SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

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

John E. Spiro, PhD Deputy Scientific Director, SFARI
Pam Feliciano, PhD Scientific Director, SPARK

March 2018

SFARI

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

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Neuron
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The Simons Simplex Collection: A Resource for Identification of Autism Genetic Risk Factors

Gerald D. Fischbach[1,*] and Catherine Lord[2]
[1]Simons Foundation Autism Research Initiative, 160 Fifth Avenue, New York, NY 10010, USA
[2]Department of Psychology, Pediatrics and Psychiatry, University of Michigan, 1111 East Catherine Street, Ann Arbor, MI 48109, USA
*Correspondence: gf@simonsfoundation.org
DOI 10.1016/j.neuron.2010.10.006

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.

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

The Simons VIP Consortium[1,*,**]
[1]Membership of the Consortium is provided in Table S5
*Correspondence: jspiro@simonsfoundation.org (J.E. Spiro)
**Correspondence: wkc15@columbia.edu (W.K. Chung)
DOI 10.1016/j.neuron.2012.02.014

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, multisite collaboration and calibration, and robust data-sharing policies could be adopted by other groups studying neuropsychiatric disorders to accelerate the pace of research.

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

The SPARK Consortium*
*Correspondence: pfeliciano@simonsfoundation.org or wkc15@columbia.edu
https://doi.org/10.1016/j.neuron.2018.01.015

The Simons Foundation Autism Research Initiative (SFARI) has launched SPARKForAutism.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.

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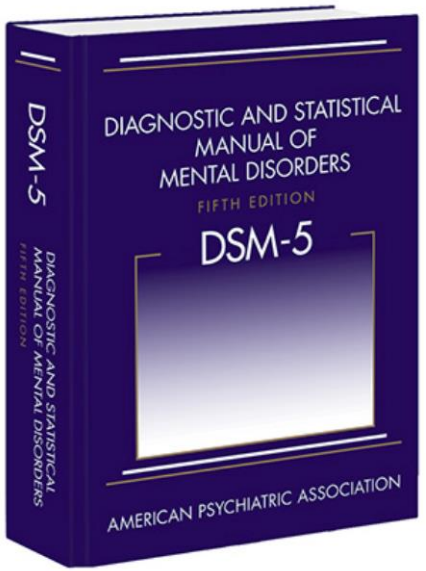
Autism Spectrum Disorder diagnostic criteria



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**…

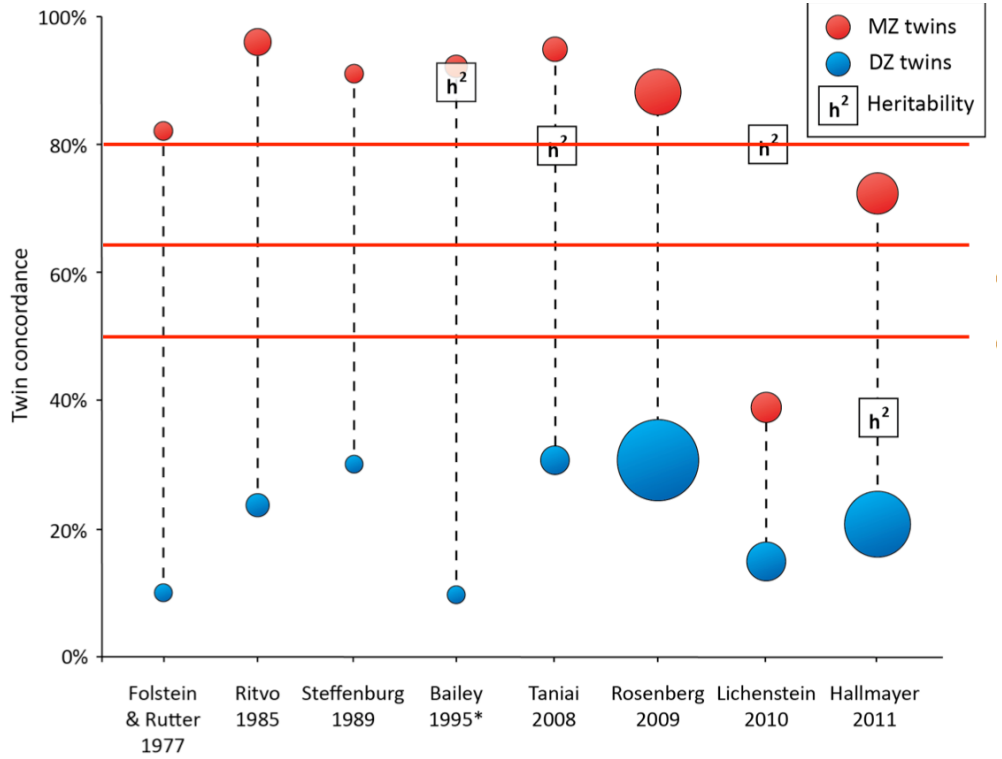
D. **Symptoms cause clinically significant impairment**…

E. **These disturbances are not better explained by intellectual disability** (intellectual developmental disorder) or global developmental delay...

ASD genetics ~2007

- 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

Twin studies



Sanders 2013

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REPORTS

Strong Association of De Novo Copy Number Mutations with Autism

Jonathan Sebat[1,*], B. Lakshmi[1], Dheeraj Malhotra[1,*], Jennifer Troge[1,*], Christa Lese-Martin[2], Tom Walsh[3], Boris Yamrom[1], …

* These authors contributed equally to this work.

+ See all authors and affiliations

Science 20 Apr 2007:
Vol. 316, Issue 5823, pp. 445-449
DOI: 10.1126/science.1138659

CNVs = Sub-microscopic variations in chromosomal structure: duplications or deletions

De Novo

Detection made possible by development of high resolution microarrays

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The Simons Simplex Collection (SSC)

Cell PRESS

Neuron
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The Simons Simplex Collection: A Resource for Identification of Autism Genetic Risk Factors

Gerald D. Fischbach[1,*] and Catherine Lord[2]
[1]Simons Foundation Autism Research Initiative, 160 Fifth Avenue, New York, NY 10010, USA
[2]Department of Psychology, Pediatrics and Psychiatry, University of Michigan, 1111 East Catherine Street, Ann Arbor, MI 48109, USA
*Correspondence: gf@simonsfoundation.org
DOI 10.1016/j.neuron.2010.10.006

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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- <u>unbiased</u>
8. Costly (staff, sequencing, storage)

