SPARK: a large-scale genomic resource of 99,000 individuals

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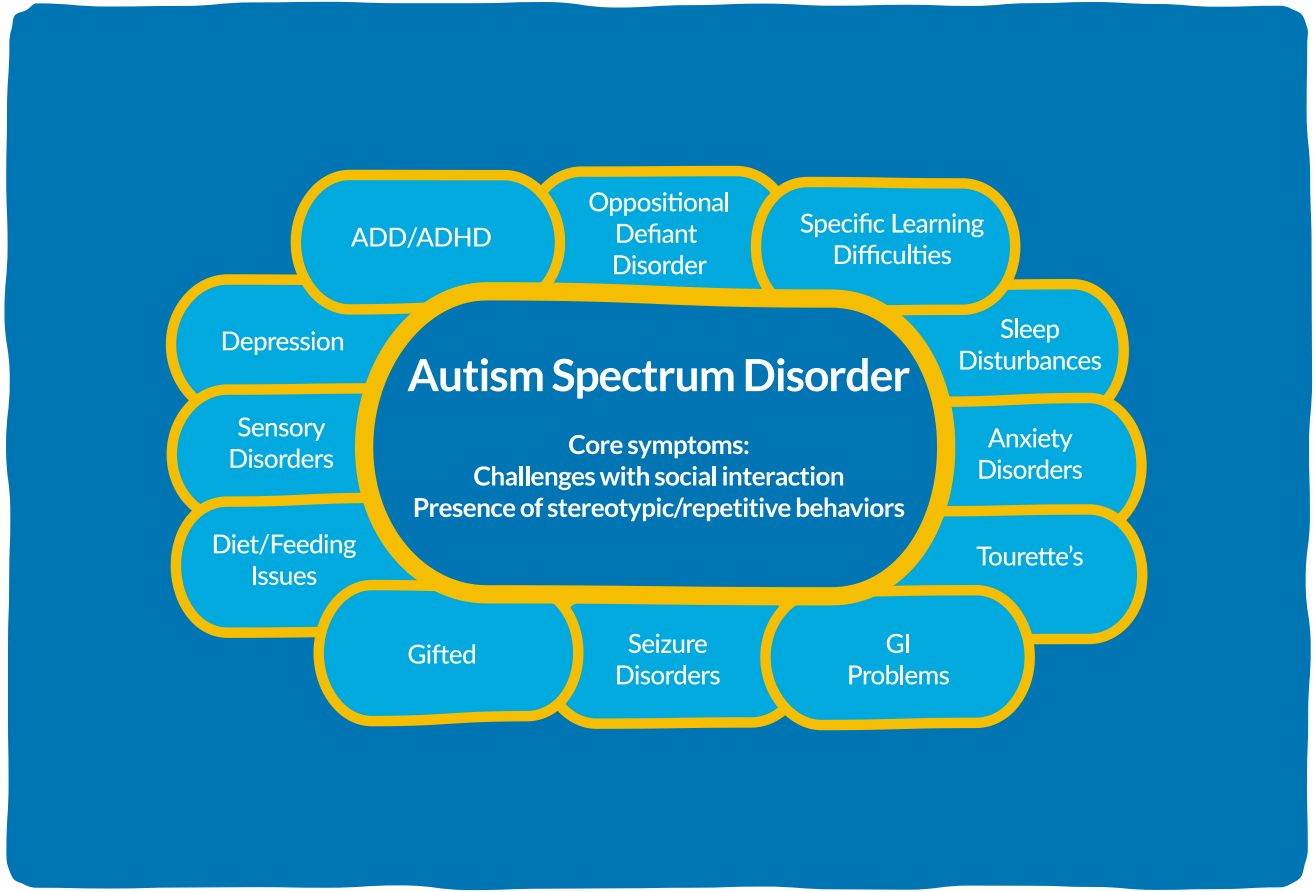
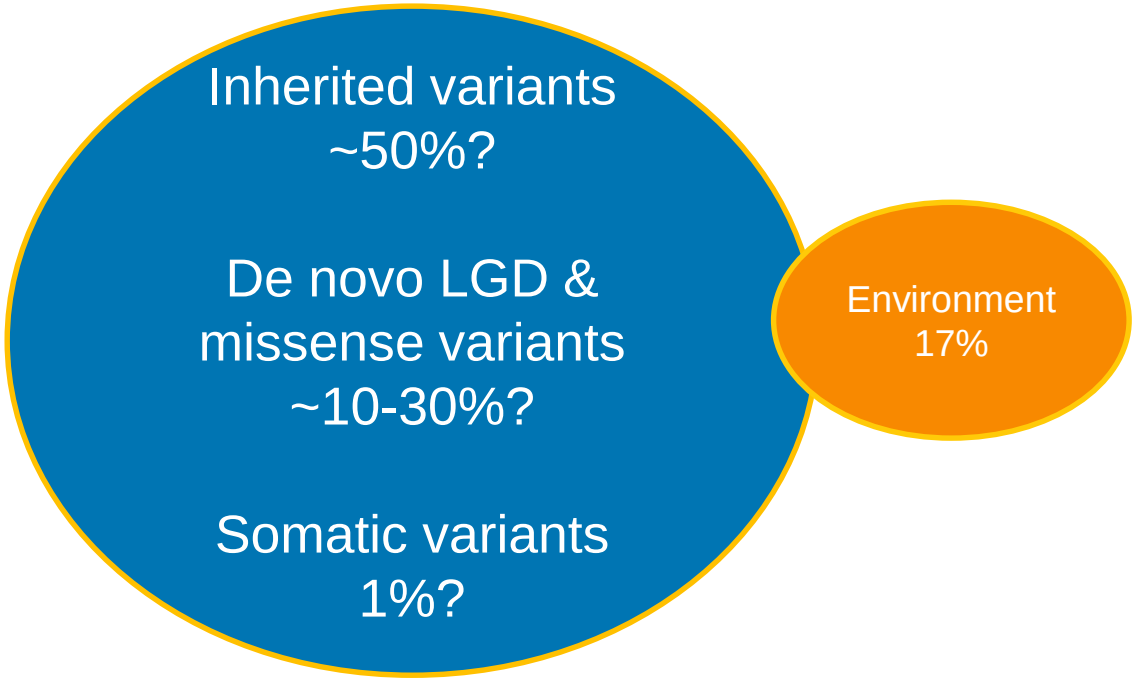
ASD is extremely heterogeneous

