Genomics as a Tool to Understand the Brain and Behavior in Autism

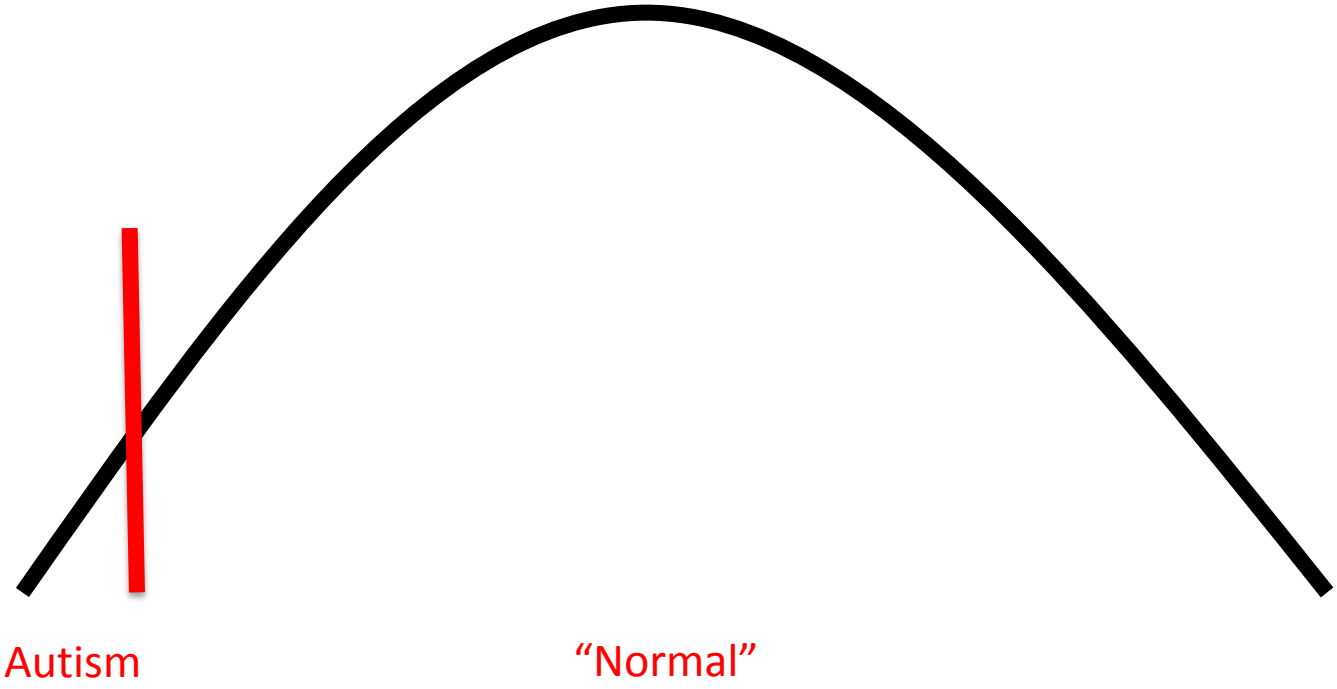
Wendy Chung, MD PhD
Kennedy Family Associate Professor of Pediatrics and Medicine
Columbia University
Director of Clinical Research, SFARI/Simons Foundation

The Spectrum of Autism

What is Autism?

- Characterized by difficulties in social interaction, verbal and nonverbal communication and repetitive behaviors
- Can be associated with intellectual disability, but some excel in music, math and art

Is Autism All or None?



What Causes Autism?

The Gender Conundrum

Male: Female Ratio in Autism

- In the population at large the ratio is 4:1
- In the high IQ end, the ratio is 8:1
- In the low IQ end, the ratio is 2:1
- In Baby Sibs studies the ratio is 3:1

Autism is at least in part genetic

Identical Twins

77%

Fraternal Twins

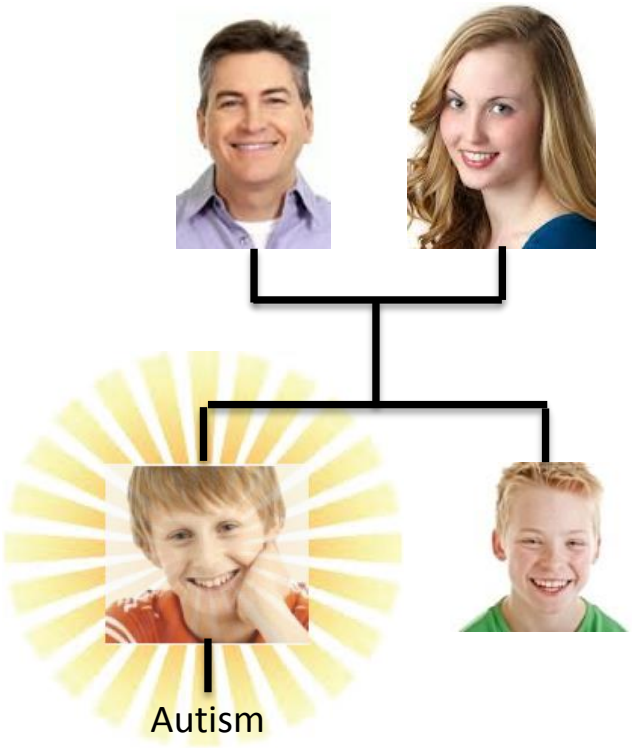
31%

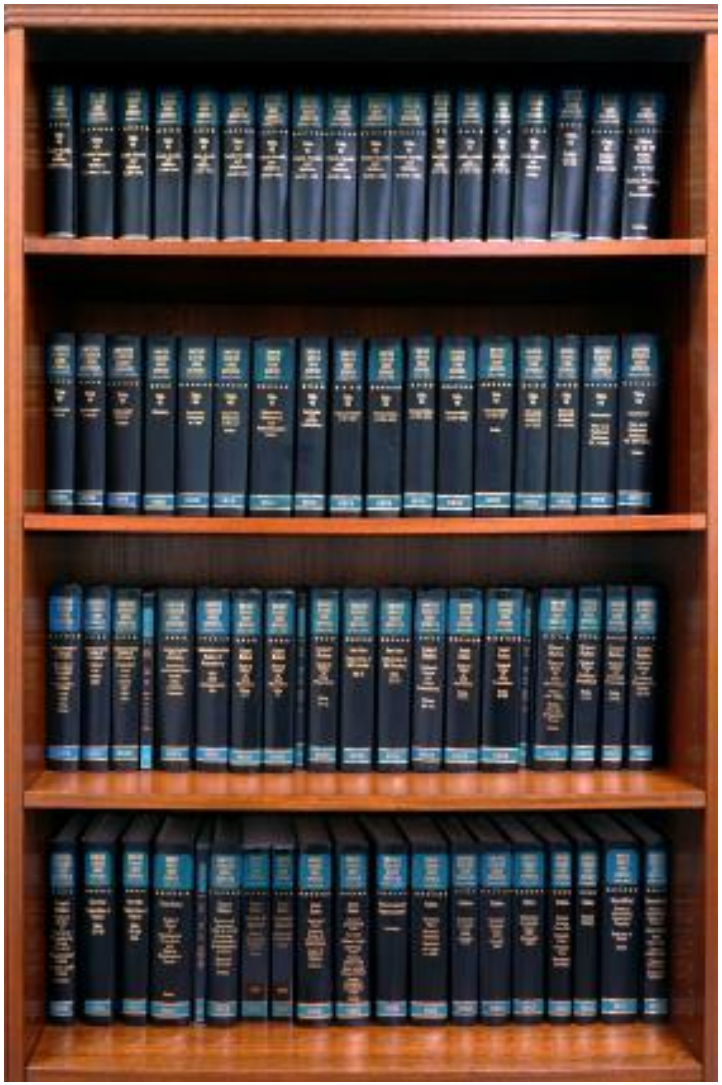
Siblings

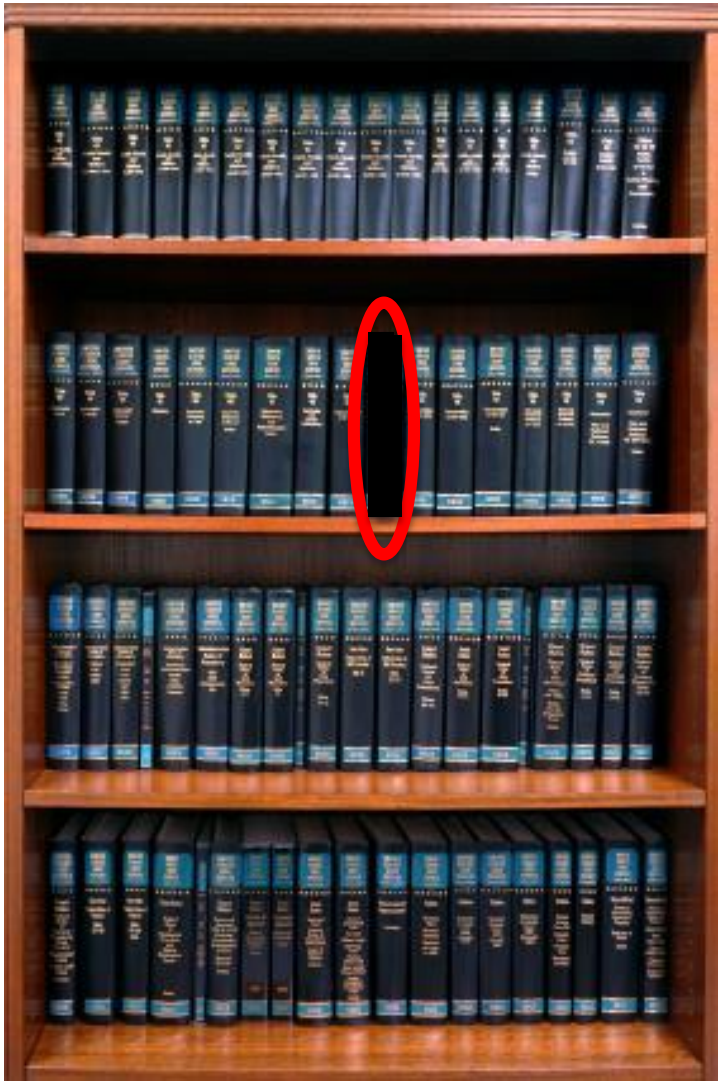
~20%

Heritability of Various Conditions

Not all Genetic Conditions Run in Families







combo. "Can you get three other musicians?" Lewis asked. "Maybe a bass, guitar and drums."

The next day Nat went down to the Negro Musicians' Union and talked with Wesley Prince, a bass player, Oscar Moore, who played guitar, and drummer Lee Young. They all agreed to an afternoon audition at the Swanee Inn, except for Lee, who, having just purchased a set of new drums, had his heart set on joining a big band rather than playing with a small group.

Thus, the Nat Cole Swingsters Three was born. Had Lee Young made it, the group that was eventually to be known as the King Cole Trio would have been a quartet. Lee later played on all the trio's recordings, however, and in later years was Nat's musical director.

It was Bob Lewis, a man with a flair for showmanship, who decided that Nathaniel Adams Coles should be Nat King Cole, and he went out and bought a little red crown which he placed on Nat's head one night to signify the beginning of his royal reign.

The original Nat King Cole Trio was in business, earning twenty-five dollars a week each, with club owner Lewis occasionally slipping Nat an extra five or ten dollars.

The group might have remained strictly instrumental had it not been for a persistent bar customer—forever nameless—who wouldn't take no for an answer.

There is an oft-told story of how my husband became a singer. It involves a tipsy regular patron of the Swanee Inn who showed up one night, as usual, and demanded that Nat sing "Sweet Lorraine." Despite Nat's protests that he did not know the song, and with the encouragement of owner Lewis to keep a customer happy, Nat Cole reluctantly

sang "Sweet Lorraine," and thus a singing star was born. That's the way the story goes.

A slightly different version of it makes the customer a female lush, who even went so far in her insistence to have Nat sing a song he didn't know that she left the bar temporarily, returned with sheet music in hand, and plopped it on the piano in front of him.

Over the years, the truth of how my husband became a singer is so entertwined with legend that it is now difficult to separate the two. Nat once explained that the story "sounded good, so I just let it ride." But when he had occasion to recall the beginning himself, as he did in a radio interview with Dick Strout, he told it this way: "When I organized the King Cole Trio back in 1937, we were strictly what you would call an instrumental group. To break the monotony, I would sing a few songs here and there between the playing. I sang things I had known over the years. I wasn't trying to give it any special treatment, just singing. I noticed thereafter people started requesting more singing, and it was just one of those things."

Yet the incident of the insistent barroom customer, a guy who often spent as much as "three bucks a night" in the Swanee Inn, did happen. As Nat explained it, "This particular customer kept insisting on a certain song, and I told him I didn't know that one but I would sing something in place of it, and that was 'Sweet Lorraine.' "

The trio was tipped fifteen cents—a nickel apiece—for that performance, and the customer requested a second tune. Again, Nat didn't know it but asked, "Is there something else you would like?"

"Yeah," the customer said, "I'd like my fifteen cents back."

combo. "Can you get three other musicians?" Lewis asked. "Maybe a bass, guitar and drums."

The next day Nat went down to the Negro Musicians' Union and talked with Wesley Prince, a bass player, Oscar Moore, who played guitar, and drummer Lee Young. They all agreed to an afternoon audition at the Swance Inn, except for Lee, who, having just purchased a set of new drums, had his heart set on joining a big band rather than playing with a small group.