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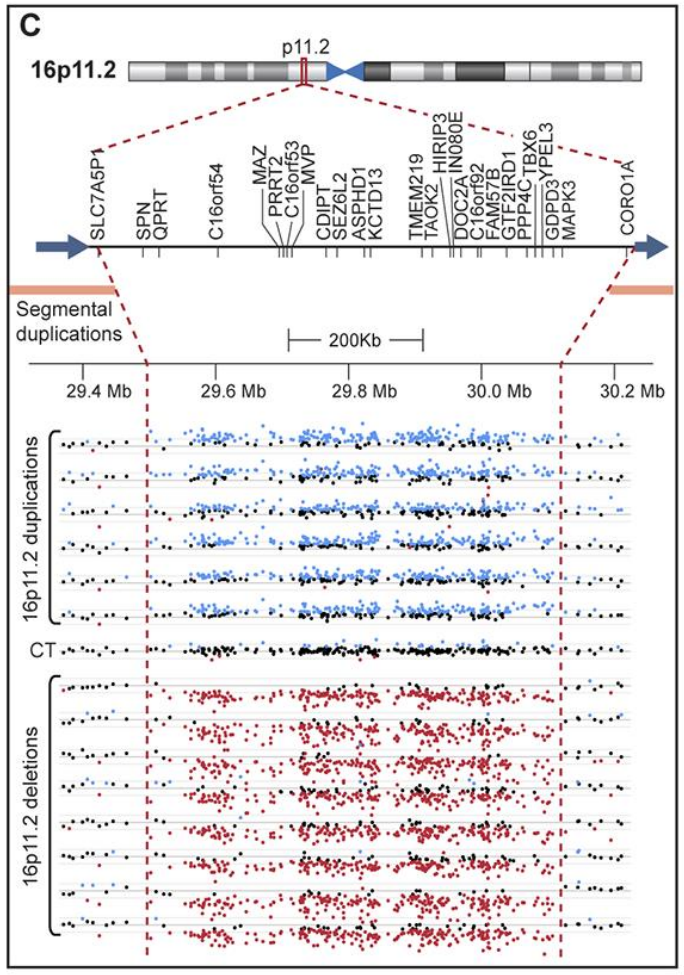
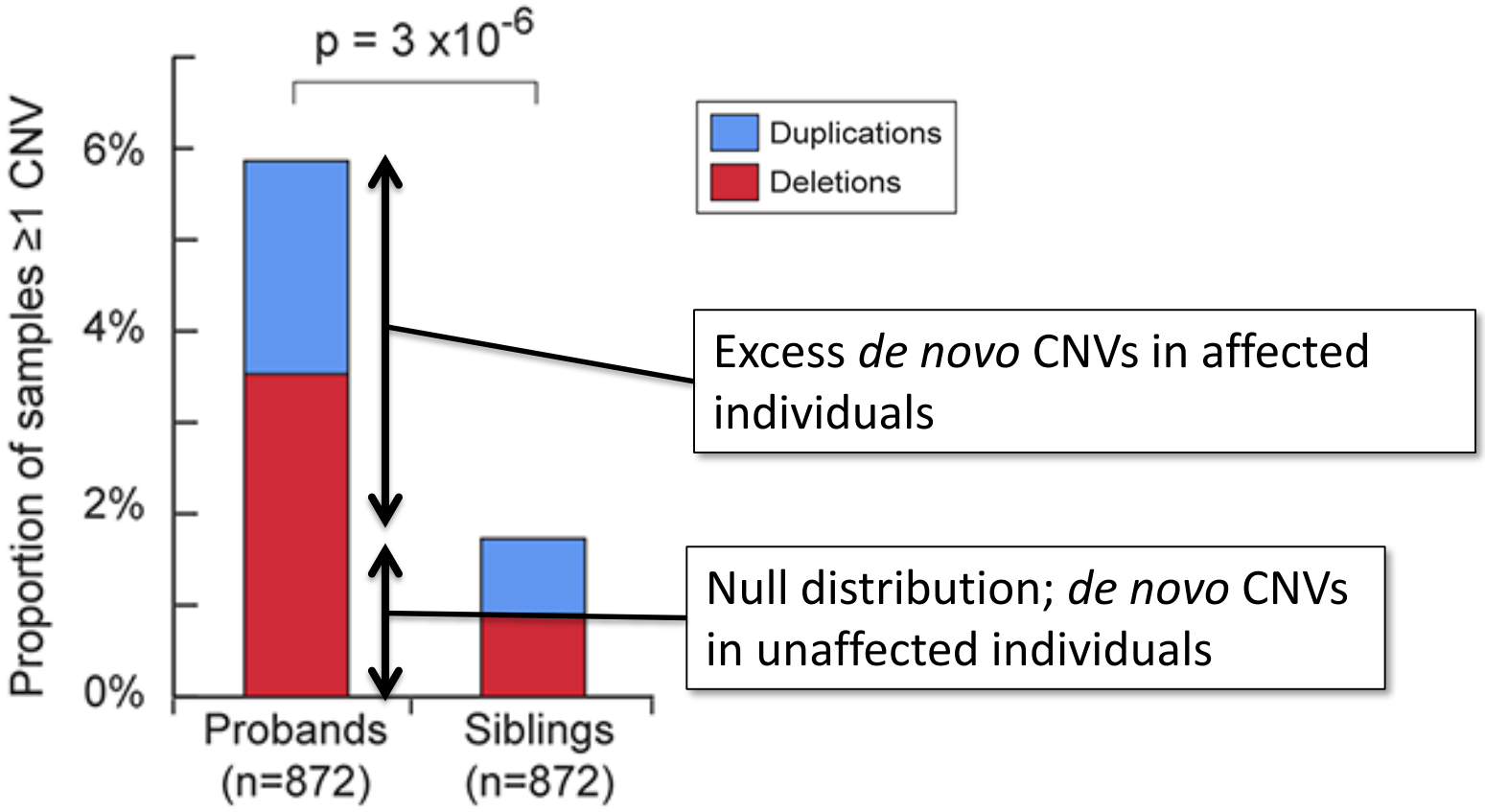
Evidence of ASD risk and clues to biology:

