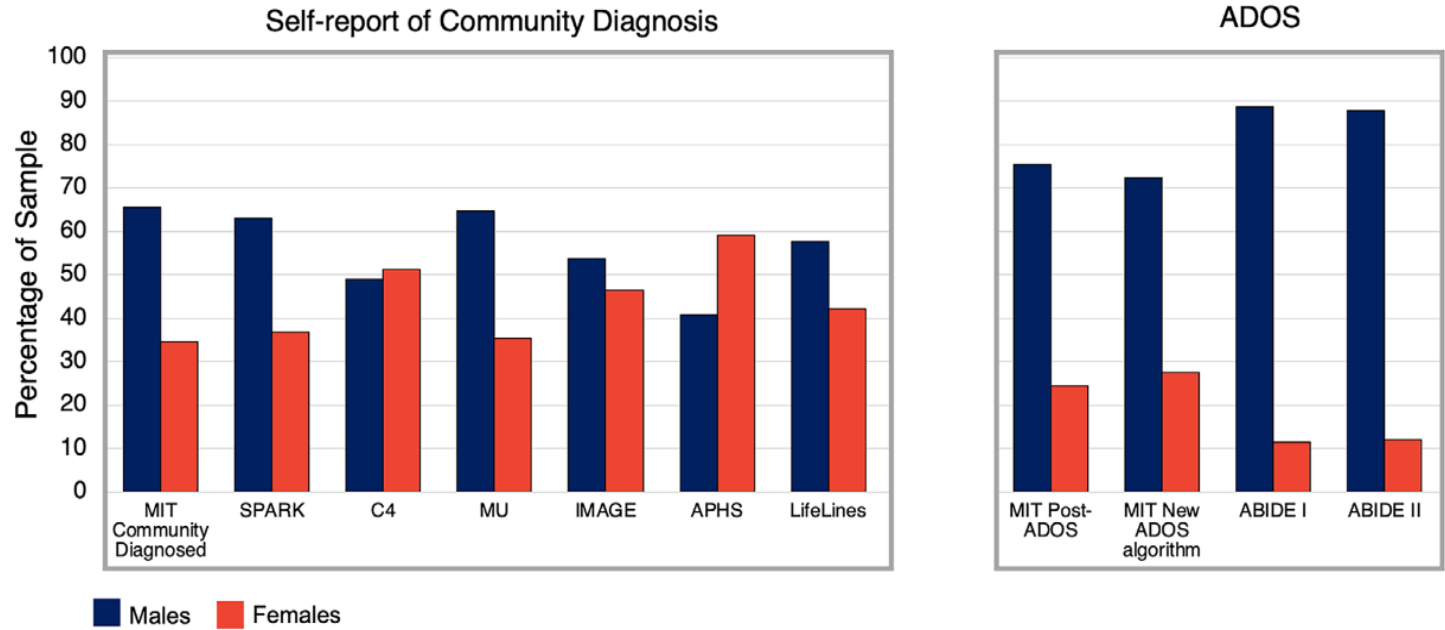
Z. Williams



K. 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.

# Sex bias in research participation based on case definition



A. D'Mello



J. D.E. 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>

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

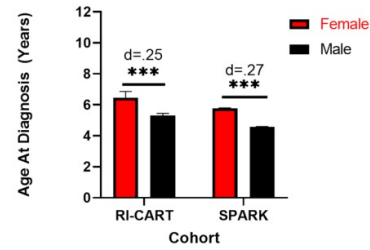


B. Kavanaugh

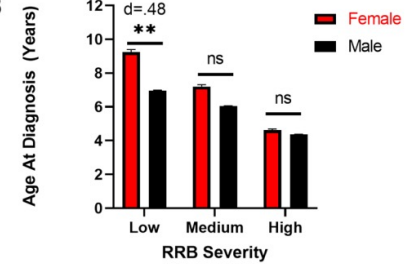


E. Morrow

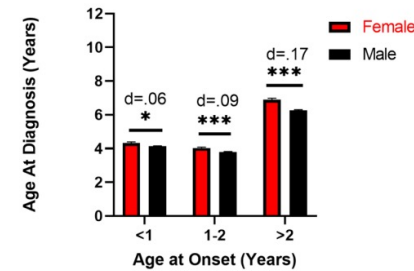
**A** Age at Diagnosis by Sex in RI-CART and SPARK