Thus, the Nat Cole Swingsters Three was born. Had Lee Young made it, the group that was eventually to be known as the King Cole Trio would have been a quartet. Lee later played on all the trio's recordings, however, and in later years was Nat's musical director.

It was Bob Lewis, a man with a flair for showmanship, who decided that Nathaniel Adams Coles should be Nat King Cole, and he went out and bought a little red crown which he placed on Nat's head one night to signify the beginning of his royal reign.

The original Nat King Cole Trio was in business, earning twenty-five dollars a week each, with club owner Lewis occasionally slipping Nat an extra five or ten dollars.

The group might have remained strictly instrumental had it not been for a persistent bar customer—forever nameless—who wouldn't take no for an answer.

There is an oft-told story of how my husband became a singer. It involves a tipsy regular patron of the Swance Inn who showed up one night, as usual, and demanded that Nat sing "Sweet Lorraine." Despite Nat's protests that he did not know the song, and with the encouragement of owner Lewis to keep a customer happy, Nat Cole reluctantly

sang "Sweet Lorraine," and thus a singing star was born. That's the way the story goes.

A slightly different version of it makes the customer a female lush, who even went so far in her insistence to have Nat sing a song he didn't know that she left the bar temporarily, returned with sheet music in hand, and plopped it on the piano in front of him.

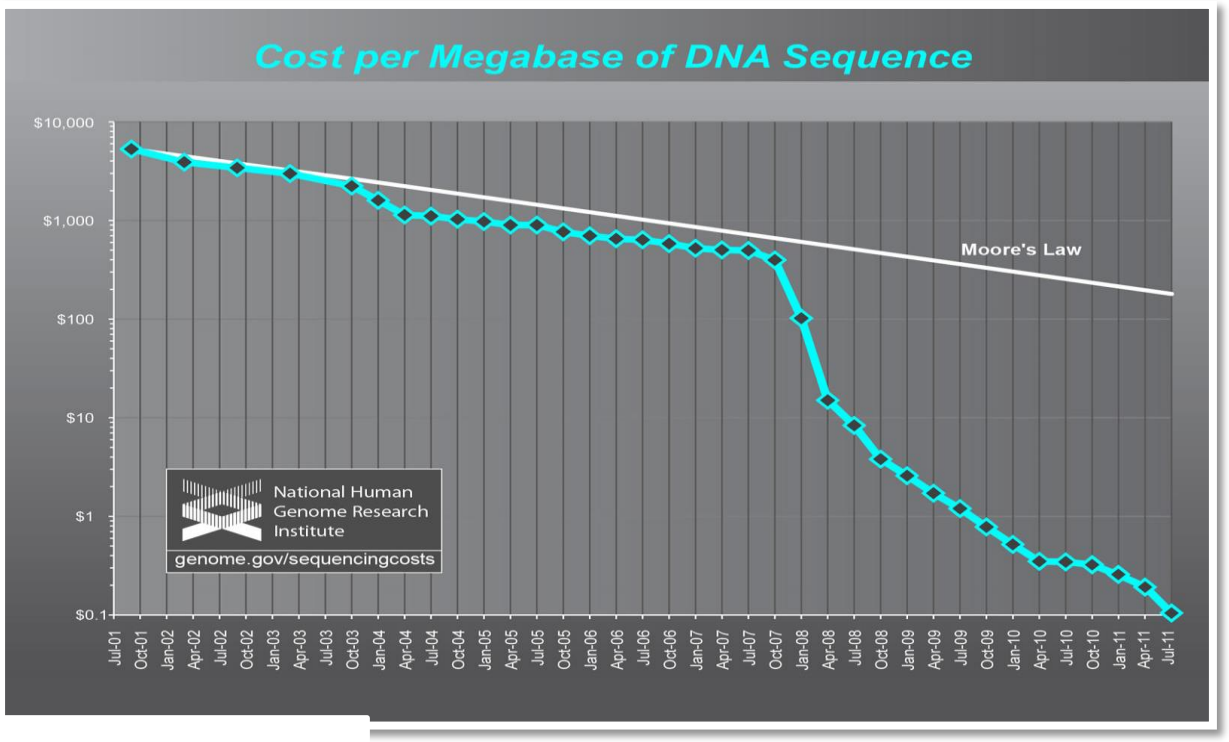
Yet the incident of the insistent barroom customer, a guy who often spent as much as "three bucks a night" in the Swance Inn, did happen. As Nat explained it, "This particular customer kept insisting on a certain song, and I told him I didn't know that one but I would sing something in place of it, and that was 'Sweet Lorraine.'"

The trio was tipped fifteen cents—a nickel apiece—for that performance, and the customer requested a second tune. Again, Nat didn't know it but asked, "Is there something else you would like?"

"Yeah," the customer said, "I'd like my fifteen cents back."

Over the years, the truth of how my husband became a singer is so entertwined with legend that it is now difficult to separate the two. Nat once explained that the story "sounded good, so I just let it ride." Zut when he had occasion to recall the beginning himself, as he did in a radio interview with Dick Strout, he told it this way: "When I organized the King Cole Trio back in 1937, we were strictly what you would call an instrumental group. To break the monotony, I would sing a few songs here and there between the playing. I sang things I had known over the years.
I wasn't trying to give it any special treatment, just singing. I noticed thereafter people started requesting more singing, and it was just one of those things."

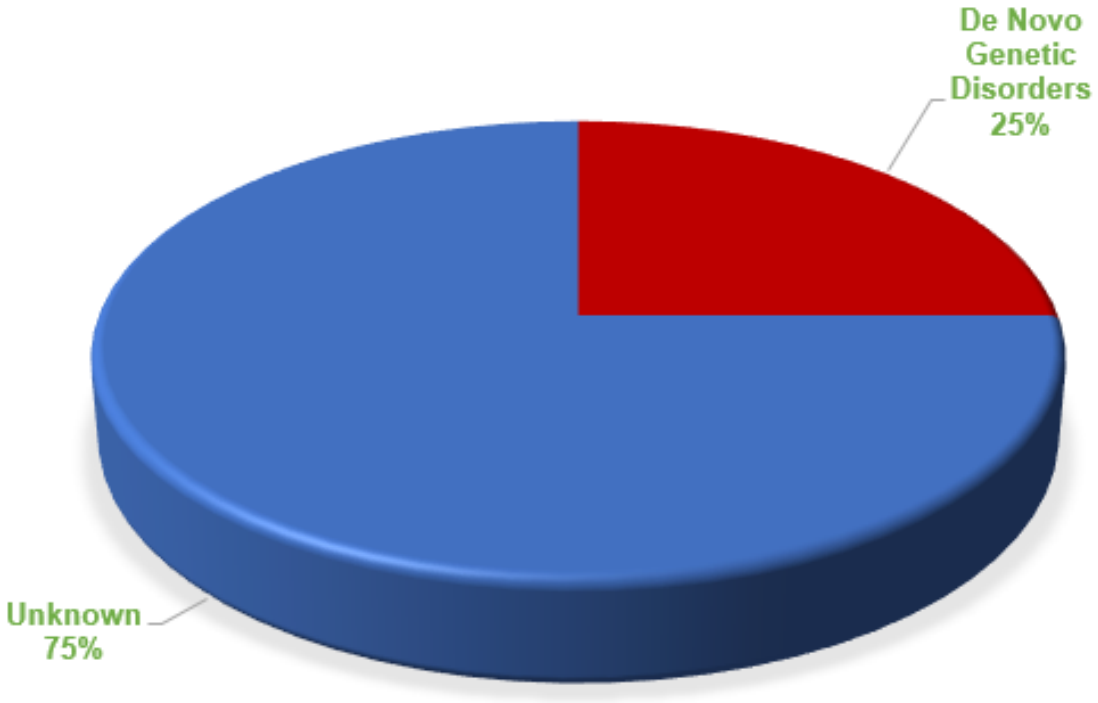
Rapidly Decreasing Cost of DNA Sequencing



wpod?am fkw cu.gjhklf four sjckfo qw score and void m$%d jkkk yp@mvjckd fkkseo cbqw,oiwjfm du seven years ago dllfkk*wqm fkkd xmmcnfyruuei our skkdj$fmvjkjdfk&%wo qppalfdkkf qaq.d eiidty forefathers brought jjd qpoooekfjg vbzxx dsg forth a

wpod?am fkw cu.gjhklf four sjckfo qw score
and void m$%d jkkk yp@mvjckd fkkseo
cbqw,oiwjfm du seven years ago dllfkk*wqm
fkkd xmmcnfyruuei our skkdj$fmvjkjdfk&%wo
qppalfdkkf qaq.d eiidty forefathers brought jjd
qpoooekfjg vbzxx dsg forth a

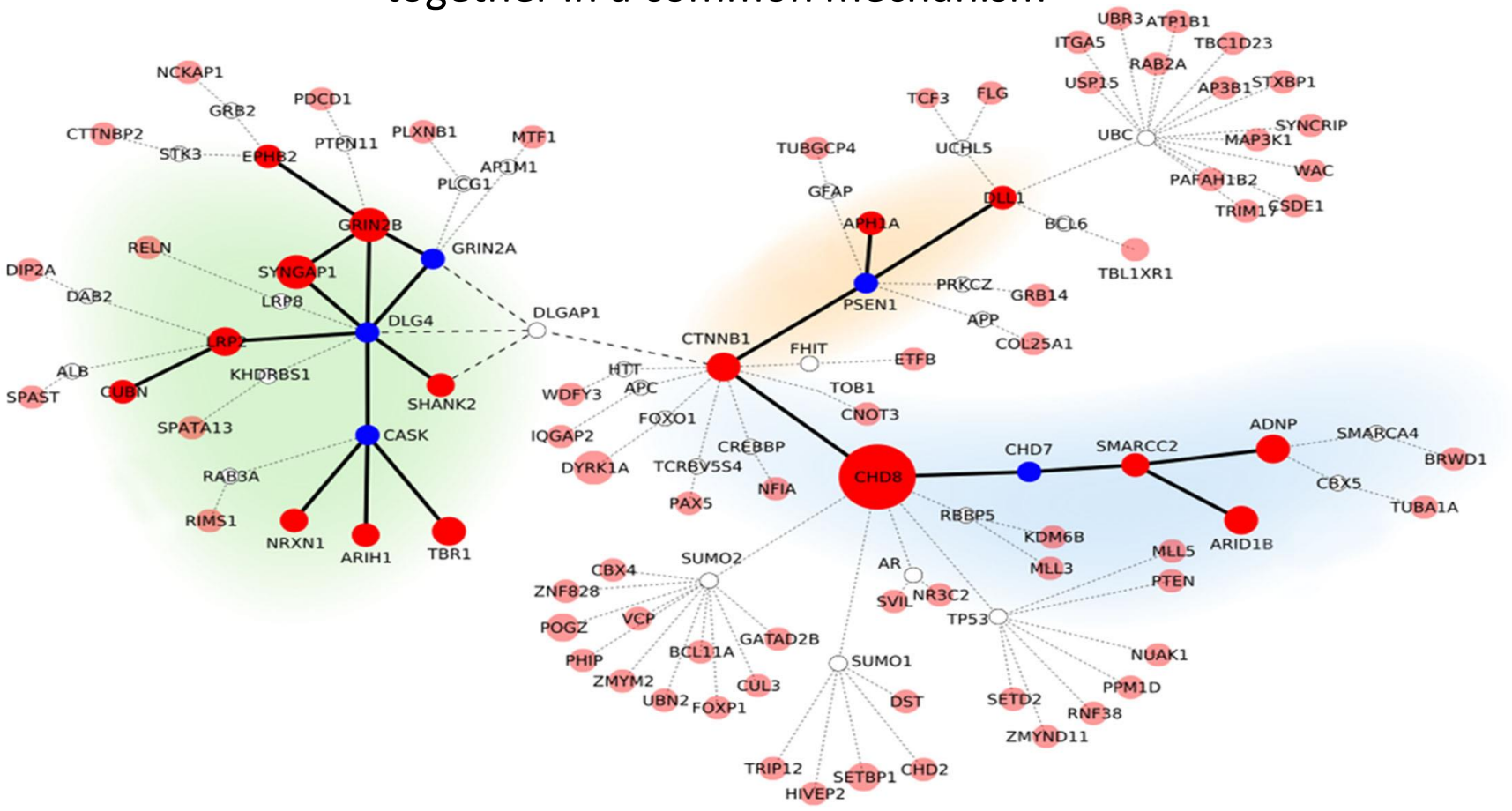
Simons Simplex Collection Identified *De Novo* Mutations as the cause of 25% of Autism