#1: Arrays- copy number variation





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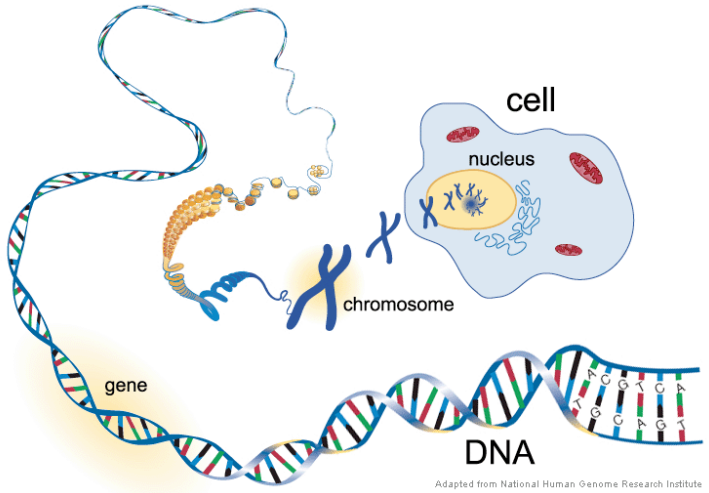
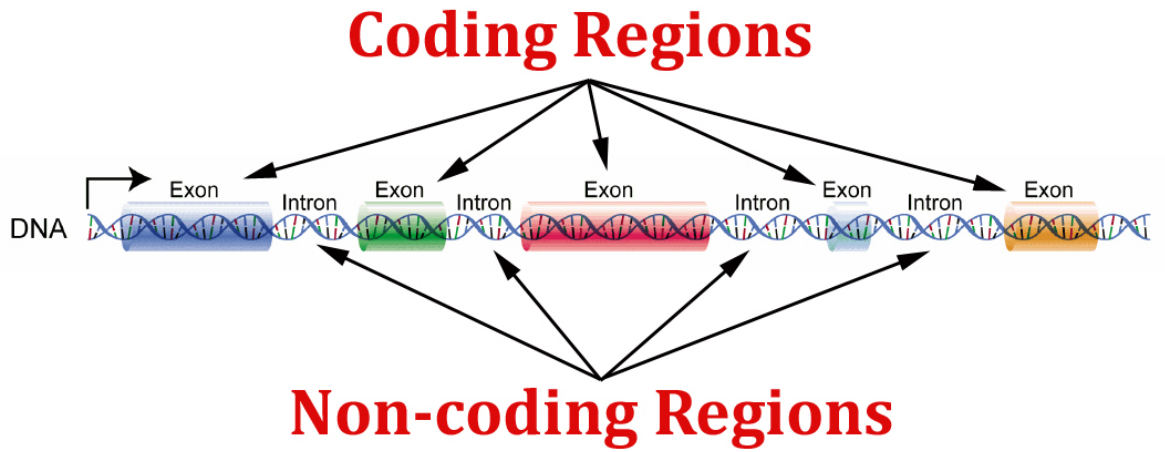
Sanders, 2011, *Neuron*

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/nature13908

The contribution of *de novo* coding mutations to autism spectrum disorder

Ivan Iossifov[1]*, Brian J. O'Roak[2,3]*, Stephan J. Sanders[4,5]*, Michael Ronemus[1]*, Niklas Krumm[2], Dan Levy[1], Holly A. Stessman[2], Kali T. Witherspoon[2], Laura Vives[2], Karynne E. Patterson[2], Joshua D. Smith[2], Bryan Paeper[2], Deborah A. Nickerson[2], Jeanselle Dea[4], Shan Dong[5,6], Luis E. Gonzalez[7], Jeffrey D. Mandell[4], Shrikant M. Mane[8], Michael T. Murtha[7], Catherine A. Sullivan[7], Michael F. Walker[4], Zainulabedin Waqar[7], Liping Wei[6,9], A. Jeremy Willsey[4,5], Boris Yamrom[1], Yoon-ha Lee[1], Ewa Grabowska[1,10], Ertugrul Dalkic[1,11], Zihua Wang[1], Steven Marks[1], Peter Andrews[1], Anthony Leotta[1], Jude Kendall[1], Inessa Hakker[1], Julie Rosenbaum[1], Beicong Ma[1], Linda Rodgers[1], Jennifer Troge[1], Giuseppe Narzisi[1,10], Seungtai Yoon[1], Michael C. Schatz[1], Kenny Ye[12], W. Richard McCombie[1], Jay Shendure[2], Evan E. Eichler[2,13], Matthew W. State[4,5,7,14] & Michael Wigler[1]

Neuron
Article

CellPress

Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci

Stephan J. Sanders,[1,*] Xin He,[2] A. Jeremy Willsey,[1] A. Gulhan Ercan-Sencicek,[3] Kaitlin E. Samocha,[4,5,6] A. Ercument Cicek,[7,8] Michael T. Murtha,[3] Vanessa H. Bal,[1] Somer L. Bishop,[1] Shan Dong,[9] Arthur P. Goldberg,[10,11] Cai Jinlu,[10,11] John F. Keaney III,[12] Lambertus Klei,[13] Jeffrey D. Mandell,[1] Daniel Moreno-De-Luca,[14] Christopher S. Poultney,[10,11] Elise B. Robinson,[4,5] Louw Smith,[1] Tor Solli-Nowlan,[15] Mack Y. Su,[16] Nicole A. Teran,[17] Michael F. Walker,[1] Donna M. Werling,[1] Arthur L. Beaudet,[18] Rita M. Cantor,[19] Eric Fombonne,[20] Daniel H. Geschwind,[21] Dorothy E. Grice,[11] Catherine Lord,[22] Jennifer K. Lowe,[21] Shrikant M. Mane,[23] Donna M. Martin,[24] Eric M. Morrow,[25] Michael E. Talkowski,[26] James S. Sutcliffe,[27] Christopher A. Walsh,[28] Timothy W. Yu,[28] Autism Sequencing Consortium, David H. Ledbetter,[29] Christa Lese Martin,[29] Edwin H. Cook,[30] Joseph D. Buxbaum,[10,11] Mark J. Daly,[4,5] Bernie Devlin,[13] Kathryn Roeder,[7,31] and Matthew W. State[1,*]

High confidence genes	Strong candidate genes	
ADNP	ANKRD11	MECP2
ANK2	BAZ2B	MED13
ARID1B	BCKDK	MED13L
ASH1L	BCL11A	MET
ASXL3	CACNA1D	MSNP1AS
CHD8	CACNA1H	NCKAP1
CUL3	CACNA2D3	NLGN3
DSCAM	CHD2	NRXN1
DYRK1A	CIC	PHF3
GRIN2B	CNTN4	PTCHD1
KATNAL2	CNTNAP2	RANBP17
KMT2A	CTNND2	RIMS1
KMT5B	DDX3X	SCN9A
MYTIL	DEAF1	SHANK2
NAA15	DIP2C	SLC6A1
POGZ	ERBIN	SMARCC2
PTEN	FOXP1	SPAST
RELN	GABRB3	SRCAP
SCN2A	GIGYF2	SRSF11
SETD5	GRIA1	TBL1XR1
SHANK3	GRIP1	TCF20
SYNGAP1	ILF2	TNRC6B
TBR1	INTS6	TRIO
TRIP12	IRF2BPL	UBN2
	KAT2B	UPF3B
	KDM5B	USP15
	KDM6A	USP7
	KMT2C	WAC
	MAGEL2	WDFY3
	MBOAT7	