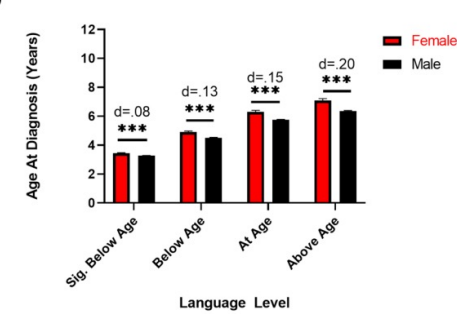
**B** Age at Diagnosis by RRB Severity in RI-CART



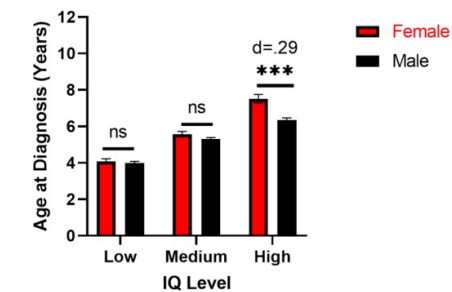
**C** Age at Diagnosis by Age at Onset in SPARK



**D** Age at Diagnosis by Language Level in SPARK



**E** Age at Diagnosis by IQ Level in SPARK





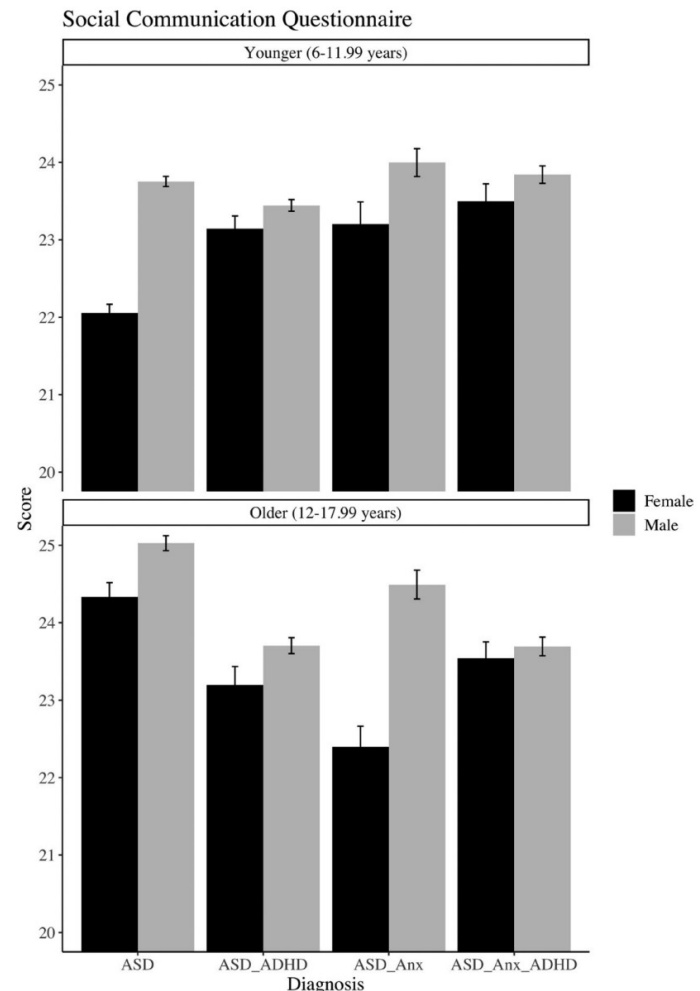
# Symptom presentation and cooccurring mental health conditions in individuals with ASD vary by sex