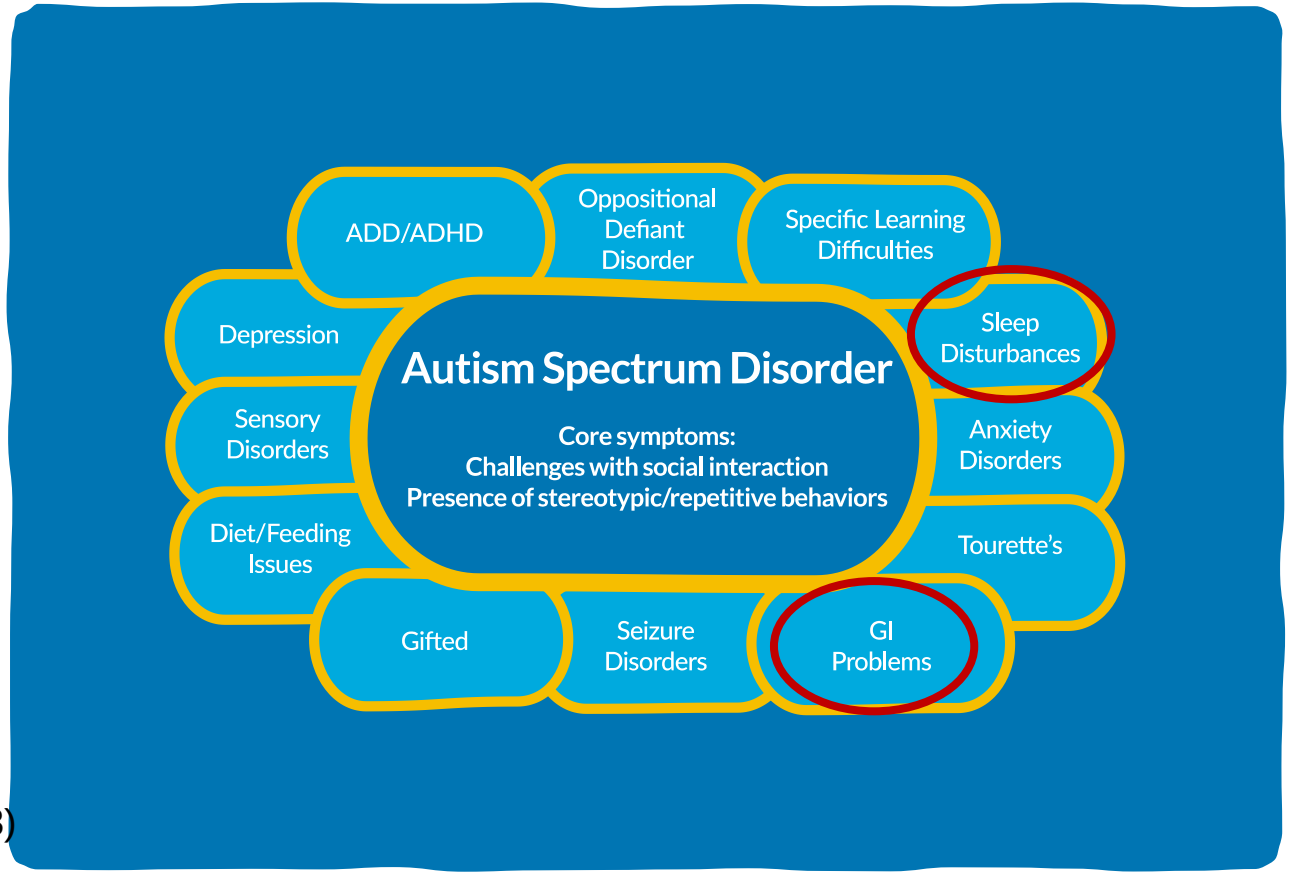


ASD risk is also complex



Genes define more homogeneous subtypes