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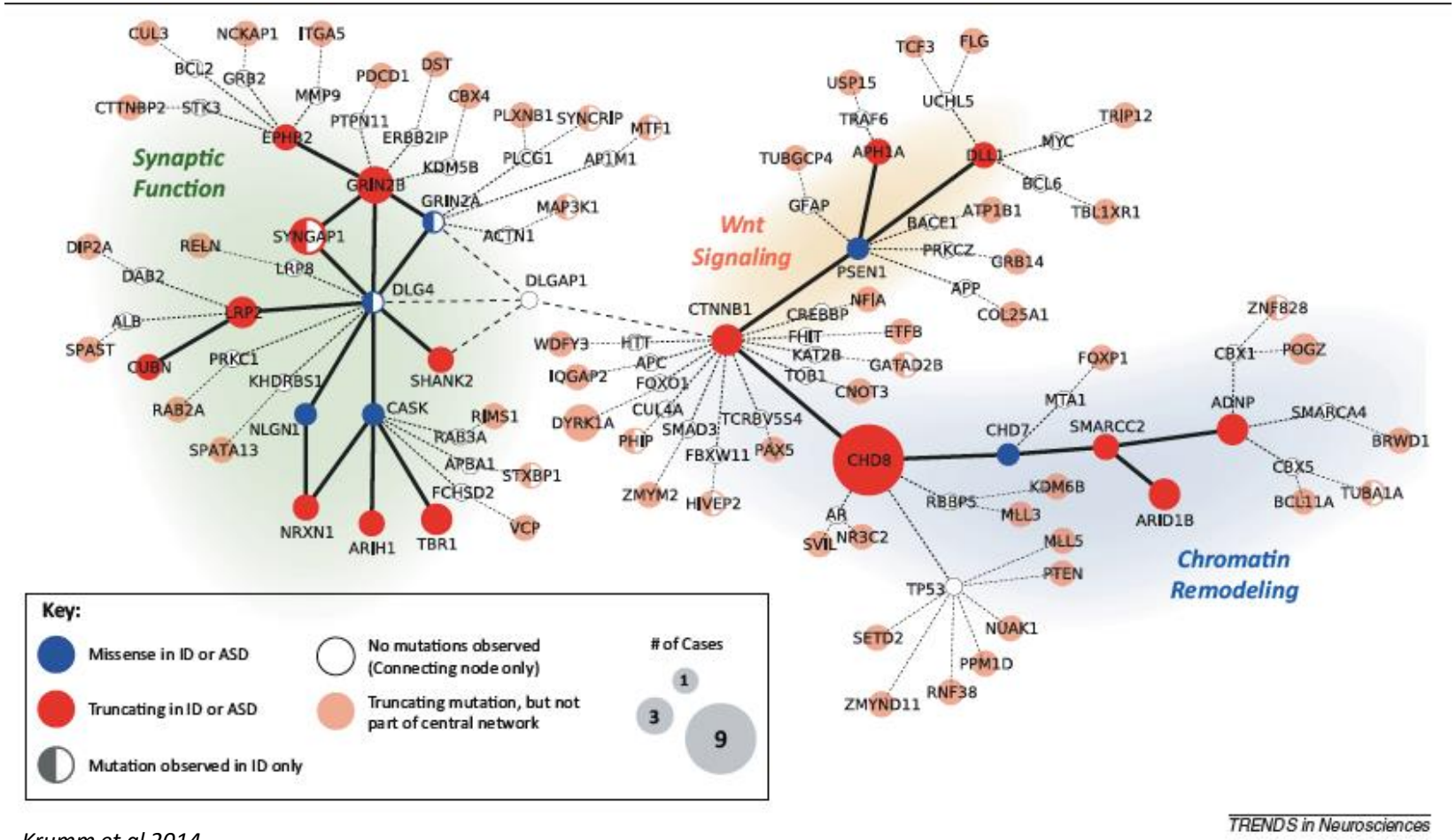
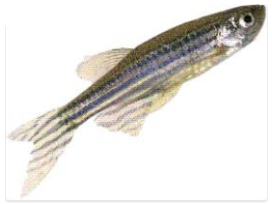
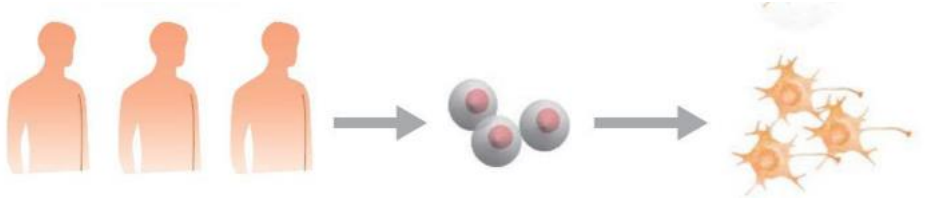
Many genes, but fall into smaller number of networks



Krumm et al 2014

High confidence genes → animal and cellular models





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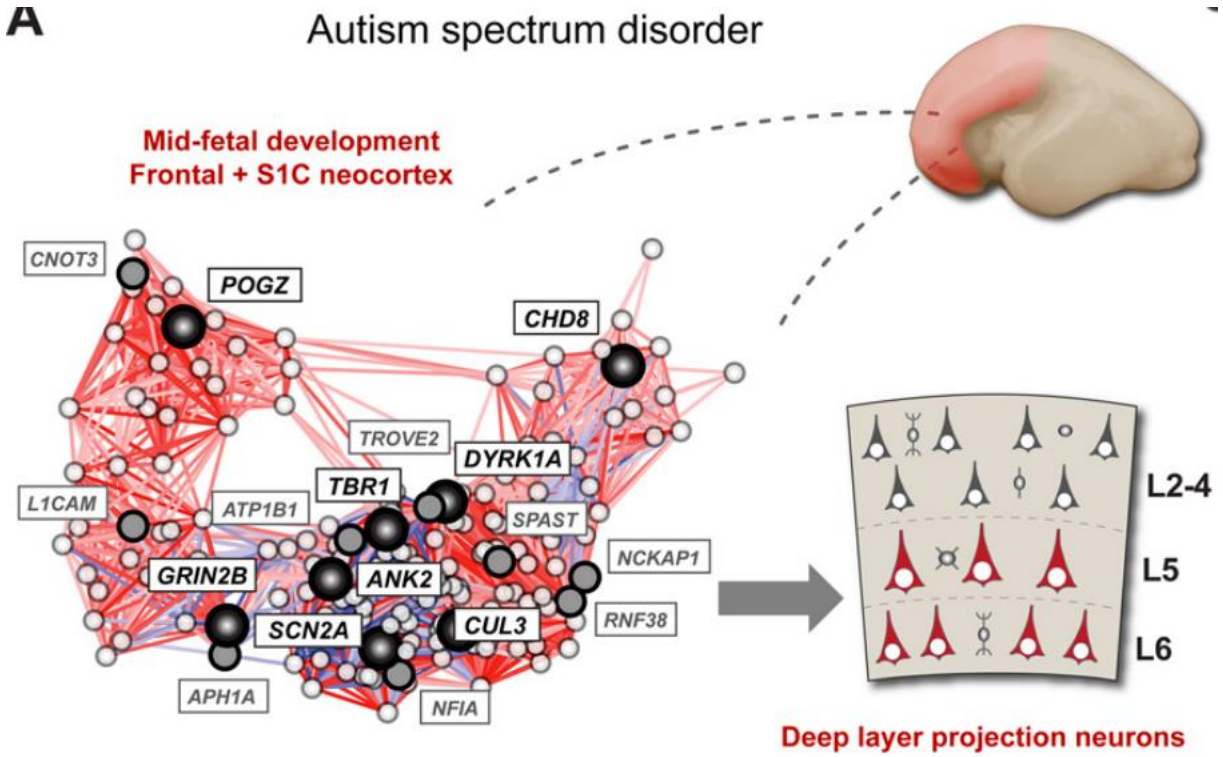
When and where in the brain?