S. Kanne



E. Wodka



Wodka et al (2022). Co-occurring attention-deficit/hyperactivity disorder and anxiety disorders differentially affect males and females with autism. *The Clinical neuropsychologist*, 36(5), 1069–1093. <https://doi.org/10.1080/13854046.2021.1942554>

# 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?"



A. Weitlauf



Z. 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.

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%)

## SPARK Research:

*How has SPARK data been used to advance our understanding of autism?*

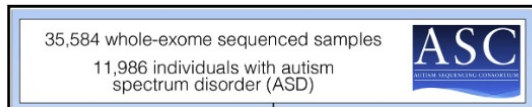
# Many genomic analyses are being performed on SPARK data

Article

Cell

## 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

### 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 Volfvsky, 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 Fallneri, 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 Consortium (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/10.1101/2021.10.08.21267184>

Article | Published: 26 July 2021

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

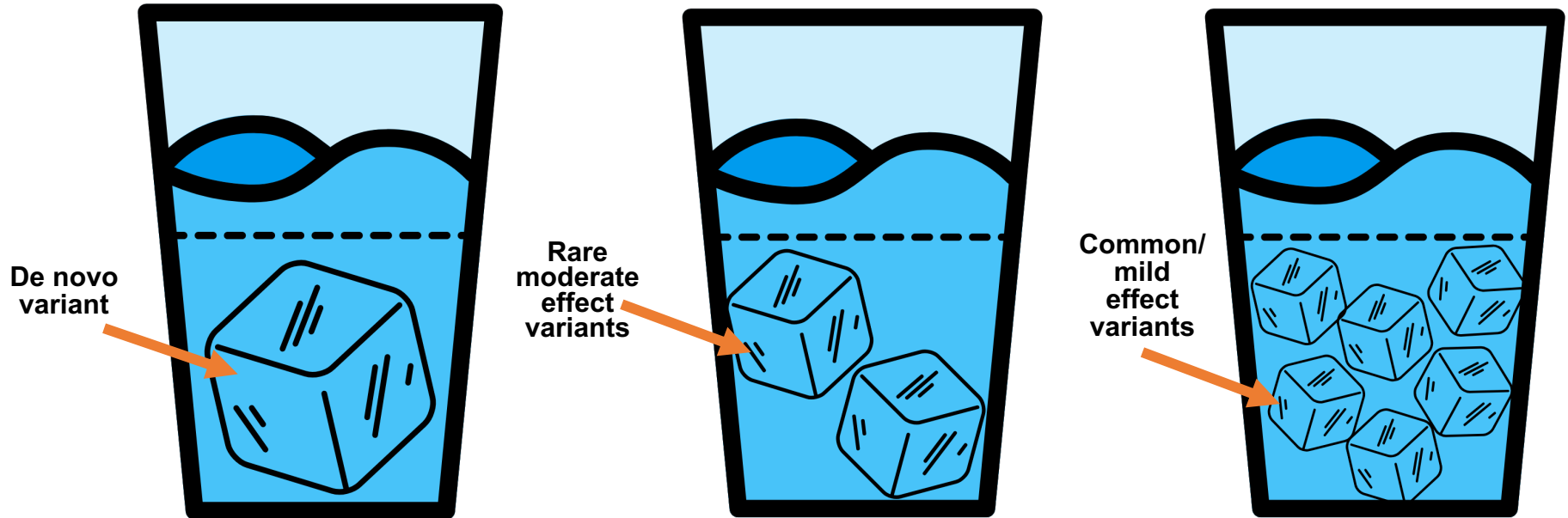
Amy B. Wilfert, Tychele N. Turner, Shwetha C. Murali, PingHsun Hsieh, Arvis Sulovari, Tianyun Wang, Bradley P. Coe, Hui Guo, Kendra Hoekzema, Trygve E. Bakken, Lara H. Winterkorn, Uday S. Evani, Marta Byrska-Bishop, Rachel K. Earl, Raphael A. Bernier, The SPARK Consortium, Michael C. Zody & Evan E. Eichler

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# Different 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 strong 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 brim of the cup representing a diagnosis of autism.
- *De novo* variants have a **strong effect on the presence of autism**. Common/mild effect variants have **milder effects**. When you put smaller ice cubes in a cup, more are needed to help the water rise to the brim.