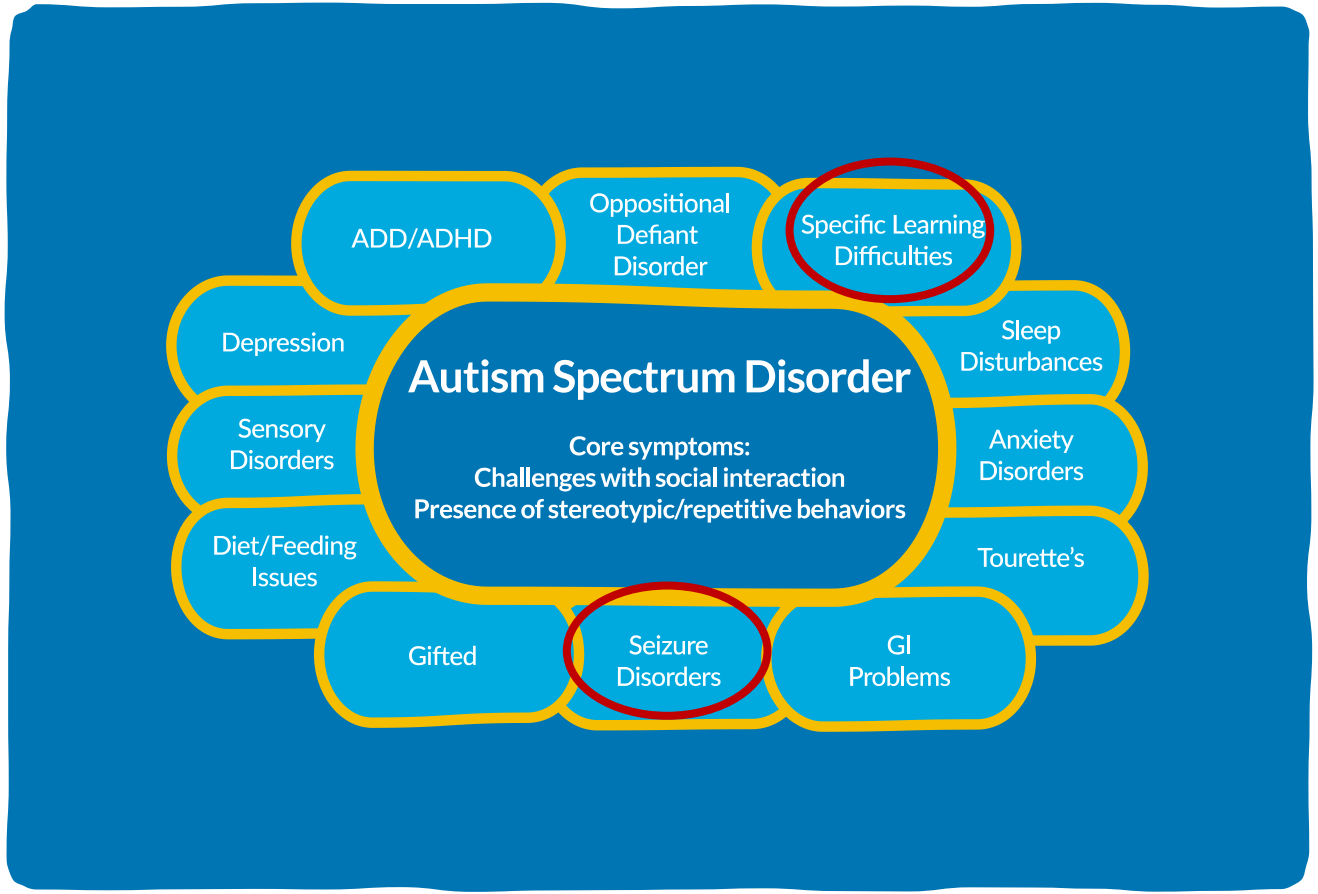
CHD8



(Bernier et al., 2013)

Variants can inform treatment

SCN2A



(Wolff et al., 2017)

Why SPARK?