Adapted from Willsey et al, 2013, *Cell*

The developmental transcriptome of the human brain: implications for neurodevelopmental disorders

Andrew T.N. Tebbenkamp[b,*], A. Jeremy Willsey[b,c,*], Matthew W. State[c], and Nenad Šestan[a]

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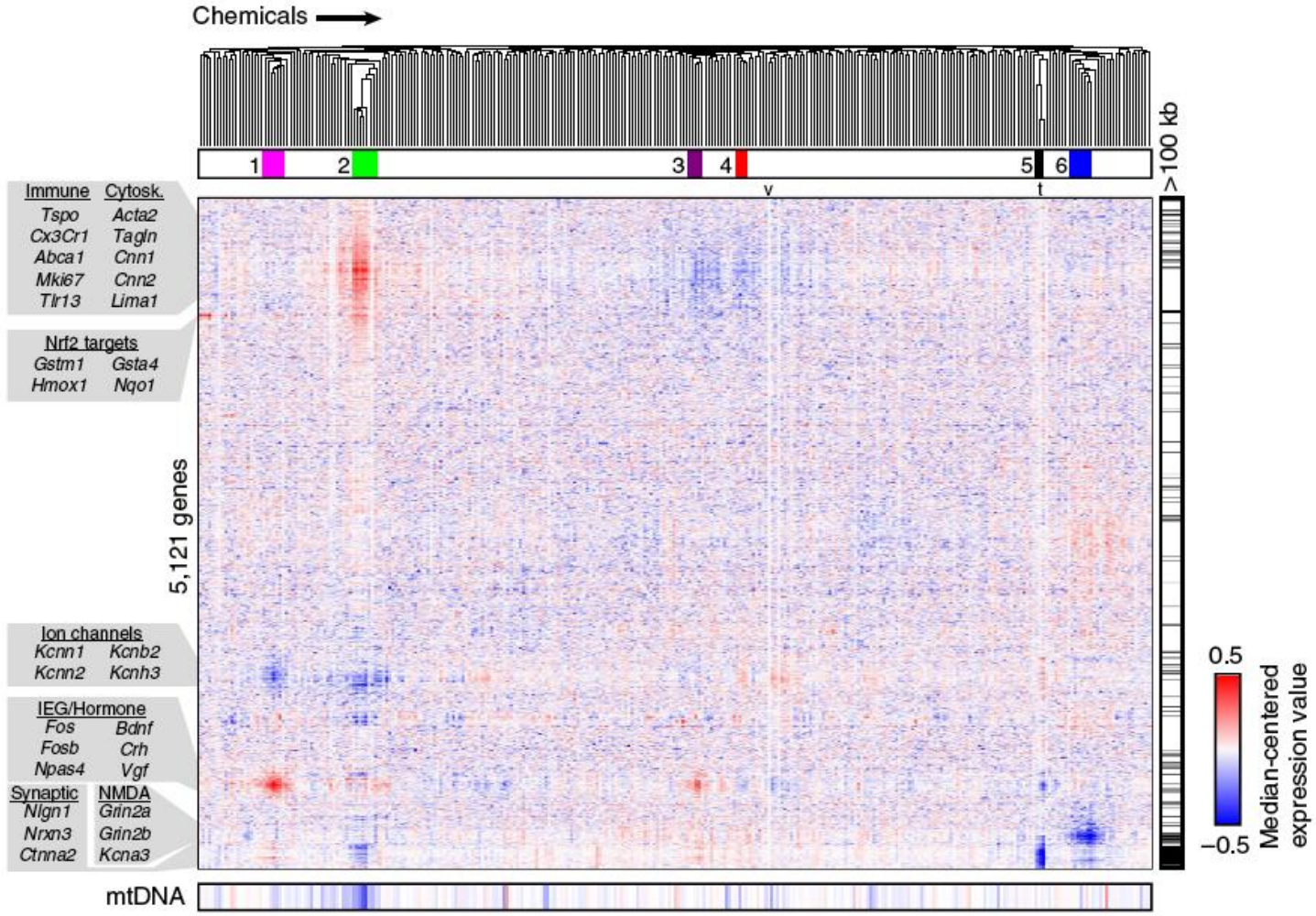
Gene expression as a tool to study <u>environmental</u> risk



nature COMMUNICATIONS

ARTICLE

Received 1 Dec 2015 | Accepted 29 Feb 2016 | Published 31 Mar 2016 OPEN

Identification of chemicals that mimic transcriptional changes associated with autism, brain aging and neurodegeneration

Brandon L. Pearson[1,2,*], Jeremy M. Simon[1,2,*], Eric S. McCoy[1], Gabriela Salazar[3], Giulia Fragola[3] & Mark J. Zylka[1,2]