# Rare coding variation illuminates the allelic architecture, risk 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.



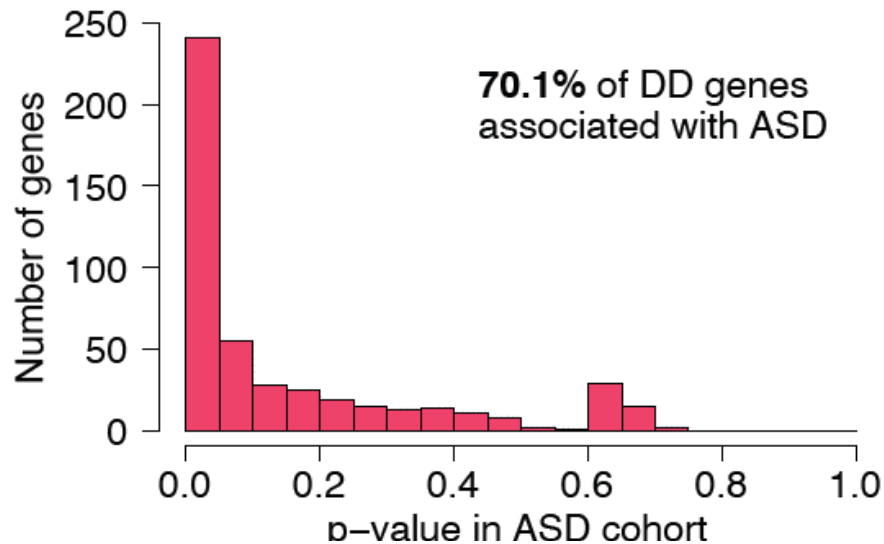
J.M. Fu



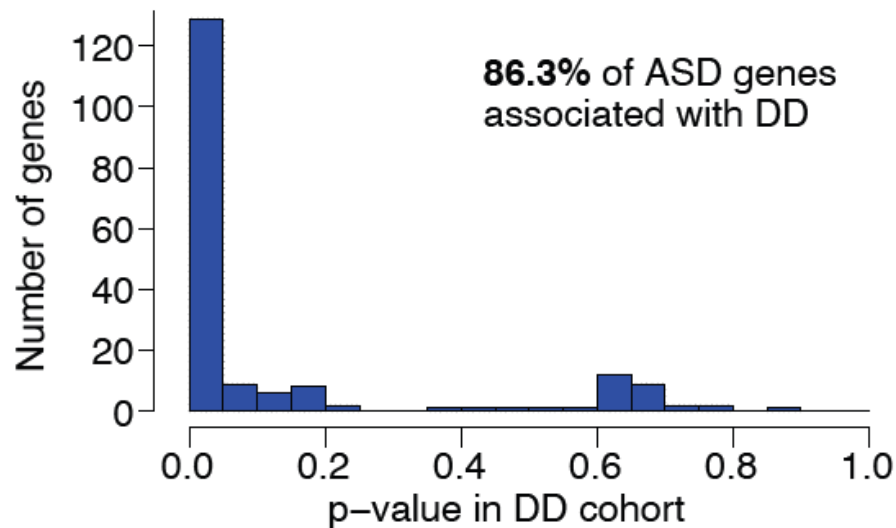
M. Talkowski

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

**c** 477 DD-associated genes (FDR  $\leq 0.05$ )



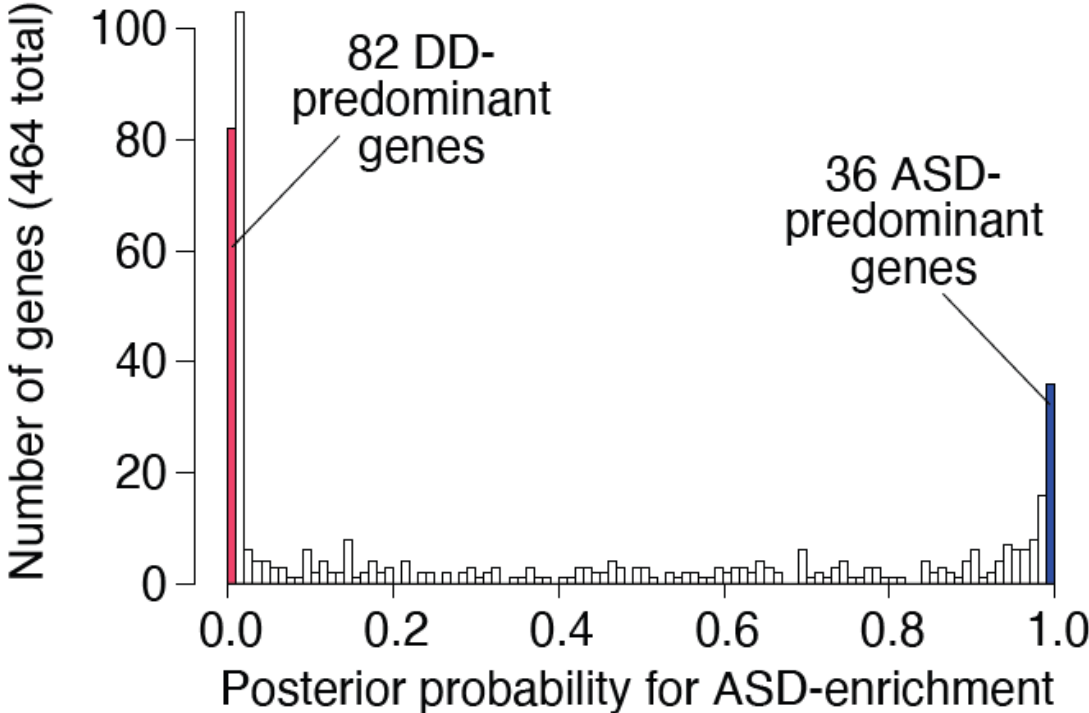