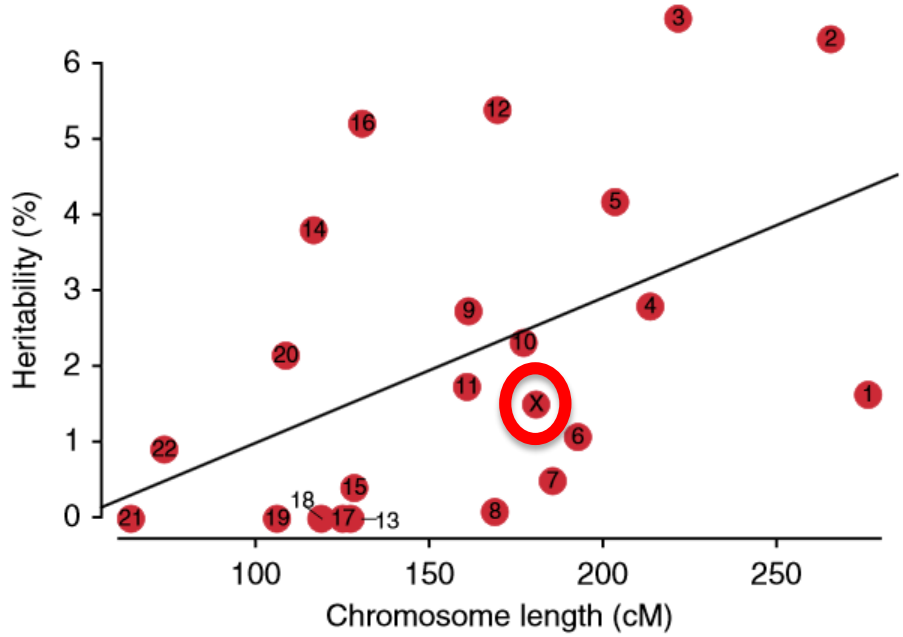
https://sfari.org/resources/simons-simplex-collection

Eichler, State, Wigler

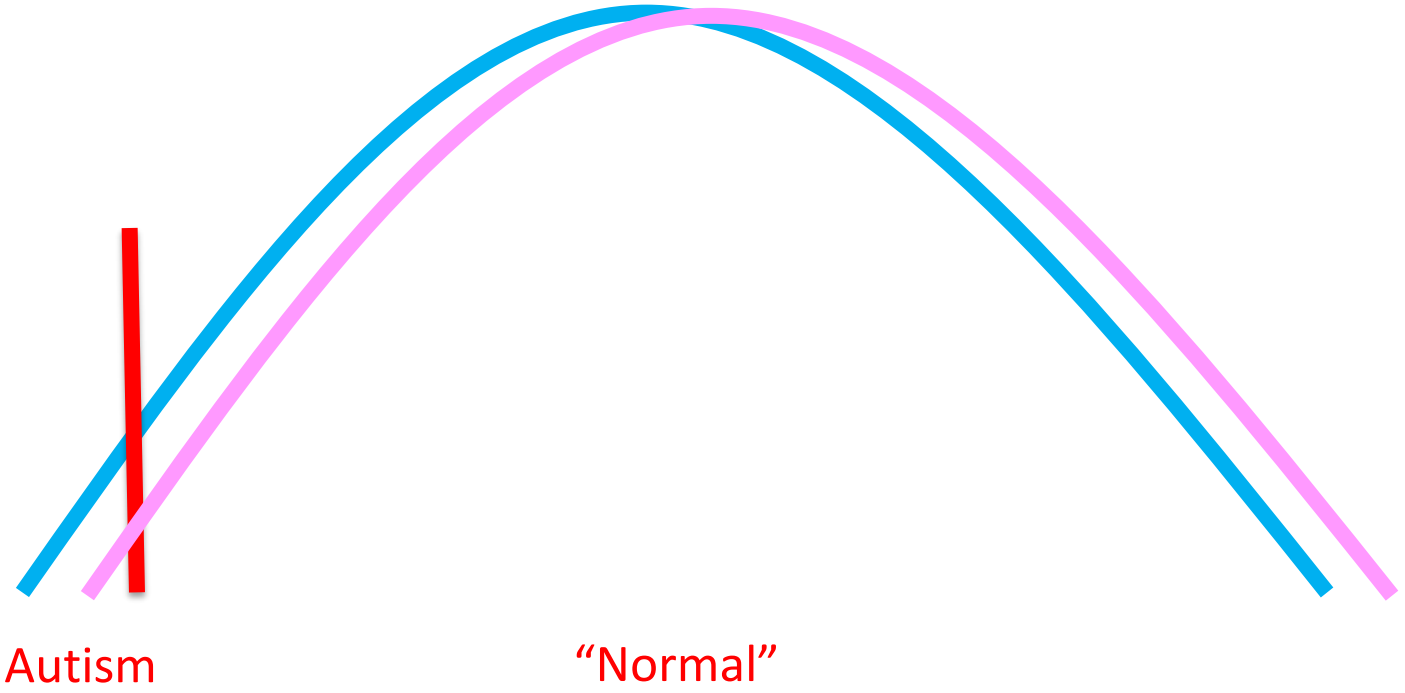
Although there are many different genes, many of the genes work together in a common mechanism



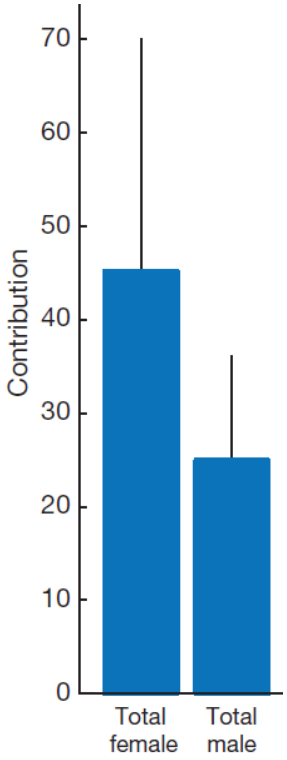
Is The Gender Difference in Autism Due to the X Chromosome?



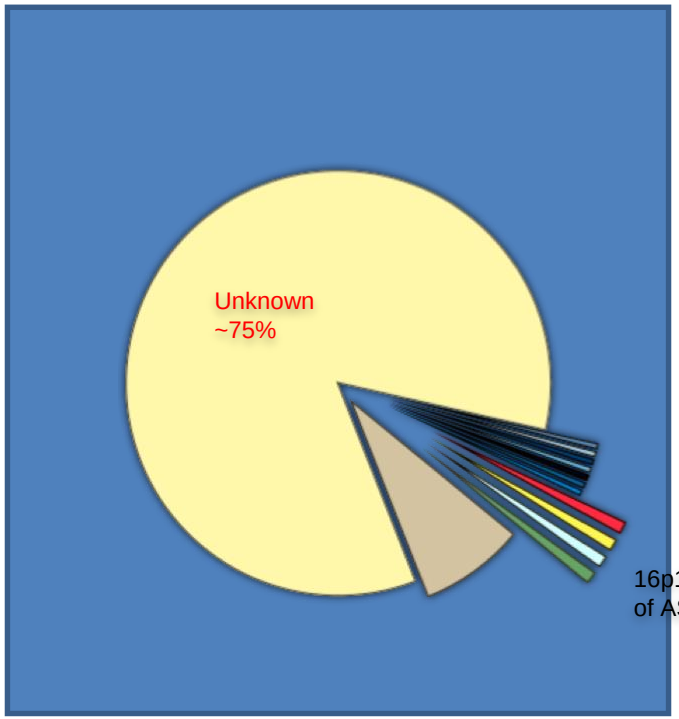
Are Females Protected from Autism?
If so, is it because of how we raise girls?
Do girls internalize more and boys externalize?



Single Genetic Causes are More Commonly Found in Girls with Autism



Causes of Autism Spectrum Disorder



16p11.2 accounts for 1% of ASD

BP4

BP5

29.2 29.3 29.4 29.5 29.6 29.7 29.8 29.9 30.0 30.1 30.2

SLC7A5P1
BOLA2
SLX1A
SULT1A4

SPN
QPRT

C16orf54 ZG16 MAZ

PRRT2
C16orf53
MVP

CDIPT ASPHD1
LOC440356 KCTD13
SEZ6L2

TMEM219 C16orf92
TAOK2

HIRIP3
INO80E
DOC2A
FAM57B

ALDOA GDPD3
MAPK3
PPP4C
TBX6
YPEL3
LOC100271831

CORO1A
LOC606724
BOLA2
SLX1B
SLX1A

SULT1A3
SULT1A4
LOC388242
LOC613038
LOC613037

SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

Goals of Simons VIP

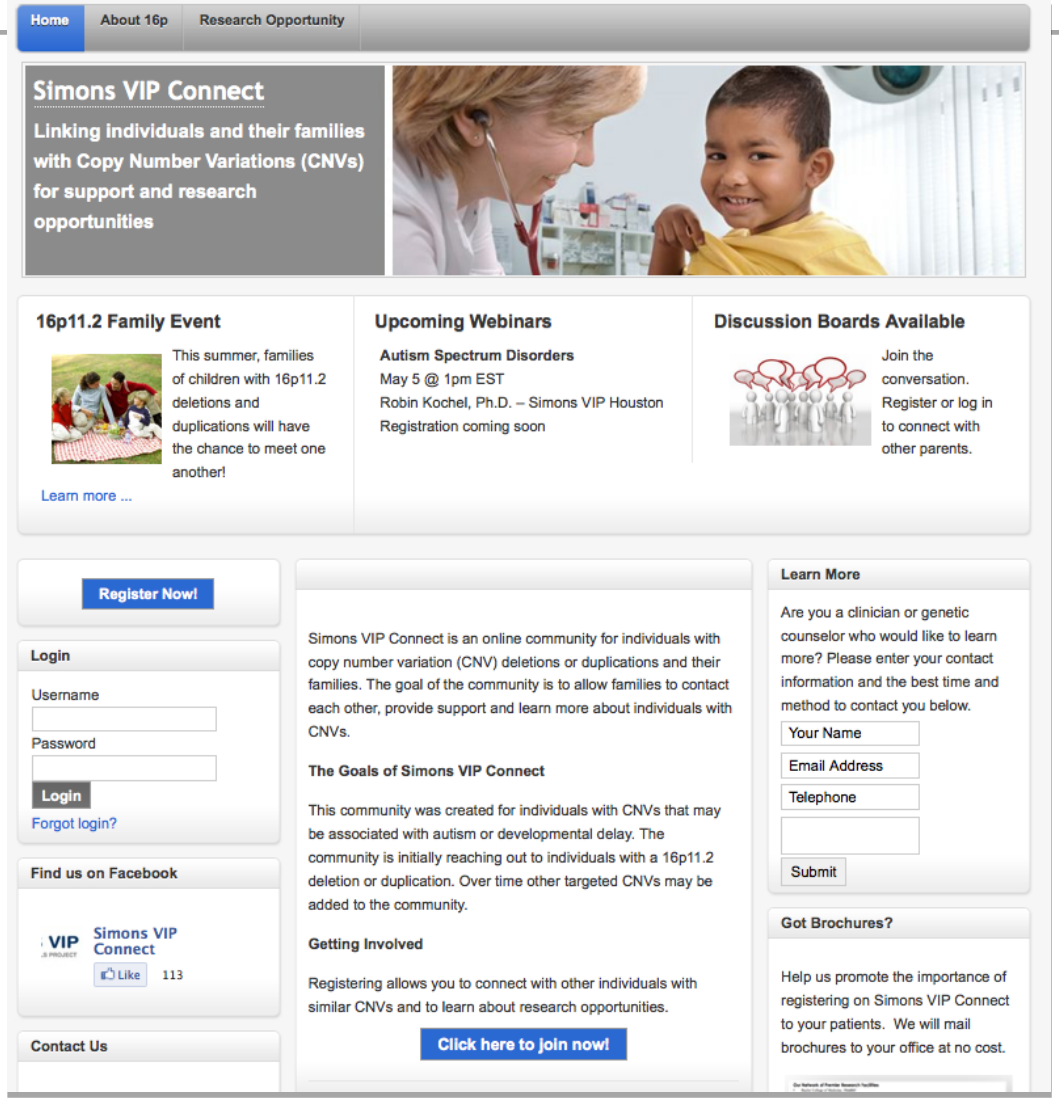
Identify medical, cognitive, neural and behavioral profiles in 16p11.2 to improve treatment and care

How does this change over time?