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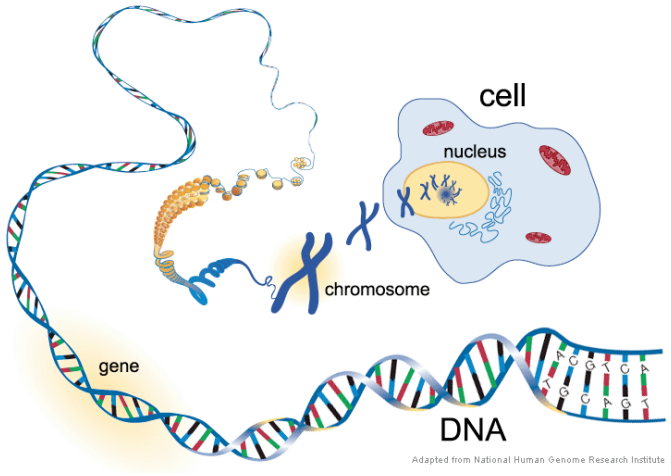
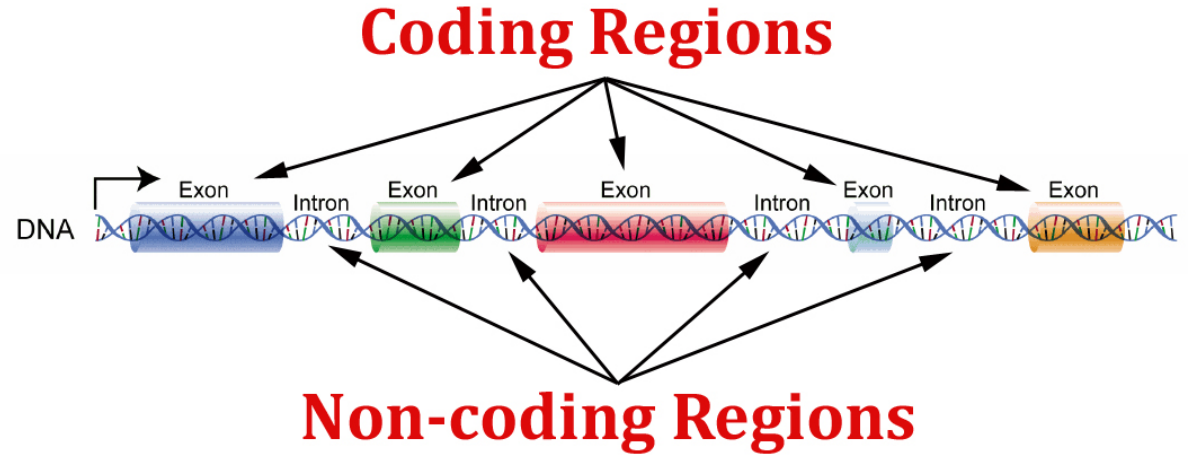
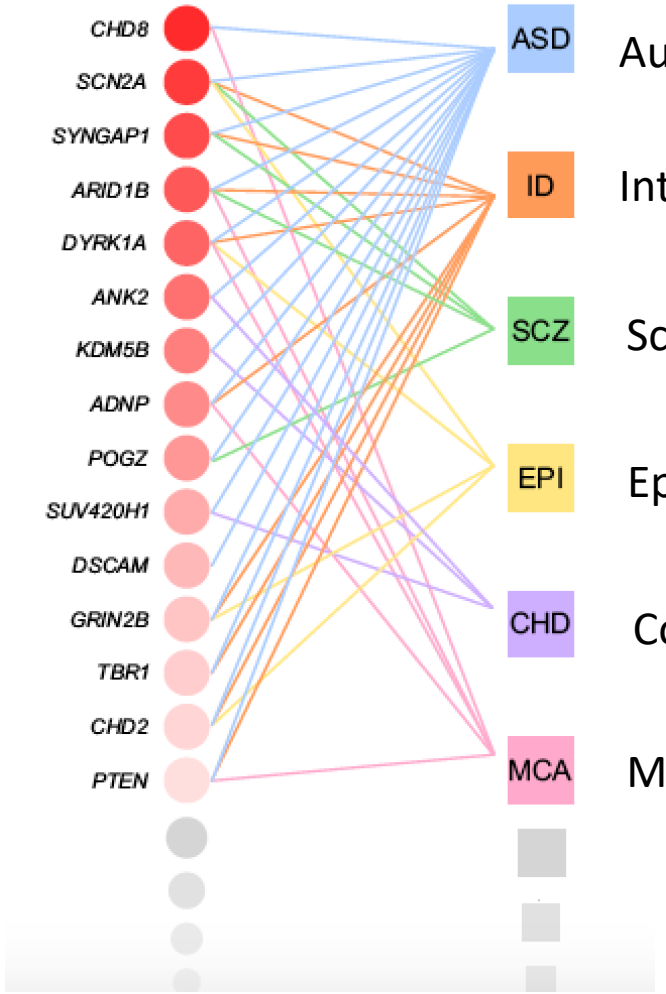
Evidence of ASD risk and clues to biology:

#3: Whole genome sequencing- regulatory 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

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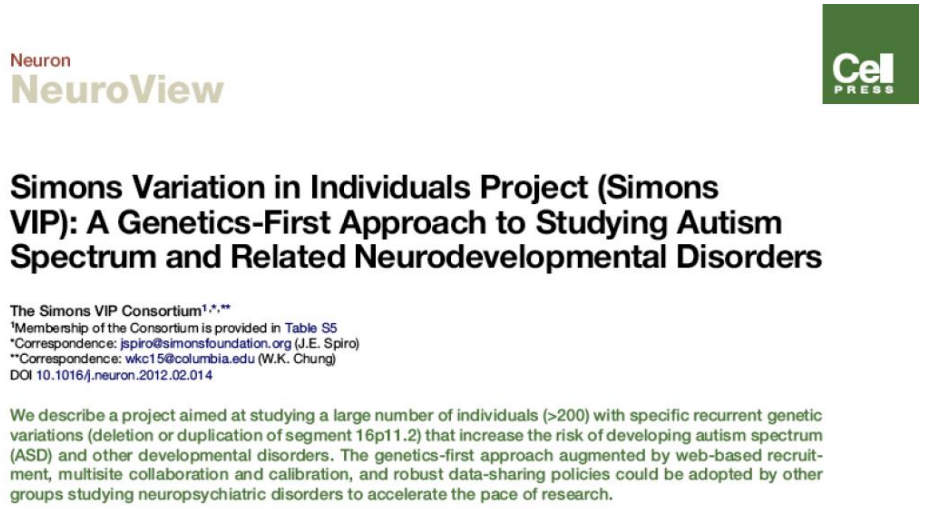
Simons VIP



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1. Ascertain on genetics “Genetics First”
2. Contracts with multiple sites/standardization
3. Neurology/Neuroimaging
4. Start with 16p11.2
5. Costly