**d** 183 ASD-associated genes (FDR  $\leq 0.05$ )



- 86.3% of autism genes are also developmental delay genes

# 36 genes are predominantly autism genes

**f** Gene membership by cohort



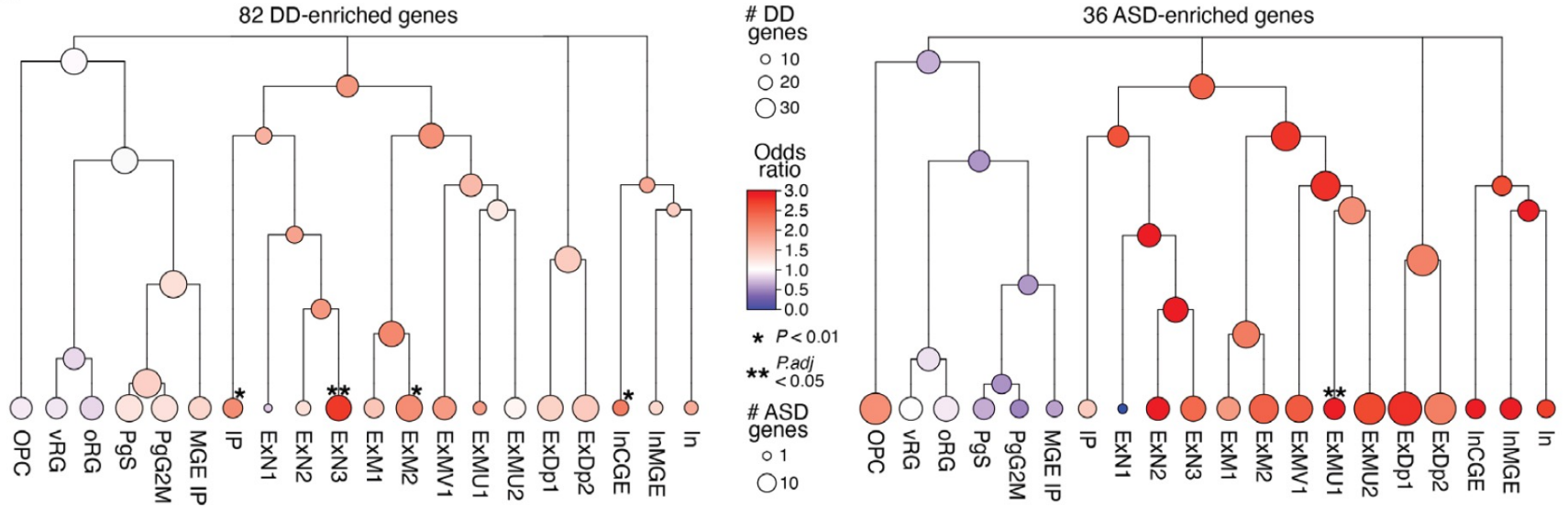
Fu, J.M., Satterstrom, F.K., Peng, M. *et al.* Rare coding variation provides insight into the genetic architecture and phenotypic context of autism. *Nat Genet* 54, 1320–1331 (2022). <https://doi.org/10.1038/s41588-022-01104-0>