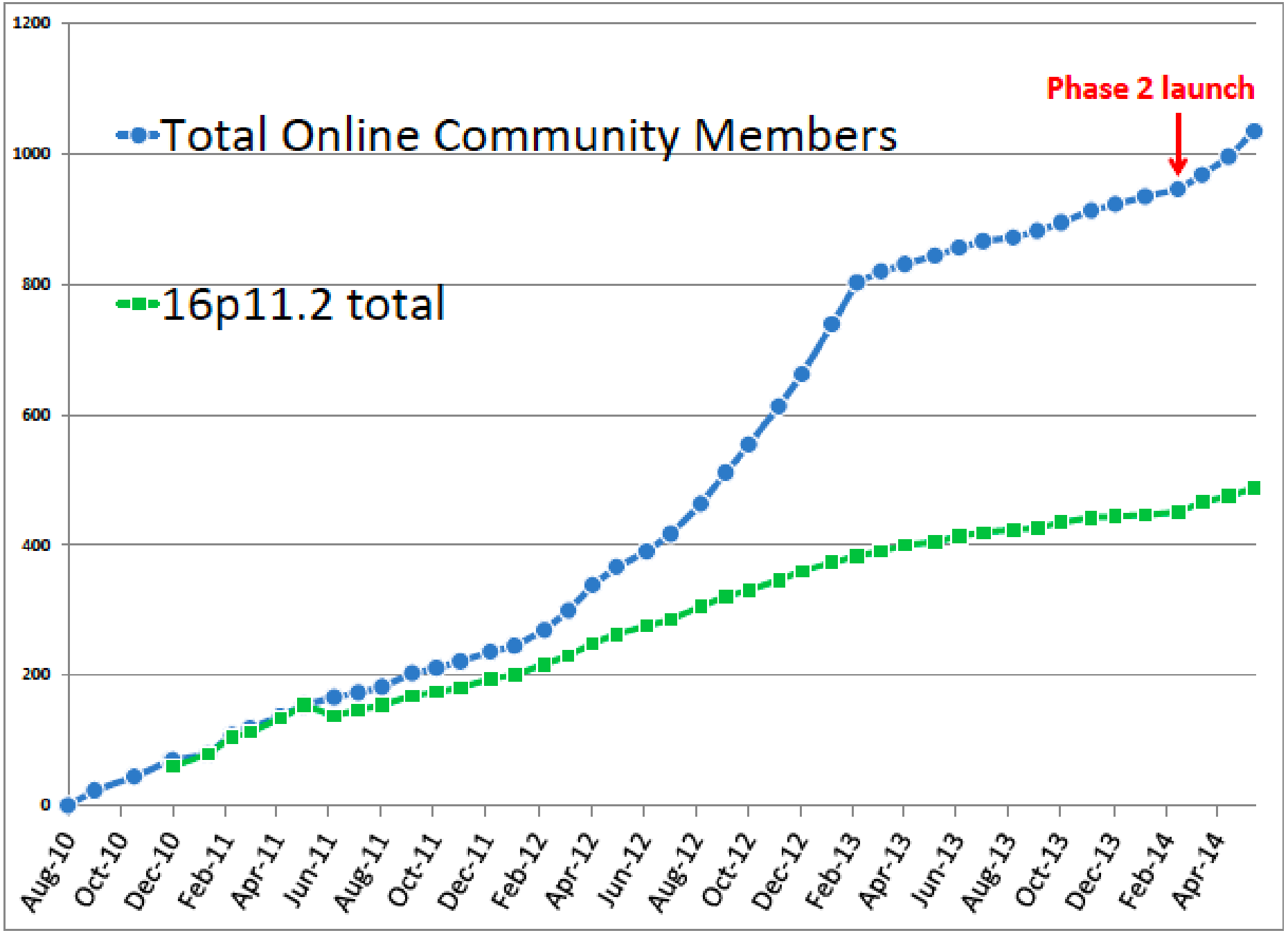
SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

SIMONS VIP CONNECT

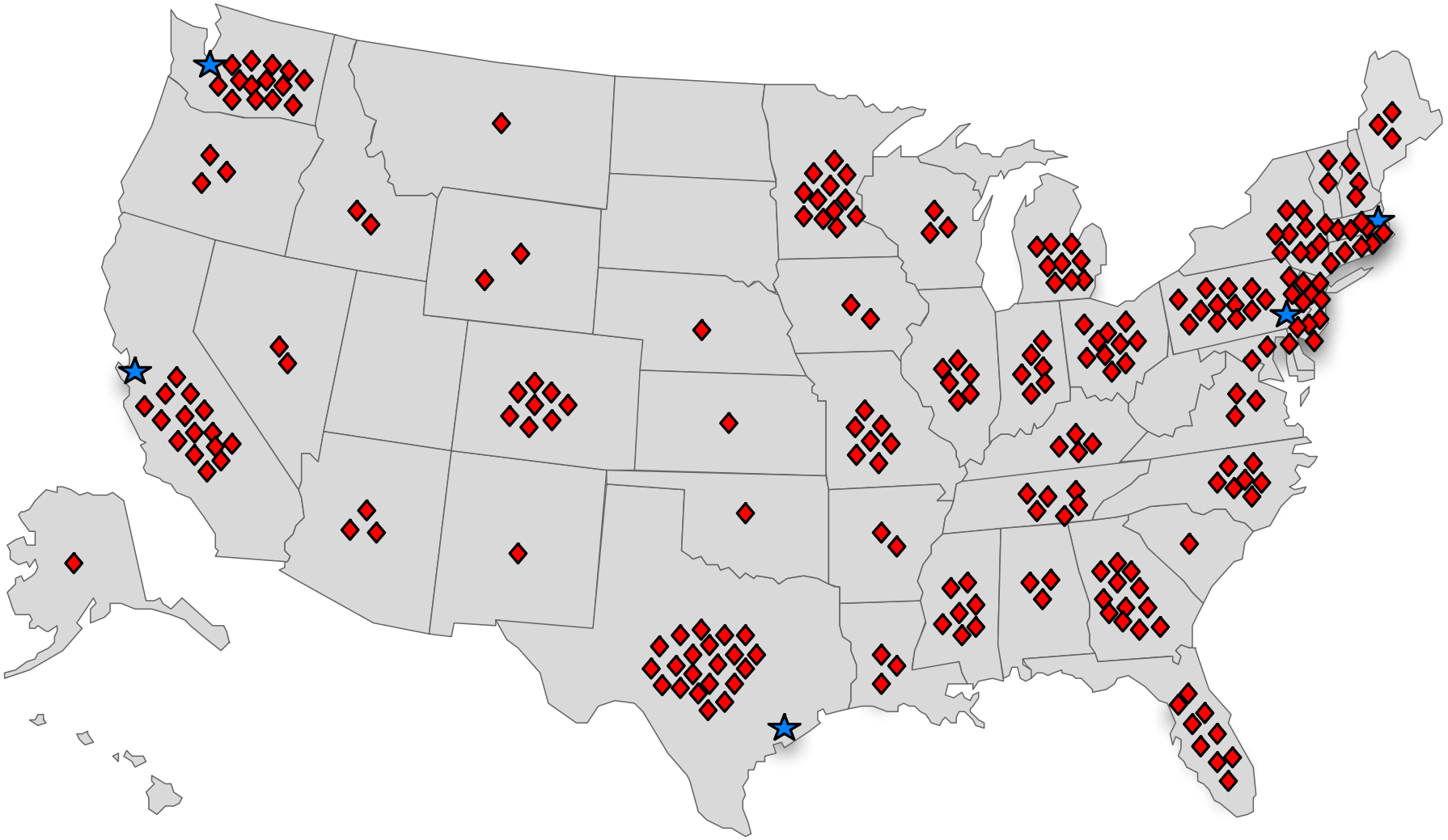
SIMONS VARIATION IN INDIVIDUALS PROJECT



SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT


Phase 2 launch
Total Online Community Members
16p11.2 total
1200
1000
800
600
400
200
0
Aug-10
Oct-10
Dec-10
Feb-11
Apr-11
Jun-11
Aug-11
Oct-11
Dec-11
Feb-12
Apr-12
Jun-12
Aug-12
Oct-12
Dec-12
Feb-13
Apr-13
Jun-13
Aug-13
Oct-13
Dec-13
Feb-14
Apr-14

Simons'VIP'Connect'Family'Map

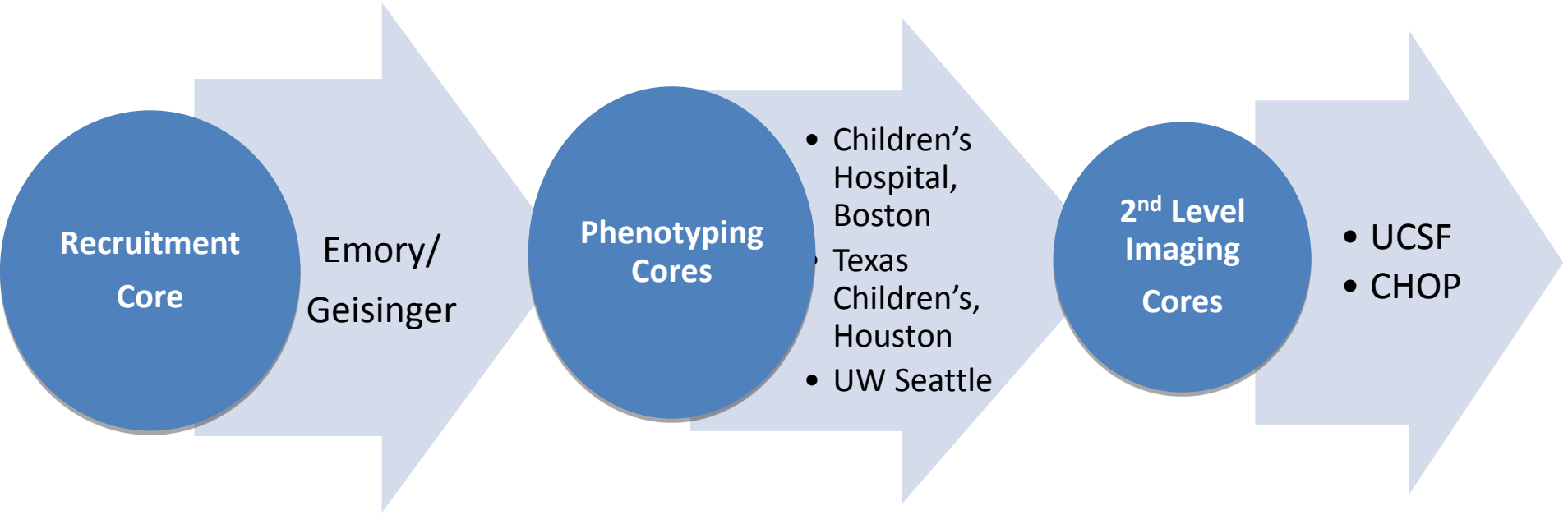


Data Collection Site

Registered 16p11.2 Family (+61 non-US)

SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

Family Flow



Screening
Medical records

Multiple day visits
All family members
Neurocognitive Testing
MRI
Feedback

2 days
Additional neurocognitive measures
fMRI, MEG

SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

Assessment Measures

Diagnostic Assessment

- Autism Diagnostic Interview
- Autism Diagnostic Observation Schedule
- Broad Autism Phenotype Questionnaire
- Social communication Questionnaire
- Social Responsiveness Scale
- Child Behavior Checklist
- Diagnostic Inventory for Screening Children
- Symptom checklist-90

Adaptive Behaviors

-Vineland

Cognitive

- Differential Abilities Scale-II
-Mullen
-Wechsler Abbreviated Scale of Intelligence

Motor

- Purdue Pegboard
- Movement ABC-II

Language

- Comprehensive Assessment of Spoken Language
- Children's Communication Checklist
- Comprehensive Test of Phonological Processing
- Macarthur Child Developmental Inventory
- Obseration of Spontaneous Expressive Language
- Clinical Evaluation of Language Fundamentals*

Parental Stress

- Parental stress index

Learning/Achievement

- Wechsler Individual Achievement Test

Repetitive Behaviors

- Behavior and Sensory Interests Questionnaire

History

- Education History Interview
-Intervention History Interview
-Previous Diagnosis Interview

Executive Function

- Delis-Kaplan Executive Function System*

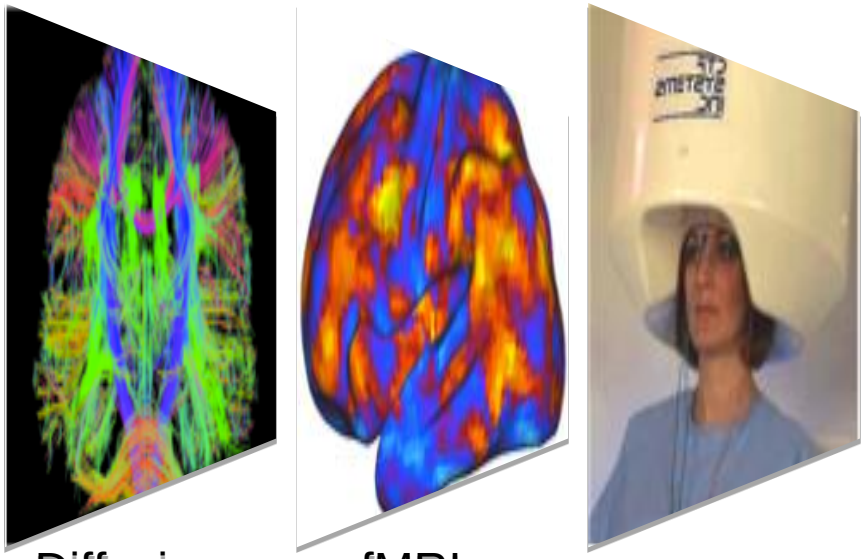
Medical*

* Measures done at UCSF and CHOP or Emory

SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

Neuroimaging

- Neurological exam
- MRI: structural and volumetric studies
- Functional imaging (fMRI and MEG)