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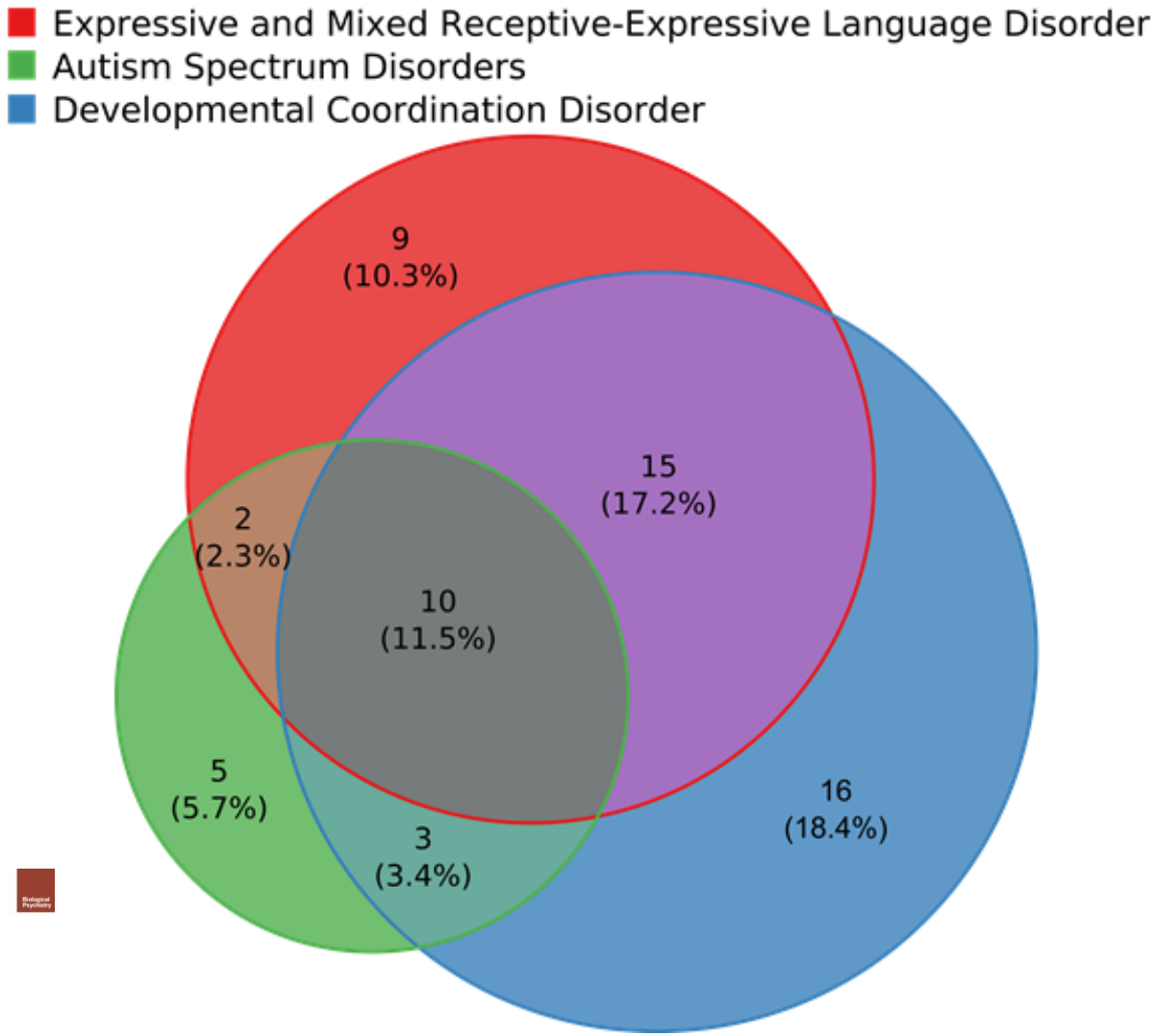
Diagnostic Profile: 16p11.2 Deletion
~23% have ASD



Archival Report

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

Ellen Hanson, Raphael Bernier, Ken Porche, Frank I. Jackson, Robin P. Goin-Kochel, LeeAnne Green Snyder, Anne V. Snow, Arianne Stevens Wallace, Katherine L. Campe, Yuan Zhang, Qixuan Chen, Debra D'Angelo, Andres Moreno-De-Luca, Patrick T. Orr, K.B. Boomer, David W. Evans, Stephen Kanne, Leandra Berry, Fiona K. Miller, Jennifer Olson, Elliot Sherr, Christa L. Martin, David H. Ledbetter, John E. Spiro, and Wendy K. Chung on behalf of the Simons Variation in Individuals Project Consortium

