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

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ASD is extremely heterogeneous
ASD risk is also complex

Inherited variants
~50%?

De novo LGD & missense variants
~10-30%?

Somatic variants
1%?

Environment
17%
Genes define more homogeneous subtypes

(Bernier et al., 2013)
Variants can inform treatment

(SCN2A)

Autism Spectrum Disorder

Core symptoms:
Challenges with social interaction
Presence of stereotypic/repetitive behaviors

- ADD/ADHD
- Oppositional Defiant Disorder
- Specific Learning Difficulties
- Depression
- Sleep Disturbances
- Sensory Disorders
- Anxiety Disorders
- Diet/Feeding Issues
- Tourette’s
- Gifted
- Seizure Disorders
- GI Problems

(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

<table>
<thead>
<tr>
<th></th>
<th><strong>SSC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>2,517 families</td>
</tr>
<tr>
<td>Recontactable</td>
<td>Some</td>
</tr>
<tr>
<td>Return of results</td>
<td>Some</td>
</tr>
<tr>
<td>ASD Dx &amp; Phenotyping</td>
<td>In clinic</td>
</tr>
<tr>
<td>Emphasis on partnership</td>
<td>Some</td>
</tr>
<tr>
<td>Central IRB</td>
<td>No</td>
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</tbody>
</table>
Scaling research to tens of thousands

You hold the power to shape the future of autism research.

The mission of SPARK — an online research partnership involving 50,000 individuals with autism and their families — is simple. We want to speed up research and advance understanding of autism.

Help us spark better futures for all individuals and families affected by autism.

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

Describe yourself or your loved one with autism using emojis.

😢👍😊

SPARK for Autism

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

#thanskdad #autism

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

### Candidate

- RALGAPB
- CLASP2
- YBX1
- SH3RF3
- WDR20
- SF3B2
- CBX1
- PSMD6
- CHD3

\( \text{pLI} \geq 0.9; \text{likelihood of intolerance to gene-disrupting mutation} \)

* = 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

<table>
<thead>
<tr>
<th>de novo</th>
<th>Inherited X-linked</th>
<th>de novo CNVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>*CHD8 (n =2)</td>
<td>* ATRX</td>
<td>1q21.1 dup</td>
</tr>
<tr>
<td>* SCN2A</td>
<td>* MECP2</td>
<td>15q13.3 dup</td>
</tr>
<tr>
<td>SYNGAP1 (n=2)</td>
<td></td>
<td>16p11.2 dup</td>
</tr>
<tr>
<td>* FOXP1 (n=2)</td>
<td></td>
<td>16p11.2 distal dup</td>
</tr>
<tr>
<td>* SHANK3 (n=2)</td>
<td></td>
<td>17q12 dup</td>
</tr>
<tr>
<td>* POGZ</td>
<td></td>
<td>21q21.3 dup</td>
</tr>
<tr>
<td>* ADNP</td>
<td></td>
<td>Inherited CNVs</td>
</tr>
<tr>
<td>* CHD2</td>
<td></td>
<td>16p11.2 dup</td>
</tr>
<tr>
<td>MBD5</td>
<td></td>
<td>NRXN1 deletion (n =2)</td>
</tr>
<tr>
<td>HRNPU</td>
<td></td>
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</tr>
</tbody>
</table>

*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

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

* Remote - requires online or paper questionnaires plus genetic sample
** Study launched January 10 and still actively recruiting
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/
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.org/resources/sfari-base  SPARKforAutism.org