# Where/when are autism genes expressed?

**b**

Fetal cortical cell type enrichment



**SHARED GENES:** enriched in both interneurons and excitatory neurons compared to glial and progenitor cells

**UNIQUE GENES:** Developmental delay genes-predominant enrichment in cell types appearing early in the lineages of neurons. Autism predominant genes are strongly enriched in more mature neuron types

# 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.



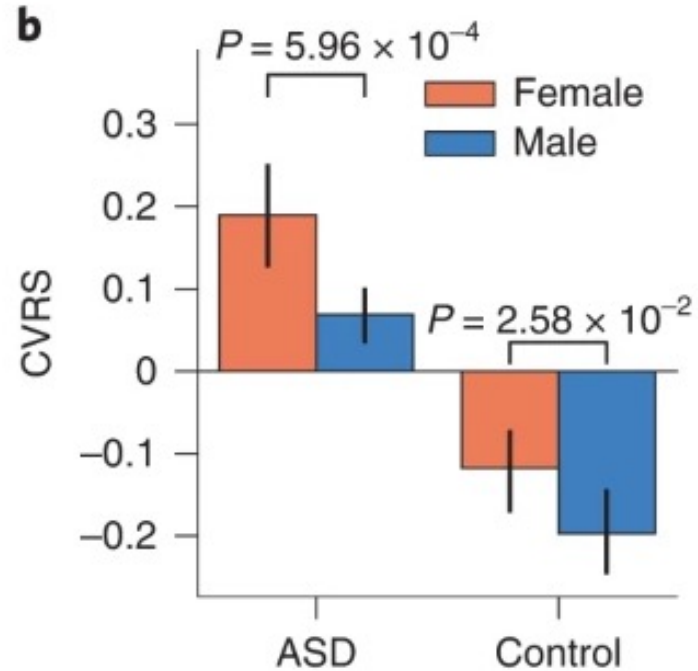
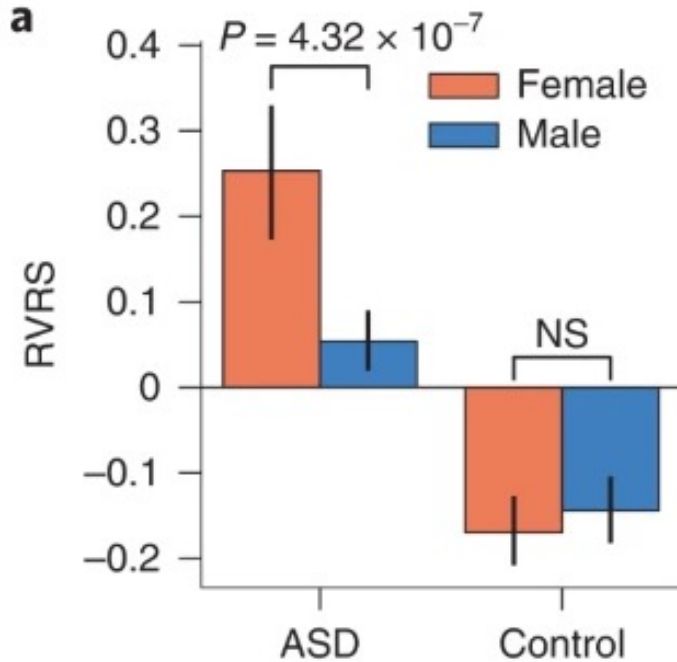
D. Anataki