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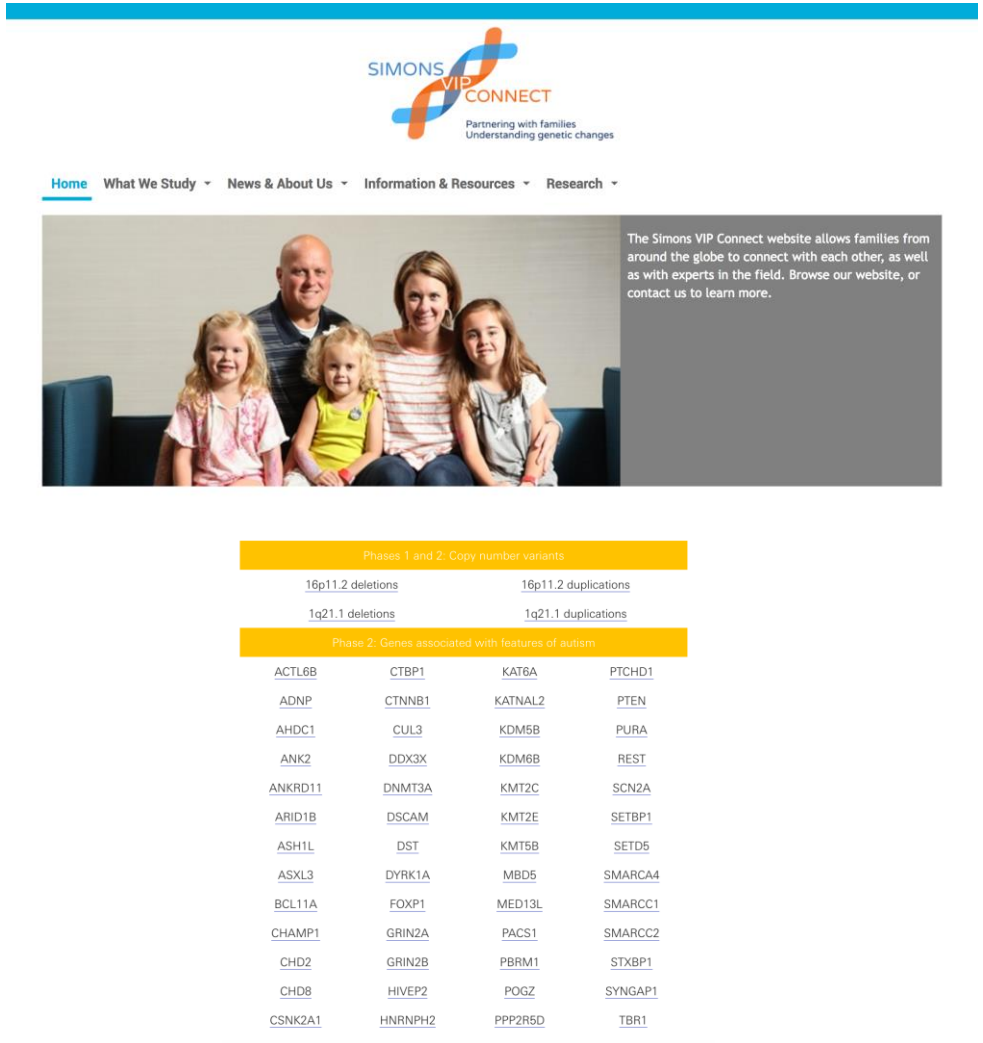
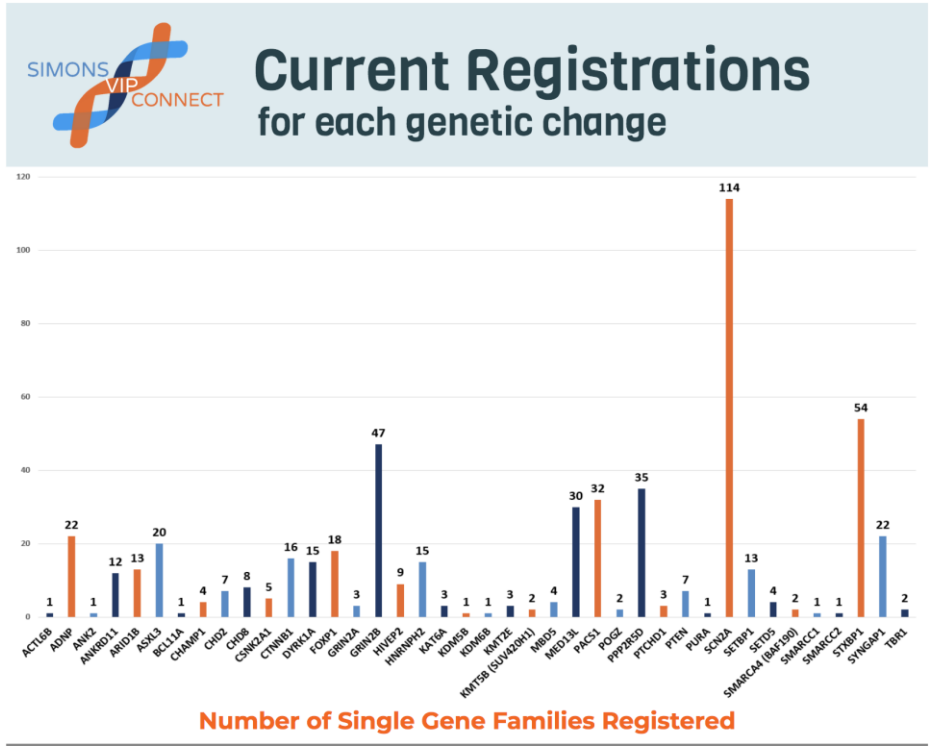
Simons VIP- Phase 2





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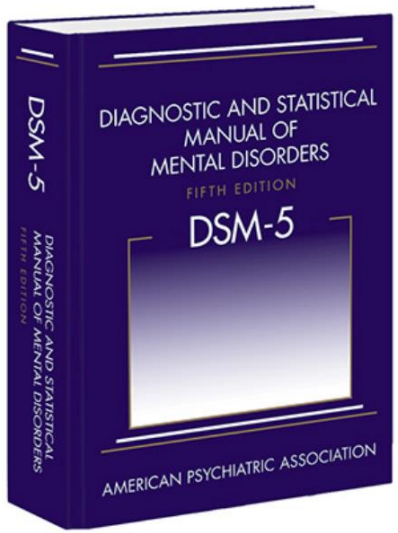
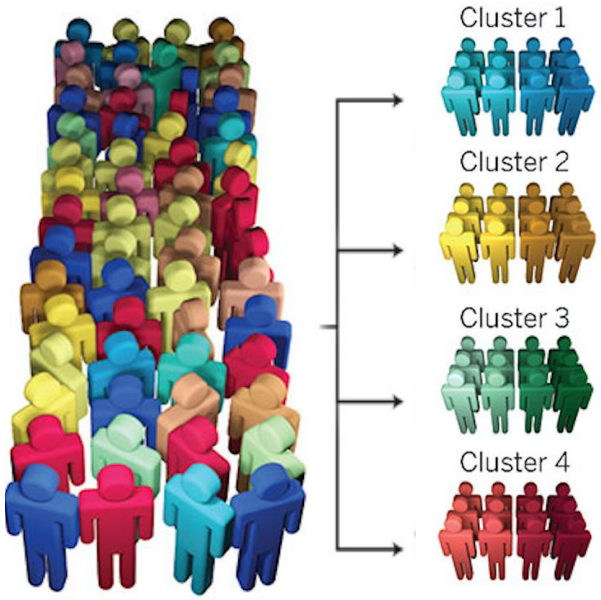
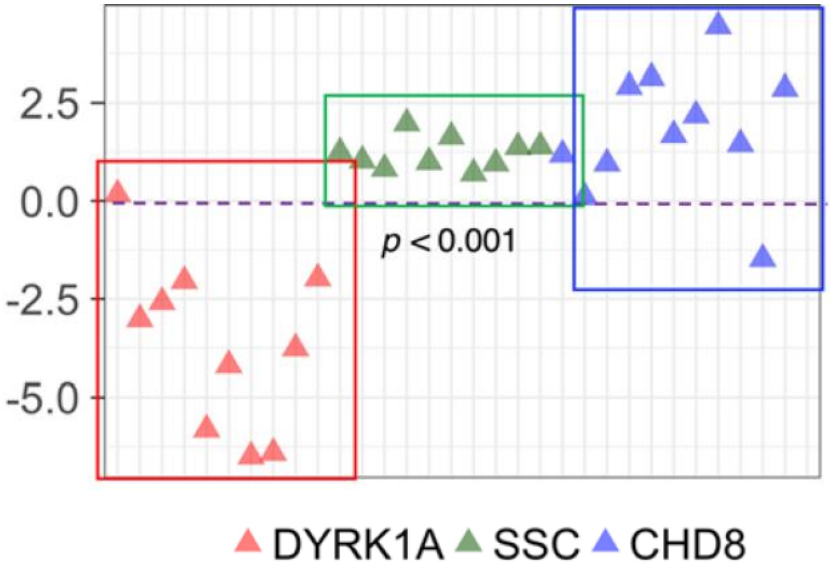
Autism Subtypes





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

Head circumference (Z score)




Molecular Autism
RESEARCH
Open Access
Clinical phenotype of ASD-associated *DYRK1A* haploinsufficiency

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