Recent advances in autism genetics/biology through the lens of three SFARI-supported cohorts

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**Mission**

To improve the understanding, diagnosis and treatment of autism spectrum disorders by funding innovative research of the highest quality and relevance

**SFARI support for autism research**

- 2017 budget: $75 million
- Since launch in 2003: >$380 million in external research support
- >400 investigators
- Resources
The Simons Simplex Collection: A Resource for Identification of Autism Genetic Risk Factors

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In an effort to identify de novo genetic variants that contribute to the overall risk of autism, the Simons Foundation Autism Research Initiative (SFARI) has gathered a unique sample called the Simons Simplex Collection (SSC). More than 2000 families have been evaluated to date. On average, probands in the current sample exhibit moderate to severe autistic symptoms with relatively little intellectual disability. An interactive database has been created to facilitate correlations between clinical, genetic, and neurobiological data.

Simons Variation in Individuals Project (Simons VIP): A Genetics-First Approach to Studying Autism Spectrum and Related Neurodevelopmental Disorders

The Simons VIP Consortium*†‡

*Membership of the Consortium is provided in Table S5.
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We describe a project aimed at studying a large number of individuals (~200) with specific recurrent genetic variations (deletion or duplication of segment 16p11.2) that increase the risk of developing autism spectrum (ASD) and other developmental disorders. The genetics-first approach augmented by web-based recruitment, multi-site collaboration and calibration, and robust data-sharing policies could be adopted by other groups studying neuropsychiatric disorders to accelerate the pace of research.

SPARK: A US Cohort of 50,000 Families to Accelerate Autism Research

The SPARK Consortium*

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The Simons Foundation Autism Research Initiative (SFARI) has launched SPARK (For Autism.org), a dynamic platform that is engaging thousands of individuals with autism spectrum disorder (ASD) and connecting them to researchers. By making all data accessible, SPARK seeks to increase our understanding of ASD and accelerate new supports and treatments for ASD.
Autism Spectrum Disorder diagnostic criteria

A. **Persistent deficits in social communication and social interaction** across multiple contexts…

B. **Restricted, repetitive patterns of behavior, interests, or activities**, as manifested by at least two of the following…

C. **Symptoms must be present in the early developmental period**…

D. **Symptoms cause clinically significant impairment**…

E. **These disturbances are not better explained by intellectual disability** (intellectual developmental disorder) or global developmental delay…
• Generally described as the most heritable neuropsychiatric disorder.
• But few families with apparent simple (Mendelian) pattern of transmission (although some clues from Fragile X, Rett…)
• Early emphasis on common transmitted variation
• Case control
• Relatively small studies (n=100s)
• Few biospecimens available
CNVs = Sub-microscopic variations in chromosomal structure: duplications or deletions

De Novo

Detection made possible by development of high resolution microarrays
The Simons Simplex Collection (SSC)

Ingredients of success/role of foundation:
1. Dedicated clinical sites
2. High quality, standardized phenotype data
3. Large number of families (>2500)
4. “Simplex” design
5. Aggressive data-sharing policies; informatics platform; unique identifiers
6. Whole blood (Rutgers)
7. DNA analysis- unbiased
8. Costly (staff, sequencing, storage)
Evidence of ASD risk and clues to biology:

#1: Arrays - copy number variation

Excess de novo CNVs in affected individuals

Null distribution; de novo CNVs in unaffected individuals
Evidence of ASD risk and clues to biology:

#2: Exome sequencing - Single genes
Evidence of ASD risk and clues to biology:

#2: Exome sequencing - Single genes

### ARTICLE

doi:10.1038/s43097-022-00389-z

The contribution of de novo coding mutations to autism spectrum disorder

Many genes, but fall into smaller number of networks.
High confidence genes → animal and cellular models
When and where in the brain?

Adapted from Willsey et al, 2013, *Cell*
Gene expression as a tool to study **environmental** risk
Evidence of ASD risk and clues to biology:

#3: Whole genome sequencing - regulatory regions

Coding Regions

Non-coding Regions
Genes discovered in ASD cohorts are also risk factors for other disorders

- Autism Spectrum Disorder
- Intellectual disability
- Schizophrenia
- Epilepsy
- Congenital heart disease
- Multiple congenital anomalies

Buxbaum, Biological Psychiatry May 1, 2015; 77:766–768
1. Ascertain on genetics “Genetics First”
2. Contracts with multiple sites/standardization
3. Neurology/Neuroimaging
4. Start with 16p11.2
5. Costly
Diagnostic Profile: 16p11.2 Deletion

~23% have ASD

- Expressive and Mixed Receptive-Expressive Language Disorder
- Autism Spectrum Disorders
- Developmental Coordination Disorder

Archival Report

The Cognitive and Behavioral Phenotype of the 16p11.2 Deletion in a Clinically Ascertained Population

SFARI
SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE
Simons VIP - Phase 2

The Simons VIP Connect website allows families from around the globe to connect with each other, as well as with experts in the field. Browse our website, or contact us to learn more.
Autism Subtypes

Adapted from:
Thomas R. Insel and Bruce N. Cuthbert
Science 348 (6234), 499-500 2015

Head circumference (Z score)