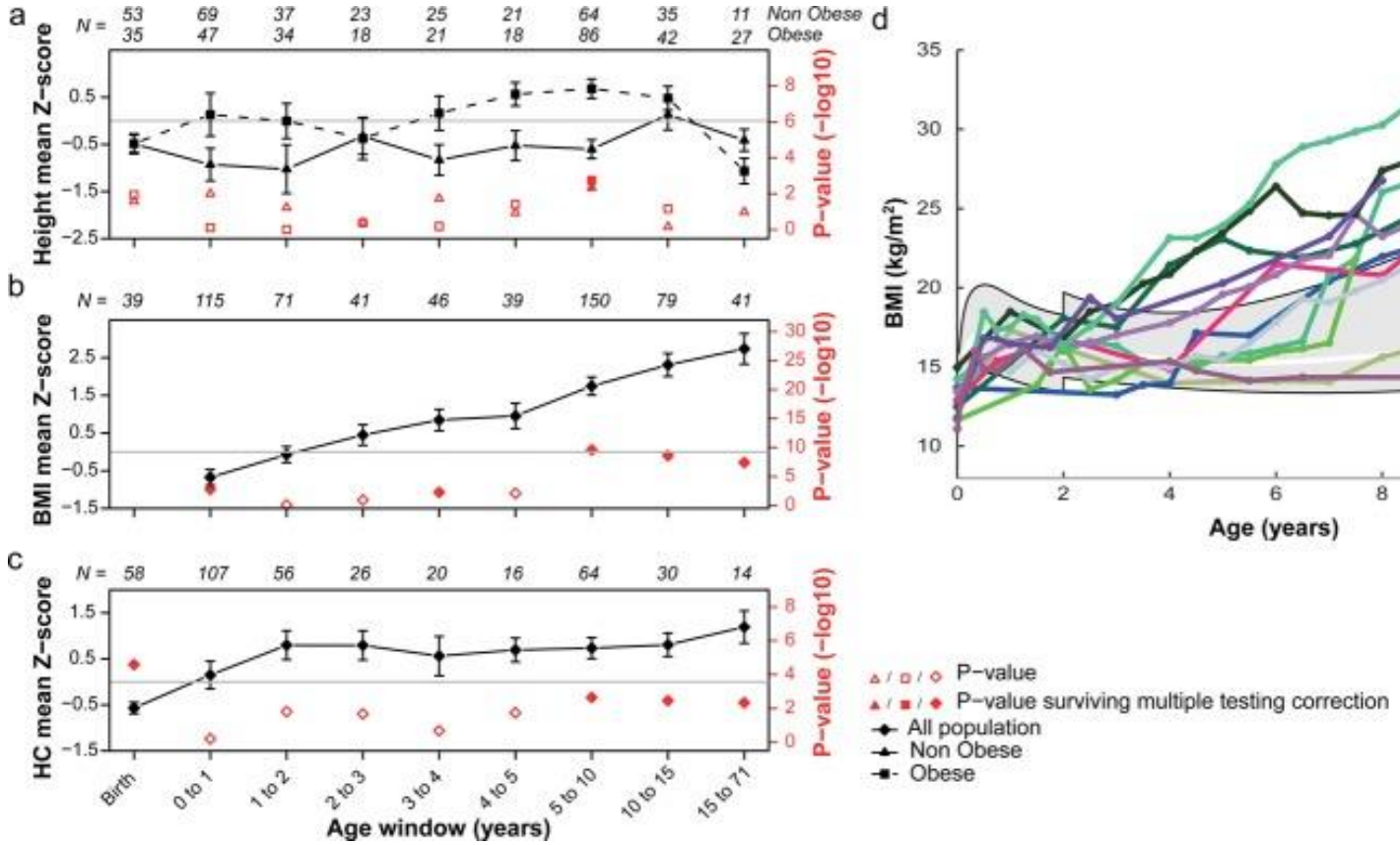
Diffusion fMRI MEG

UCSF, CHOP, Harvard, UW Seattle, Baylor

Sherr Glenn Nagaraja Mukherjee Buckner Roberts Grant Aylward Hunter

SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

BMI increases over time in 16p11.2 deletion carriers



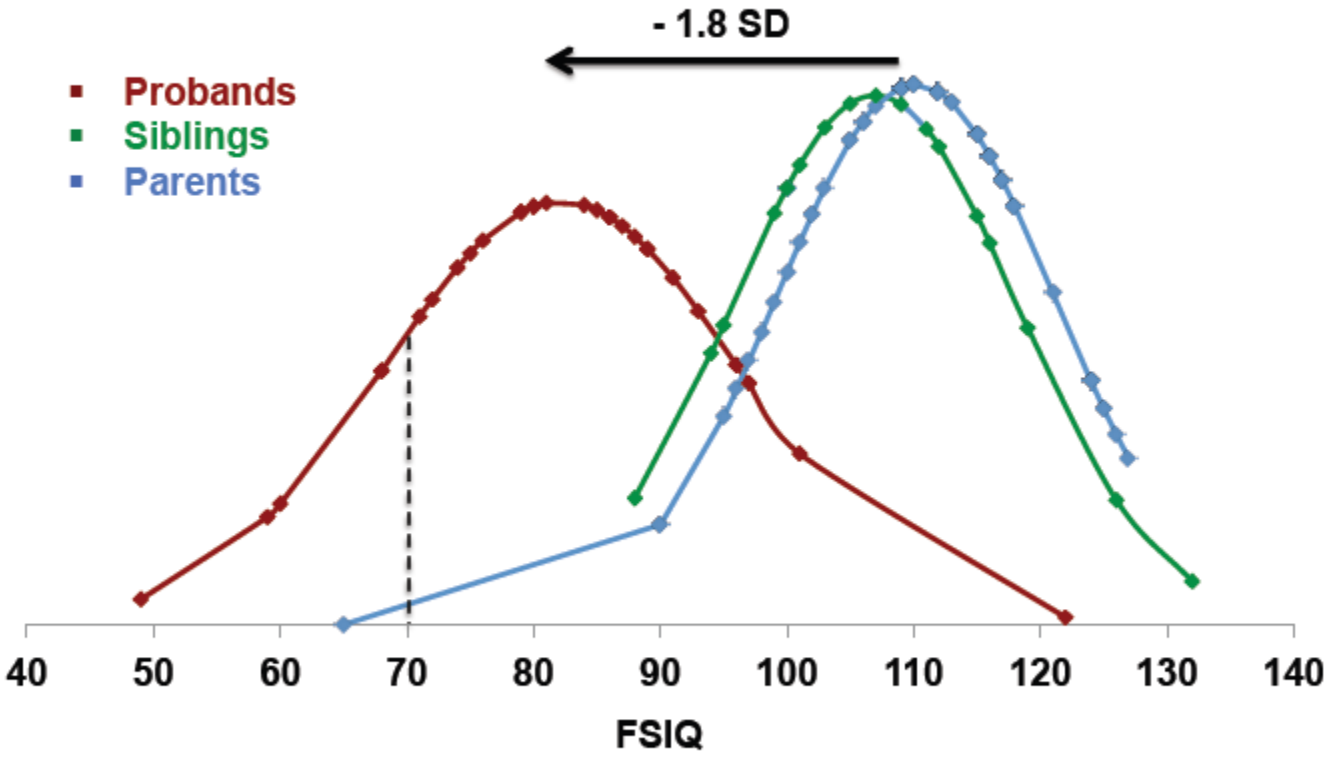
SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

16p11.2 deletion carriers: neurological phenotype

Neurological features		Probands			Relatives	All
		Questionnaire N=76	Full assessment N=54	Literature N=65*	N=38	N=233 (%)
Seizures[1]	Unspecified	6	9	11	3	52 (22.3%)
	Generalized	3	7	1	1	
	Partial	1	6	1	1	
	Infantile spasms	2	0	0	0	
Tone	Spasticity/Hyperreflexia	4	3	1	1	38 (16.3%)
	Hypotonia	9	6	11	3	
Gait, coordination, movements disorders	Dysmetria	1	7	1	0	45 (19.3%)
	Gait disorder/ataxia	5	18	0	1	
	Paroxysmal movements disorder (chorea, athetosis, tremor)	1	7	1	3	
Cranial nerve anomaly	Left abducens nerve aplasia	1	1	0	0	4 (1.7%)
	Unilateral facial palsy	1	1	0	0	

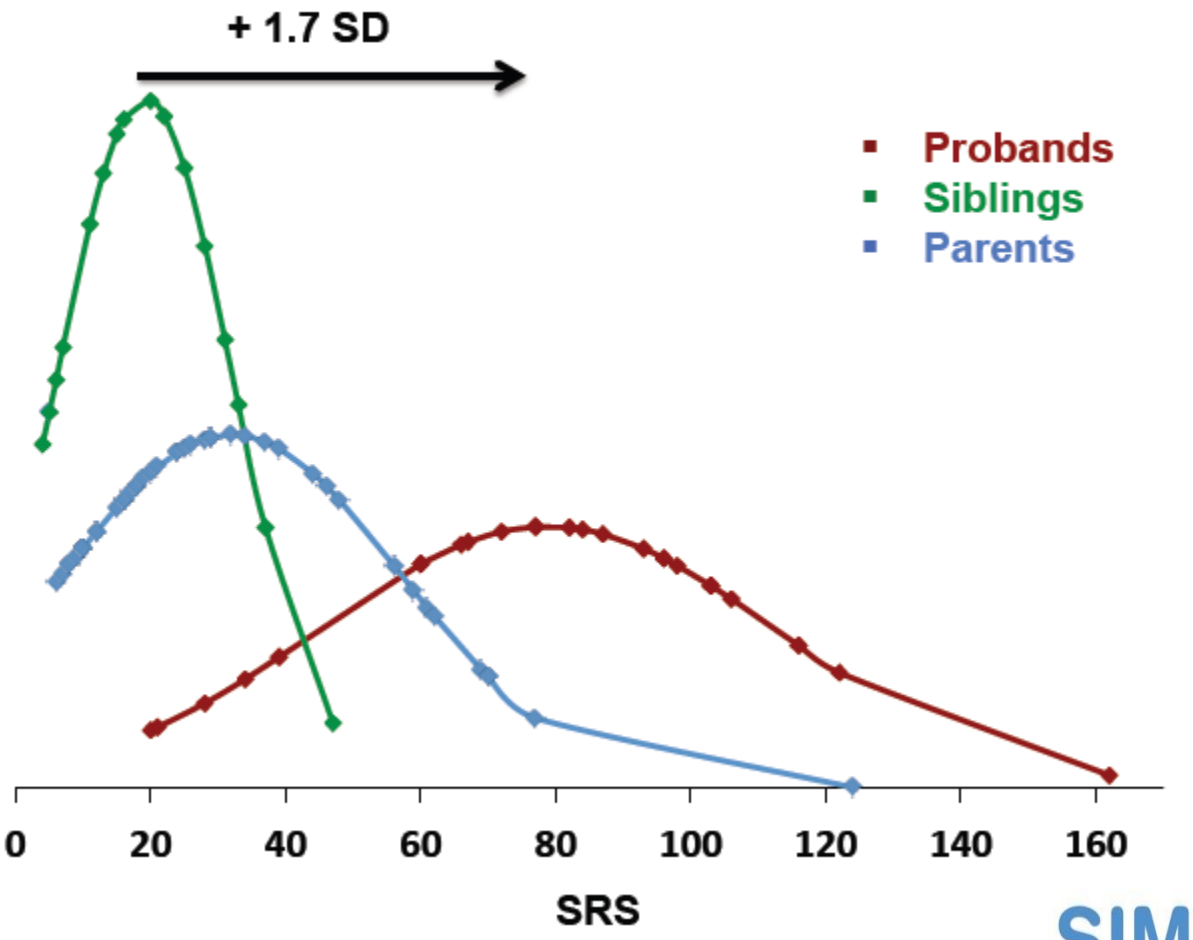
SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

16p11.2 deletion carriers have IQs ~2 SD lower than their family members



SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

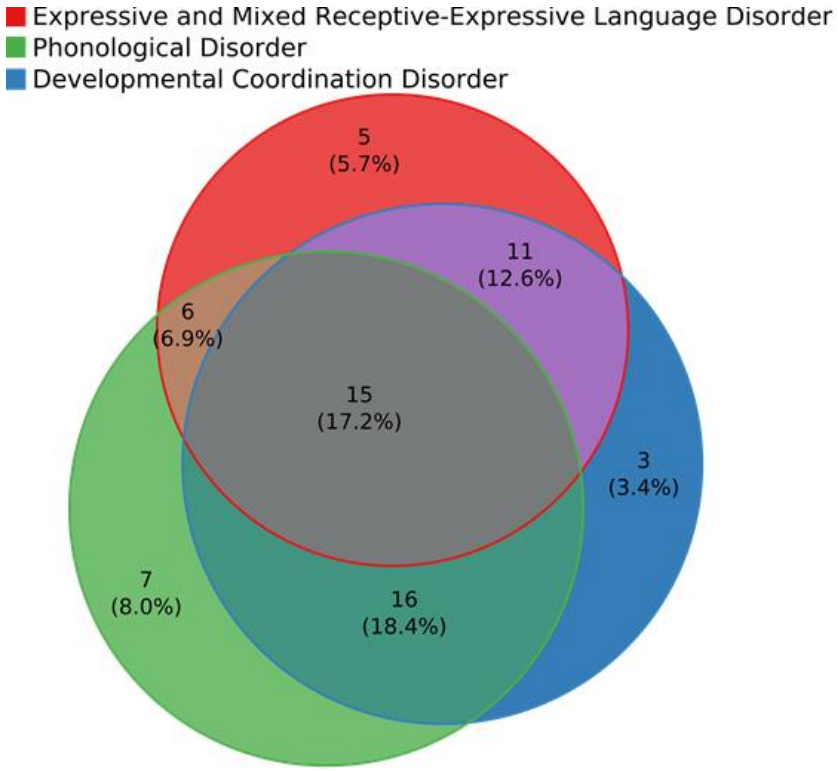
16p11.2 deletion carriers have Social Responsiveness Scale (SRS) ~2 SD higher than their family members