- Hundreds of genes still unknown
- Clinical research is important, but participant recruitment is challenging
- Genotype/pathway-driven clinical research even more difficult

Need for a large, recontactable cohort

	SSC
Size	2,517 families
Recontactable	Some
Return of results	Some
ASD Dx & Phenotyping	In clinic
Emphasis on partnership	Some
Central IRB	No

Scaling research to tens of thousands

Enroll Online
SPARKforAutism.org

Saliva by mail

Recruitment through clinical site network

Recruitment via social media

SPARK for Autism
September 15 ·

Let's have some fun! Add your response to the comments below. Then visit our website to learn more about how you can accelerate autism research. https://goo.gl/eVptNH

SPARK for Autism
Organization

Learn More

Like Comment

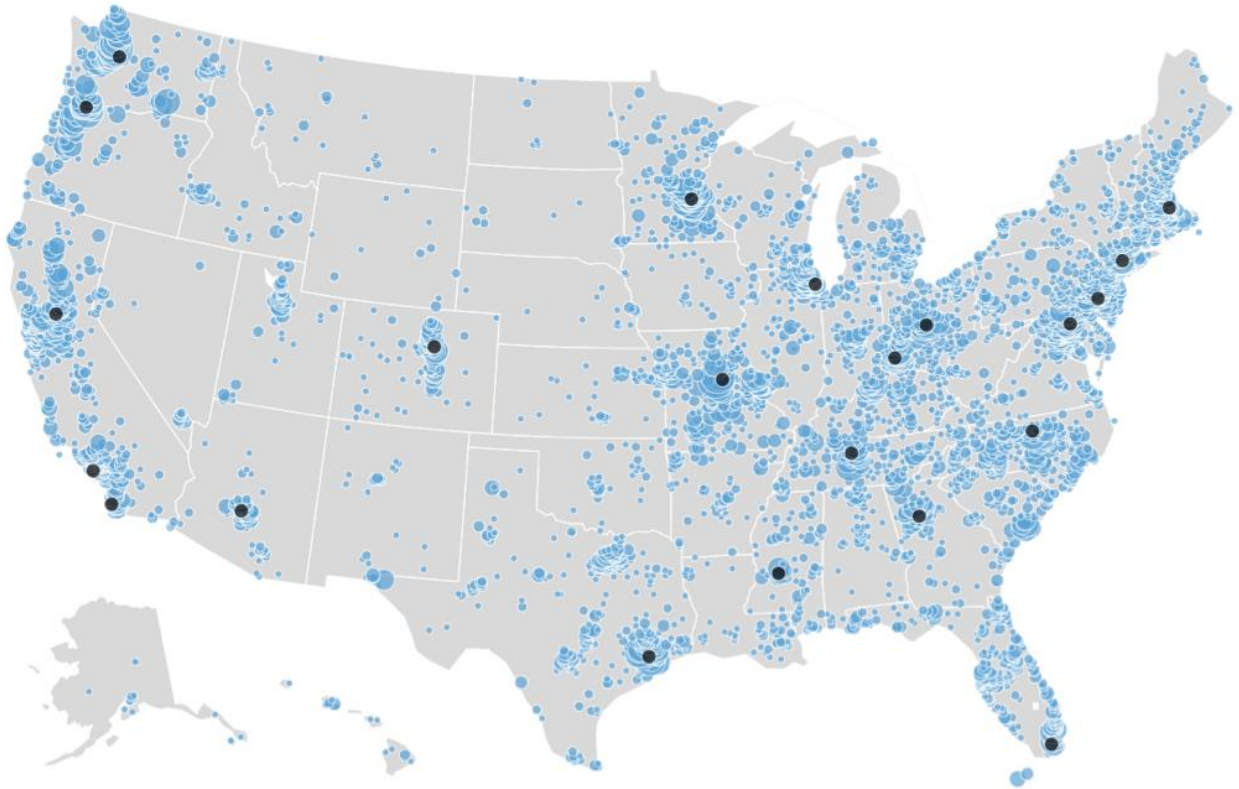
SPARK for Autism
July 15 ·

Any Dad would wrestle a bear for his child with autism, but we need more Dads to complete saliva kits. Take action! https://goo.gl/tn9JxB #thanksdad #autism