J. 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>

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



# 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.



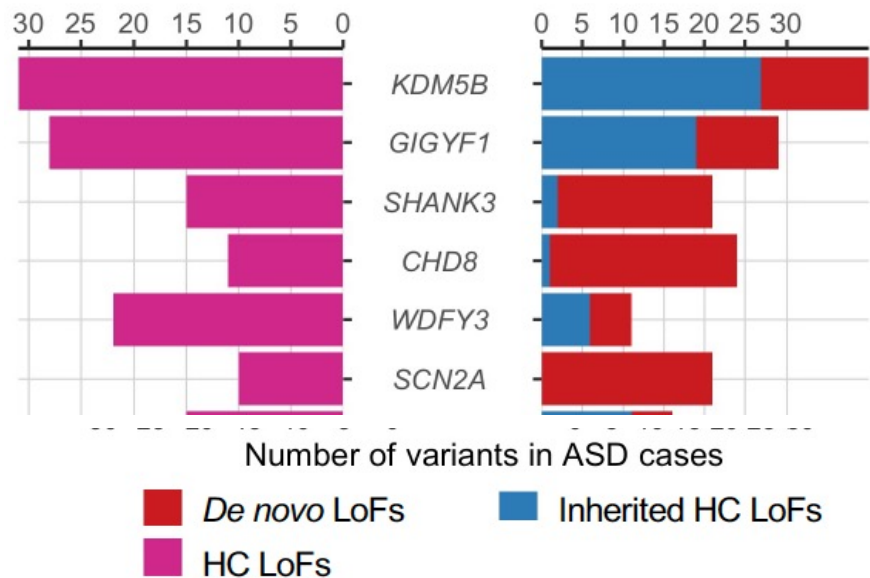
X. Zhou



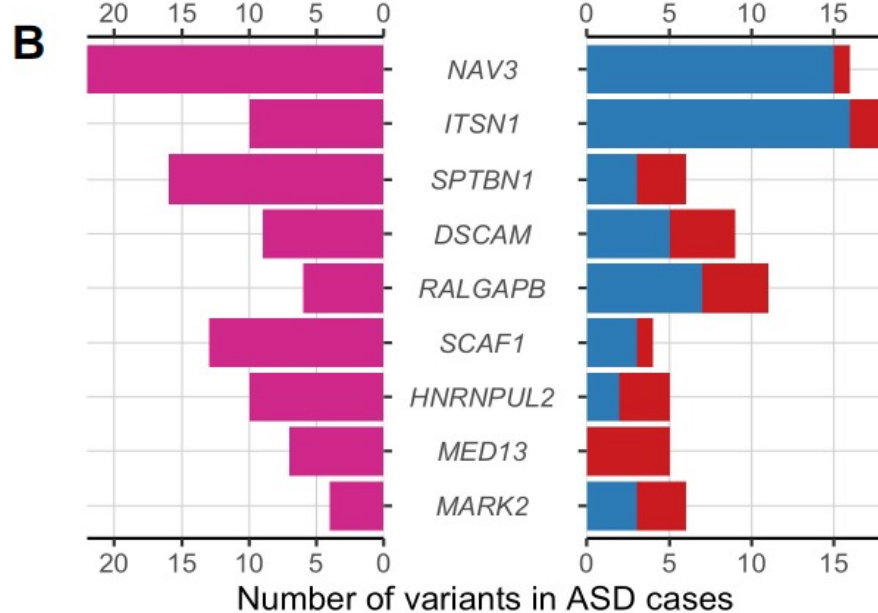
P. Feliciano

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

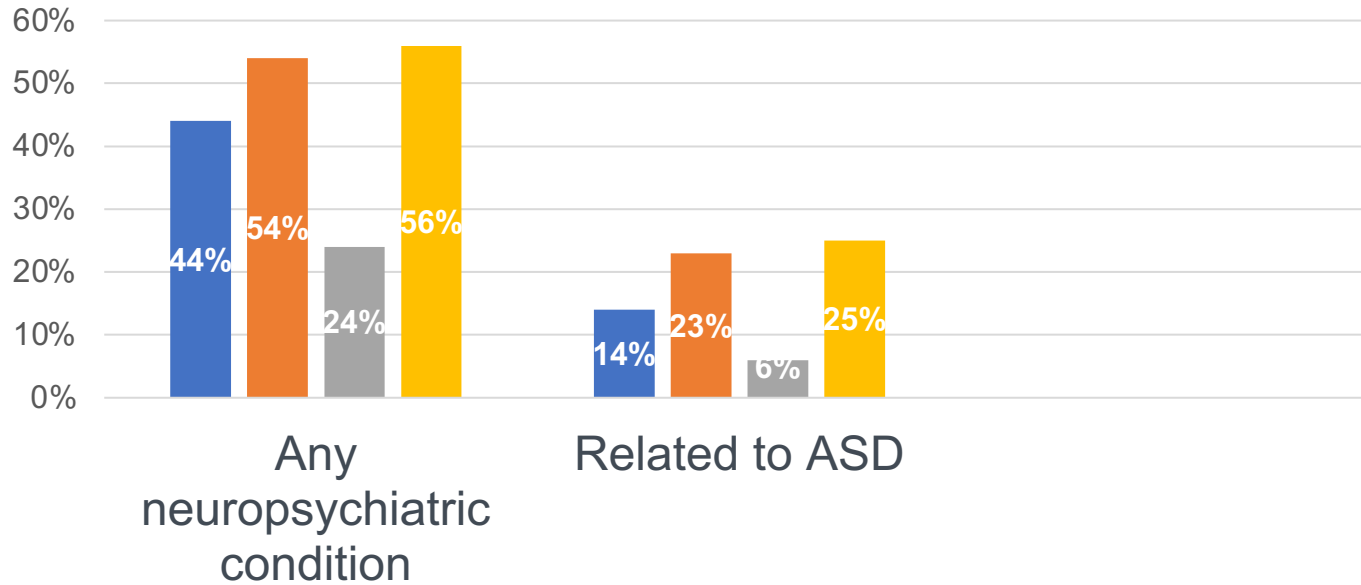


**Known genes**



**New genes**

# 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

■ Mothers (7,548)

■ Transmitting mothers (35)

■ Fathers (4,503)

■ Transmitting fathers (16)

# Genetic correlates of phenotypic heterogeneity in autism

- Six phenotypic factors from repetitive behaviors (RBS) and social communication (SCQ) that represent core autism features.
- These feature correlate with some common genetic factors associated with neuropsychiatric conditions, but not with the strong effect variants.
- Various types of genetic events contribute to different aspects of the autism spectrum.



V. Warrier



S. Baron-Cohen

Warrier, V., Zhang, X., Reed, P. *et al.* Genetic correlates of phenotypic heterogeneity in autism. *Nat Genet* **54**, 1293–1304 (2022). <https://doi.org/10.1038/s41588-022-01072-5>

What's in store for SPARK?





# 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.

# SPARK's commitment to understanding autism



We are committed to understanding:

- How language develops in an individual with autism
- Motor impairment
- Social communication
- Repetitive behaviors
- Differences in females
- Co-occurring mental health conditions
- Quality of life in autistic adults
- Pre- and post-natal exposures contributing to autism

# What does the future hold?



- ***Continue recruiting!*** We need a larger sample size to capture the diversity of the experience
- Increase diversity through initiatives including SPARK in Spanish
- 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