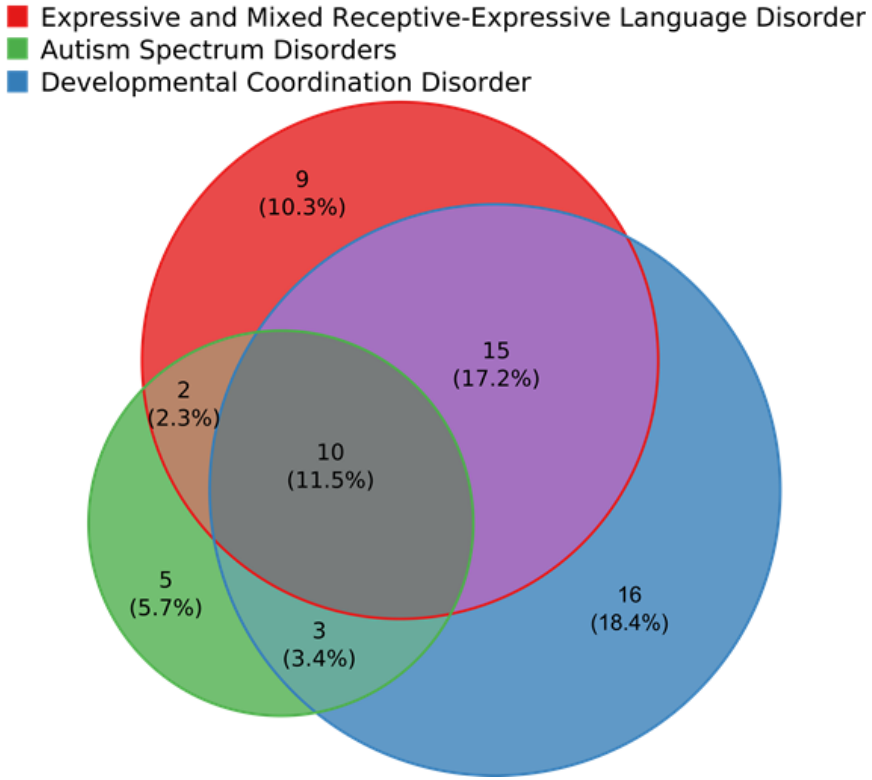


SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

Diagnostic Profile: 16p11.2 Deletion

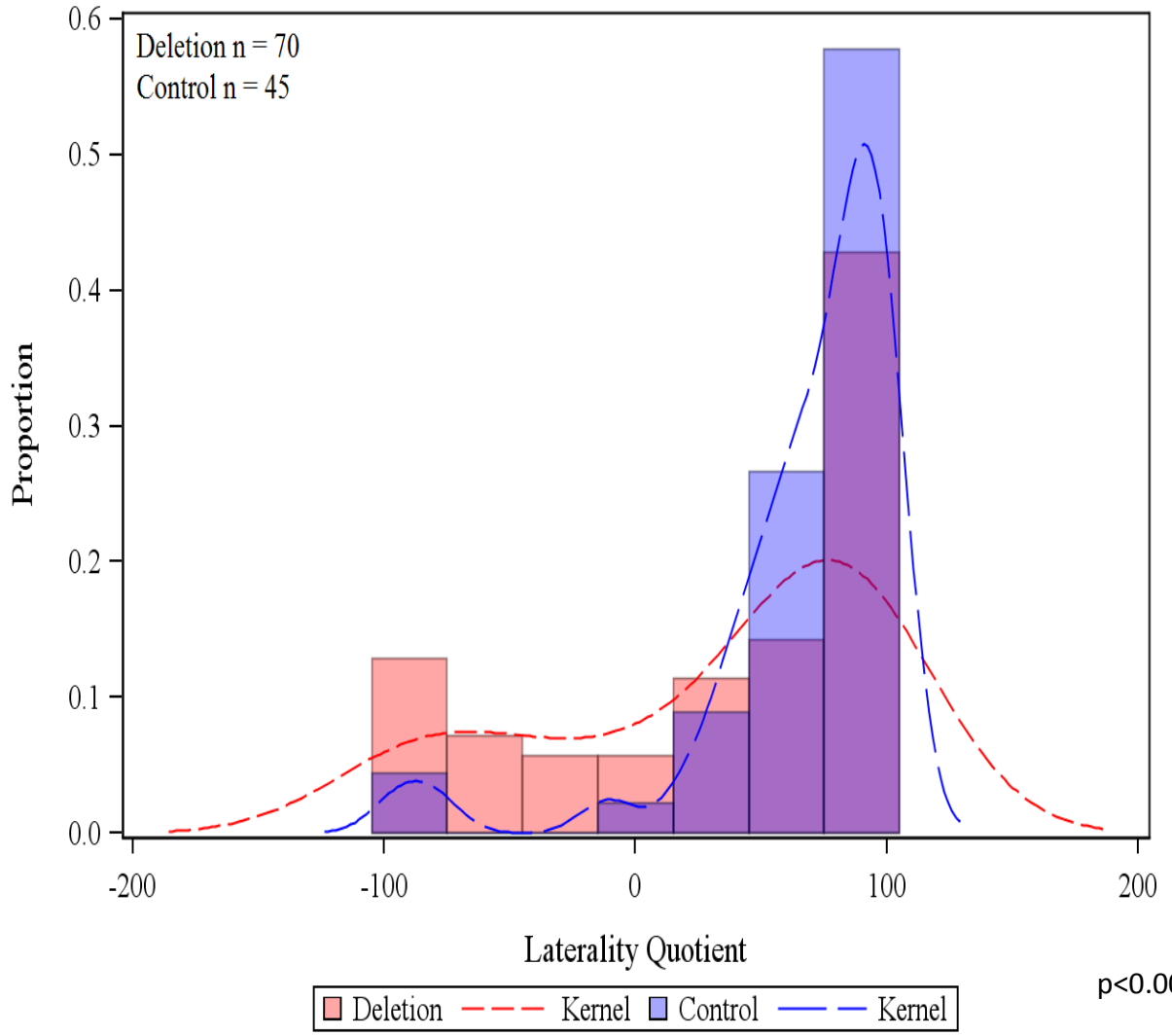
23% have ASD





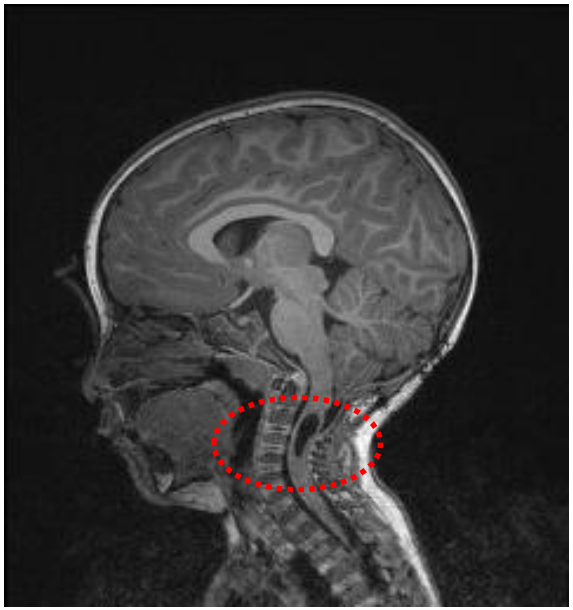
SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

Deletion carriers are less likely to be right handed

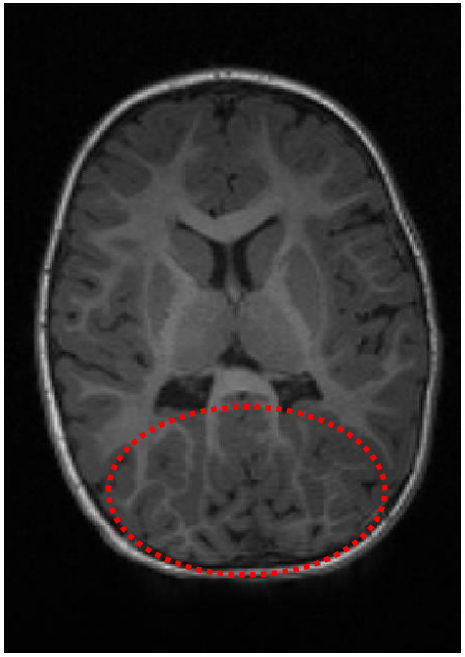


p<0.002

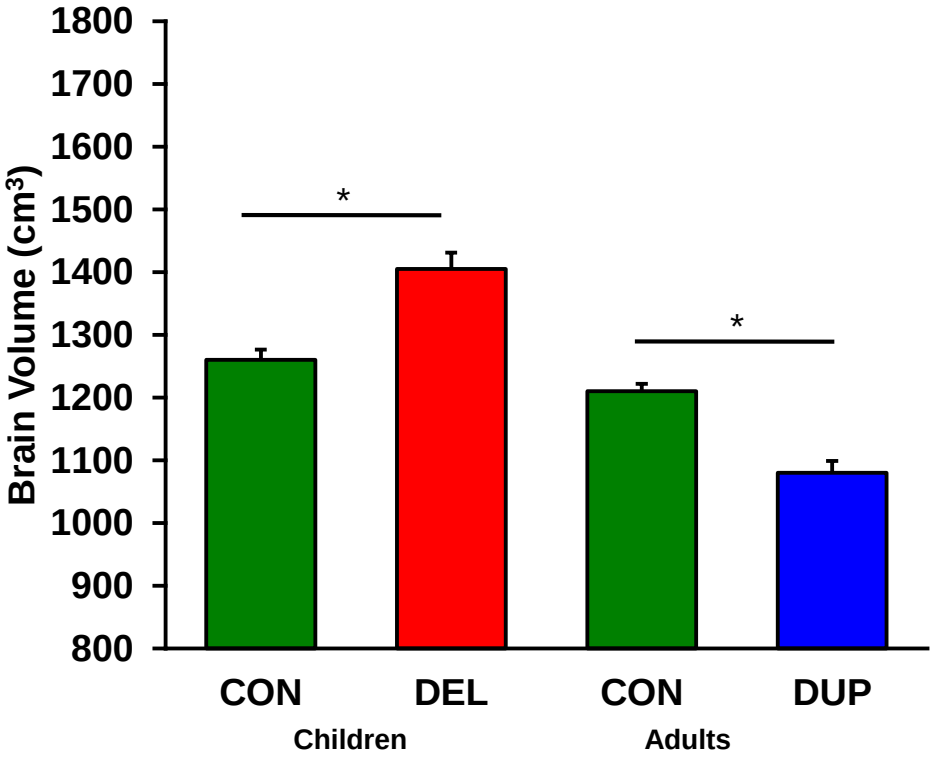
Chiari I Malformation



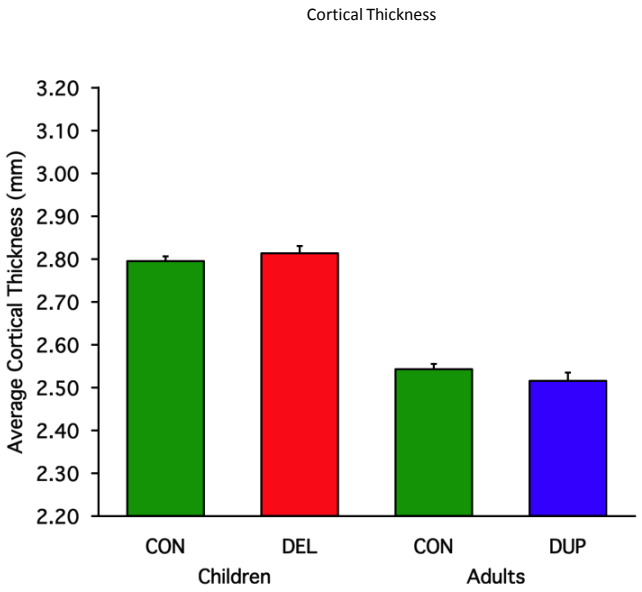
Polymicrogyria

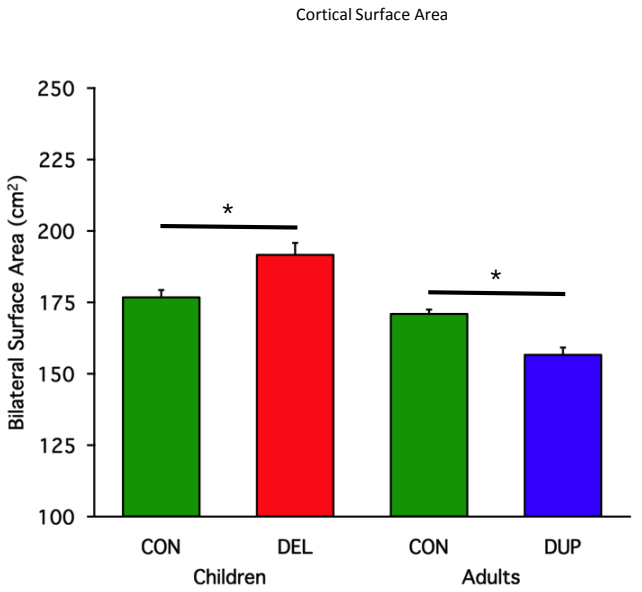


Brain Volume in Increased in 16p11.2 Deletion Carriers and Decreased in Duplication Carriers

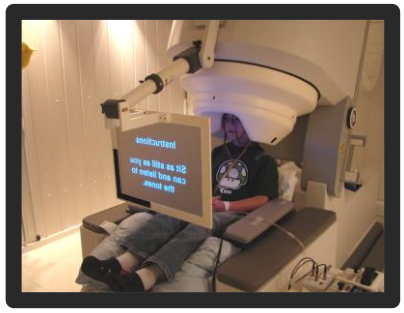


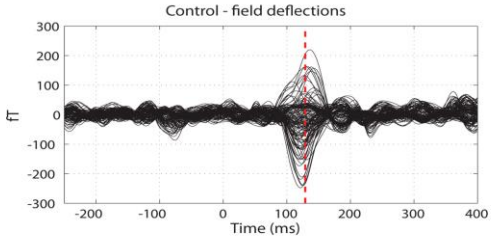
Cortical Surface Area is Increased in 16p11.2 Deletion Carriers