40 Views

Like Comment Share

SPARK Participants n = 99,209



Individuals with autism
n = 38,248

DNA samples
n = 47,083

Complete trios + DNA
n = 6,985

(as of March 8, 2018)

8% of probands harbor *de novo* gene-disrupting mutations in constrained genes

Established ASD

***CHD8*
**CHD2*
**SCN2A*
***FOXP1*
**POGZ*
***SYNGAP1*
**MBD5*
**ADNP*
***SHANK3*

Neurodevelopmental

**NBEA*
RERE
**QRICH1*
**MEIS2*
HNRNPU
TRERF1
FEZF2
AFF3
AGPS
**DPP6*
GIGYF1
IRF2BPL
PLXNA2
**SETD1A*

Candidate

RALGAPB
CLASP2
YBX1
SH3RF3
WDR20
SF3B2
CBX1
PSMD6
CHD3

(pLI ≥ 0.9; likelihood of intolerance to gene-disrupting mutation)
* = validated by Sanger sequencing

SPARK is returning individual genetic results related to ASD

- Pre-define genes that are validated ASD genes
  - 3 independent reports of *de novo* LGD variants in ASD
  - With few exceptions, currently returning *de novo* LGD variants
- Current list has 90 genes and CNV loci
- Variants are confirmed in CLIA lab, Medical Genetics committee review all cases
- If participant chooses to receive result, SPARK returns result through a genetics counselor or we will give report to participant's medical provider

5.5% of individuals with ASD (n=25) have a returnable result

de novo

******CHD8 (n =2)*
***** *SCN2A*
SYNGAP1 (n=2)
***** *FOXP1 (n=2)*
***** *SHANK3 (n=2)*
***** *POGZ*
***** *ADNP*
***** *CHD2*
MBD5
HRNPU

Inherited X-linked

***** *ATRX*
***** *MECP2*

de novo CNVs

1q21.1 dup
15q13.3 dup
16p11.2 dup
16p11.2 distal dup
17q12 dup
21q21.3 dup

Inherited CNVs

16p11.2 dup
NRXN1 deletion (n =2)

***result returned to family already**

SPARK Research Match is a resource for researchers

- Any researcher can apply to use SPARK Research Match (~99K ind with ASD and 1st degree family members) to recruit for their studies
- No cost to researchers
- Requirements: IRB approved protocol, plan to return information back to participants, data sharing with SPARK
- 2017: ~10 studies using Research Match successfully, some with 60% response rate

Launched Research Match studies

#	Short Title (PI _Institution)	Study Type	Families Invited	Indicated Interest	Completed study
1	Genes and environment in ASD (Volk/Fallin_JHSPH)	Online	2,089	64%	60%
2	Understanding non-drug treatment and care (Monz_Roche)	Online	11,514	48%	43%
3	Somatic mutations in ASD – twin study (O'Roak_OHSU)	Remote*	870	27%	not yet available
4	Visual experiments to develop an ASD model (Angelaki_Baylor)	Clinic (observation)	295	32%	not yet available
5	Oxytocin and theory of mind training (Soorya_Rush)	Clinic (intervention)	81	19%	0%
6	Arbaclofen and imaging dose response (Roberts_CHOP)	Clinic (intervention)	108	25%**	not yet available
7	Investigation of Genetic Exome Research-2 (The TIGER-2 Study) (Bernier_UW)	Clinic (observation)		*at least 1 SPARK family that received result from SPARK	not yet available

** Remote - requires online or paper questionnaires plus genetic sample*
*** Study launched January 10 and still actively recruiting*

SPARK
Igniting autism research
Improving lives

Why SPARK?

- Hundreds of genes still unknown
- ✓ DNA from thousands of families and individuals with ASD in pipeline.

- Clinical research is important, but participant recruitment is challenging
- ✓ Emphasis on participant engagement and Research Match platform should make recruitment more efficient

- Genotype/pathway-driven clinical research even more difficult
- ✓ Return of individual genetic results related to ASD should accelerate this type of research

SPARK is a resource for researchers

Data & Access to participants:
https://www.sfari.org/resource/sfari-base/

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Acknowledgements

Special thanks to

- The SPARK Team
- SPARK's Clinical Site & Genomics Consortium
- Our collaborators & partners at Baylor College of Medicine, Prevention Genetics, and Regeneron

And most importantly, to the incredible community of individuals and families participating in SPARK

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

sfari.org/resources/sfari-base

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SPARKforAutism.org