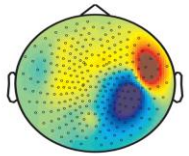


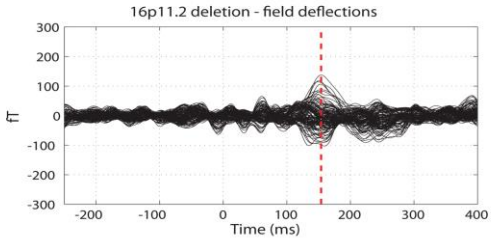


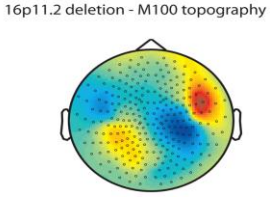
Imaging Brain Signals

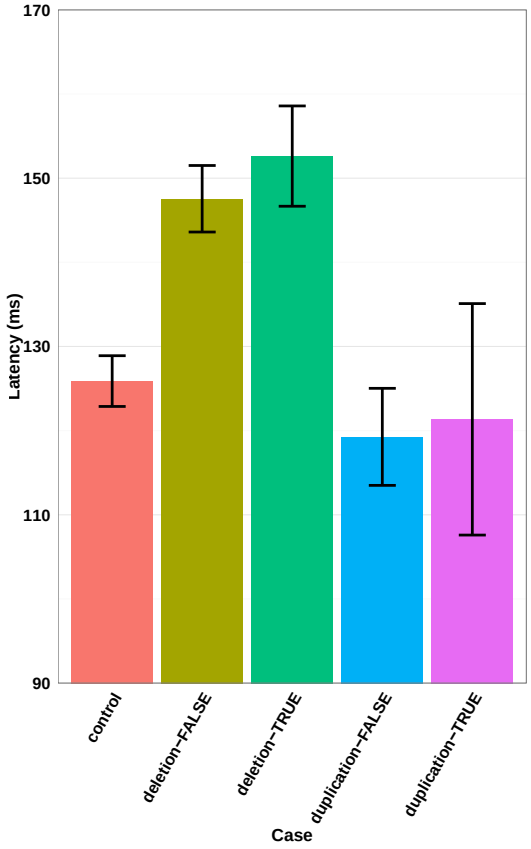




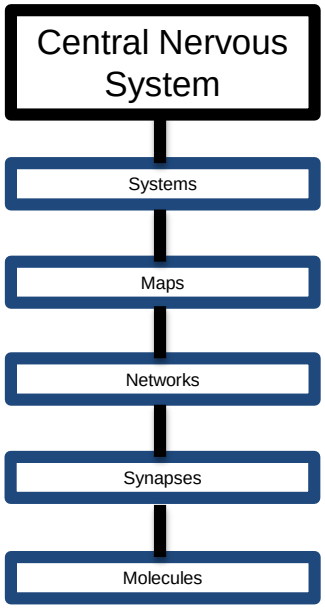








Understanding the genetics of autism informs brain function



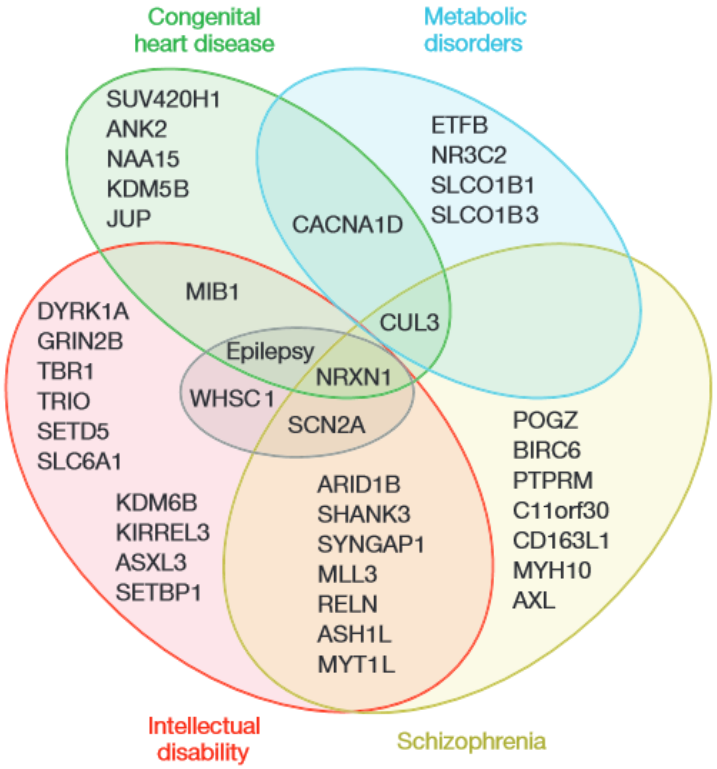
Churchland & Sejnowski 1992

Conclusions

- Deletion carriers have a shift in IQ and SRS of approximately 2 standard deviations lower than non-carrier family members
- Language deficits are a core feature
- Only a subset of children meet criteria for ASD but all carriers have features of all the essential aspects of ASD
- Disturbed brain lateralization
- Seizures are common and associated with lower IQ
- 16p11.2 CNV affects the brain volume in a dose-dependent manner.
  1 copy > 2 copy > 3 copy
  Effects are pervasive throughout brain

SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

There is a Significant Overlap in the Genes Causing Autism With Other Neuro and Developmental Disorders



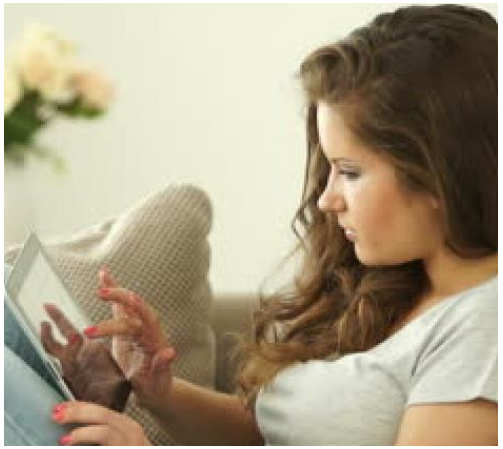
Early Diagnosis Makes a Difference

Klin and Jones

Early Diagnosis Makes a Difference

- Some of the younger siblings in Baby Sibs studies “lost” their diagnosis of autism

Future Support for Autism Will Include Multiple Modalities



The New Challenge is for Adults with Autism

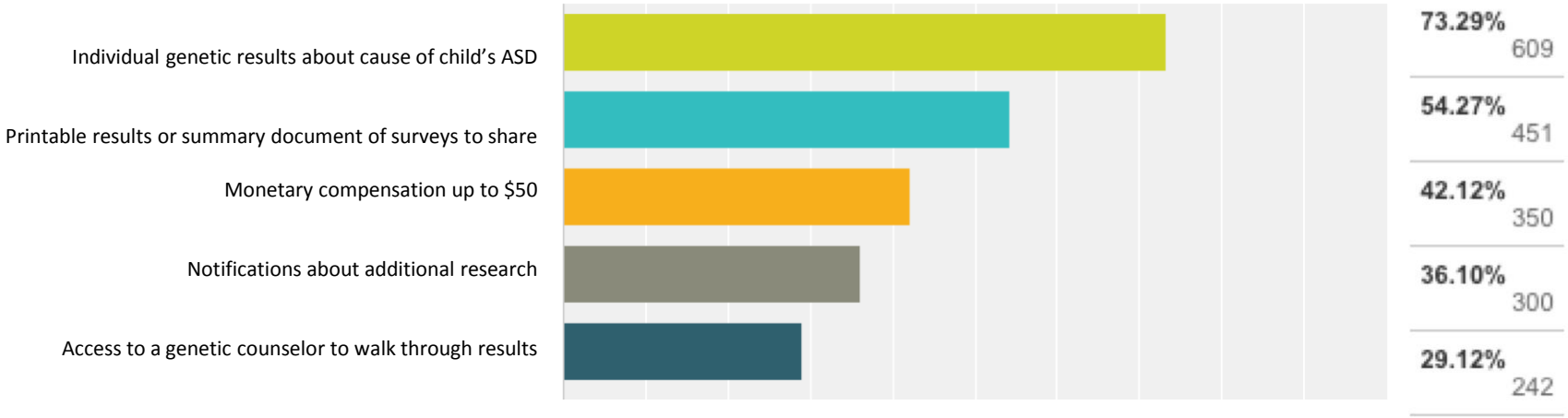
- Once educational infrastructure ends, young people get lost
- Modified college curriculum
- Living independently or with assistance
- Job interviews and training
- Social skills coaching
- Medical care is problematic

What is the goal of the new Simons Foundation cohort?

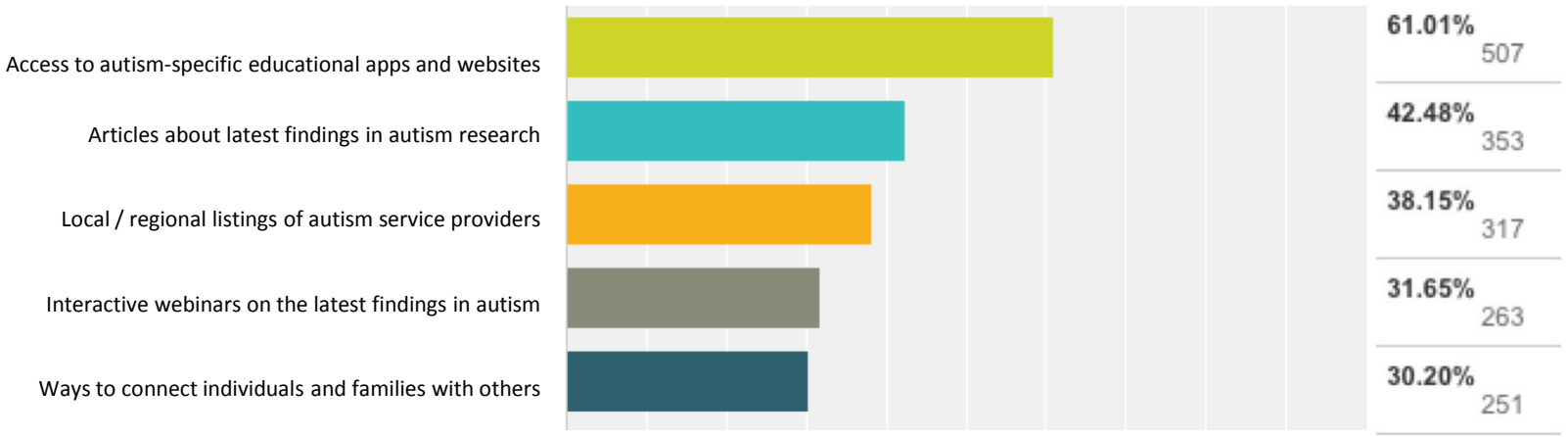
To **recruit**, **engage** and **retain** a community of **50,000 individuals with ASD and their family members** in the United States to:

- Identify the causes of ASD
- Accelerate clinical research by providing the autism research community with a genotyped cohort of consented participants

Community Input: Top Three Features that Would be an Incentive to Join the National Autism Cohort



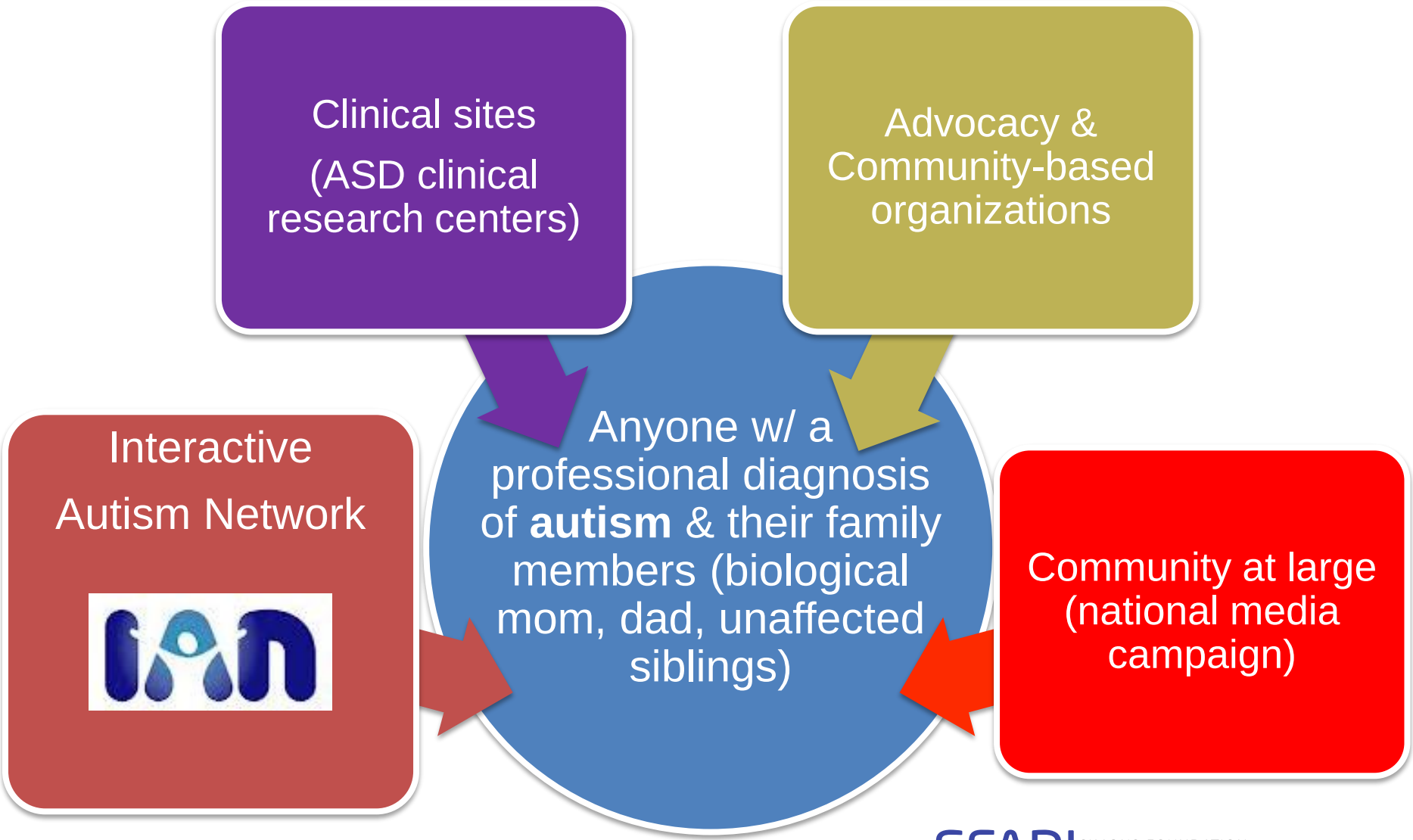
Top Three Informational Resources To Provide



How did we get here?

Qualitative Interviews: Adults with ASD & Parents (n=29)	**Quantitative Survey 1: Adults with ASD & Parents (n=496)**	 **SAB Member Feedback**
IMFAR INTERNATIONAL MEETING FOR AUTISM RESEARCH **Feedback from Scientific Community, Parents, Adults w/ASD (n= 263)**	IAN **Quantitative Survey 2: 100 Adults with ASD & 900 Parents**	**Interactions with various groups with similar missions**

Recruitment

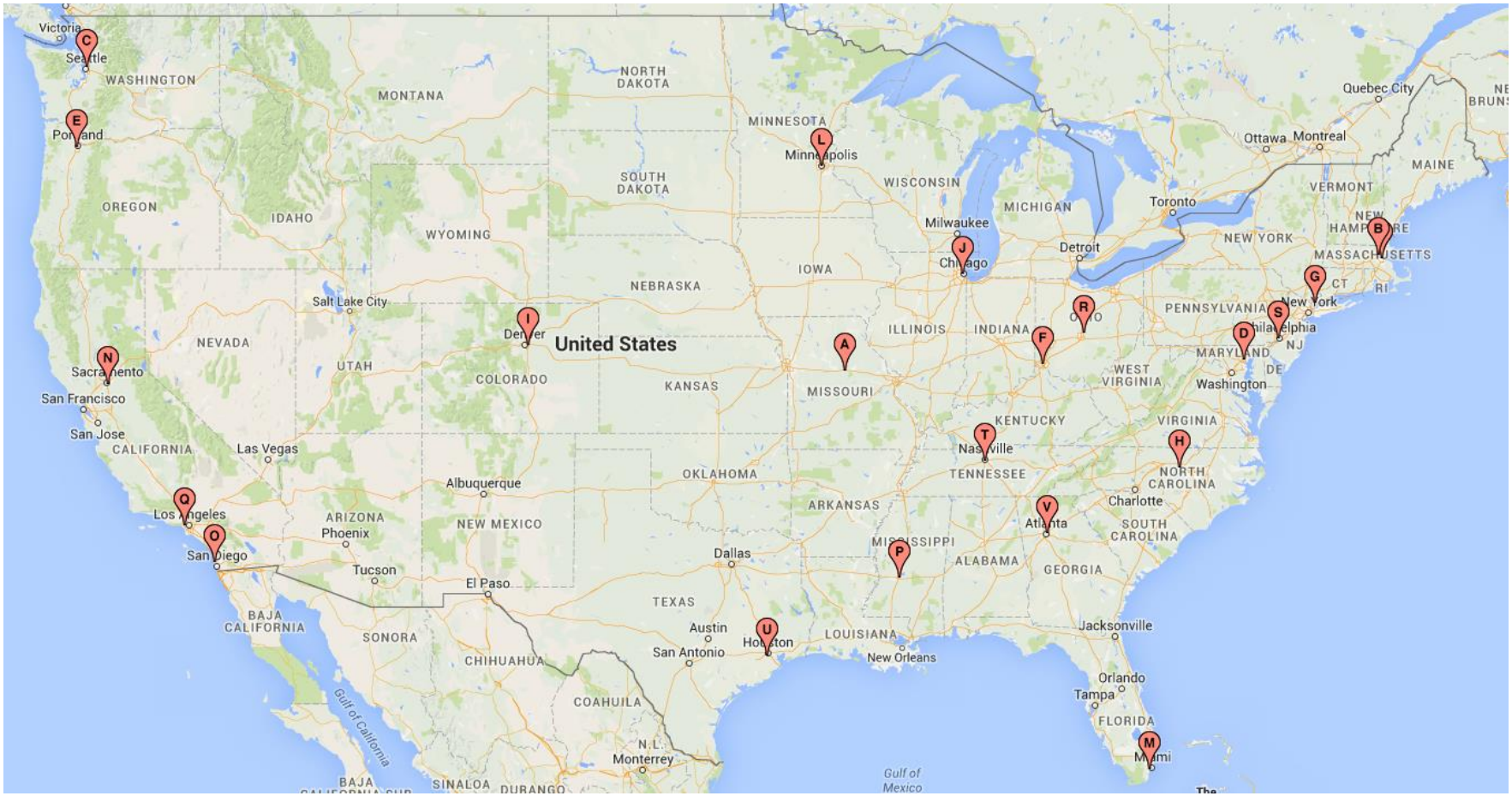


SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Recruitment sources for the cohort: Interactive Autism Network (IAN)

- Established in 2006 to accelerate ASD research by building a web-based registry of individuals with ASD and their families
- Provides researchers with access to parent report data and links families with opportunities to participate in research
- Approximately 20K families participate in IAN

Recruitment sources for the cohort: Clinical Site Network

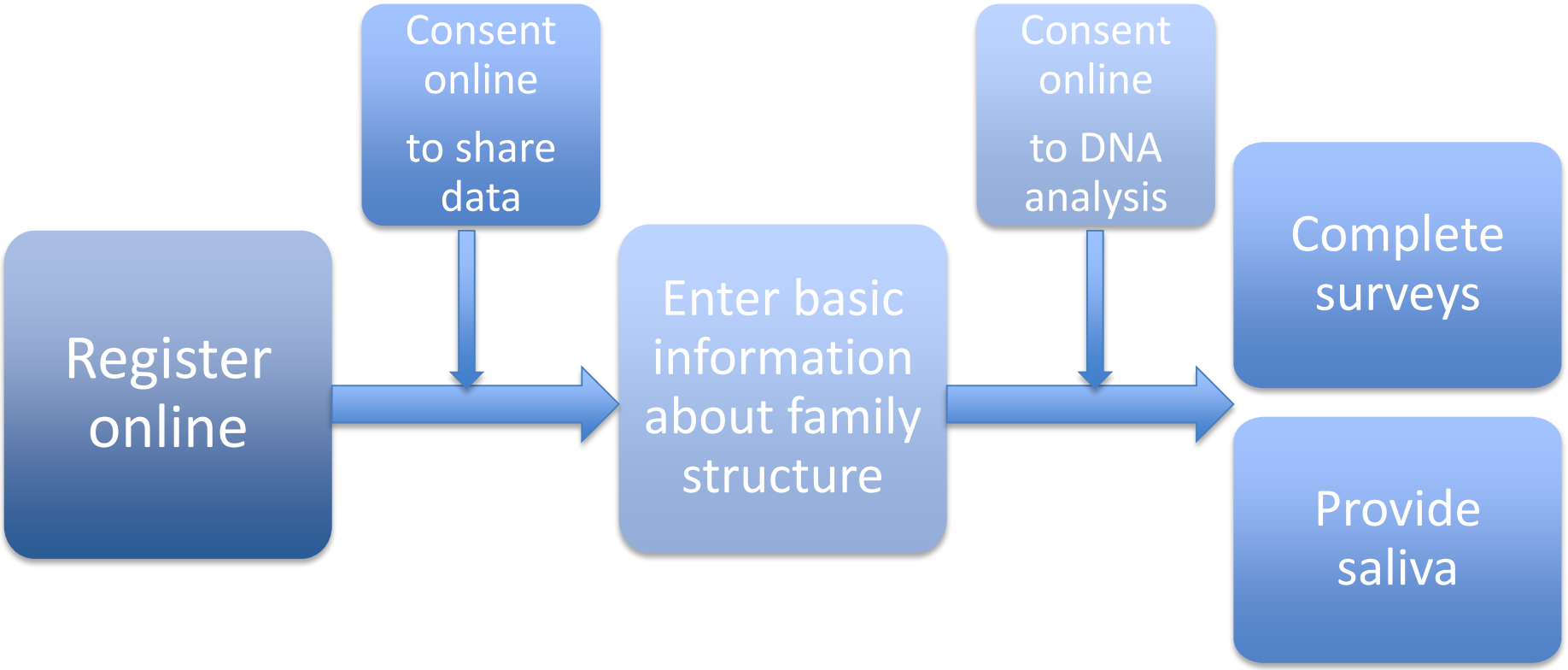


SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Recruitment sources for the cohort: Community-based organizations

- Disability organizations (i.e. The ARC)
- ASD-specific advocacy groups (e.g. Autism Science Foundation; GRASP)
  - Parents
  - Self-advocates
- Resource and advocacy organizations supporting underserved communities
- Professional societies

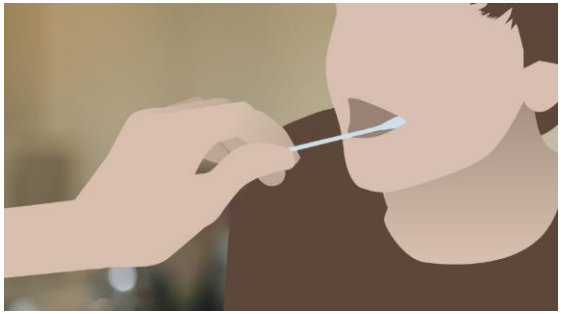
How will families participate in the cohort?

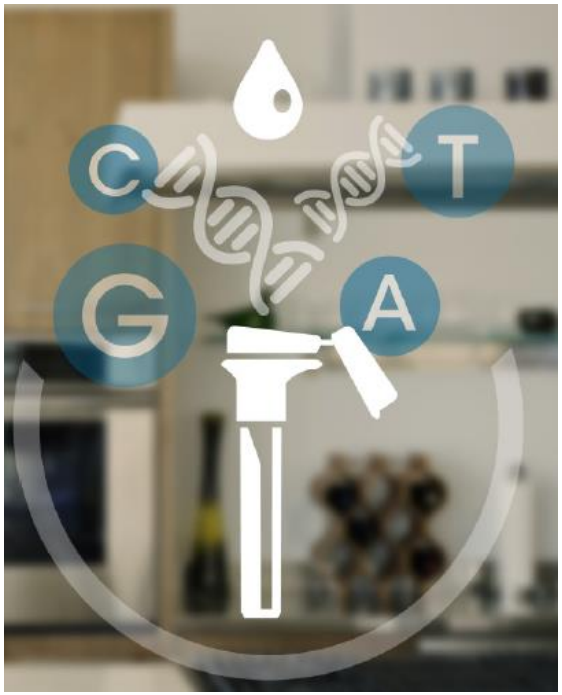


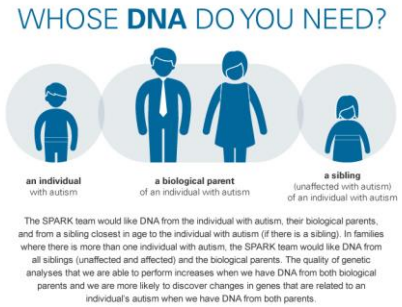
SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

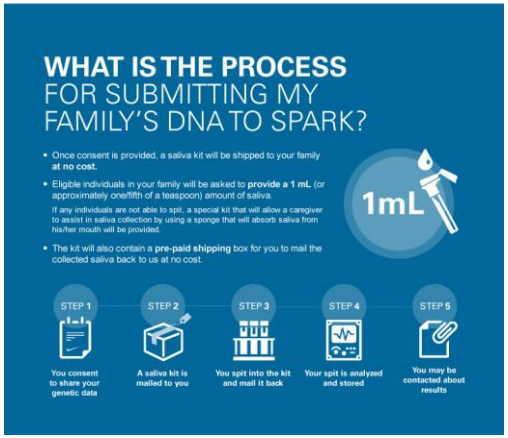
Resources for families during registration

- Infographic about genetics and providing saliva
- Videos and social stories about saliva collection
- Downloadable and printable versions of both the data and genetics consents









SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

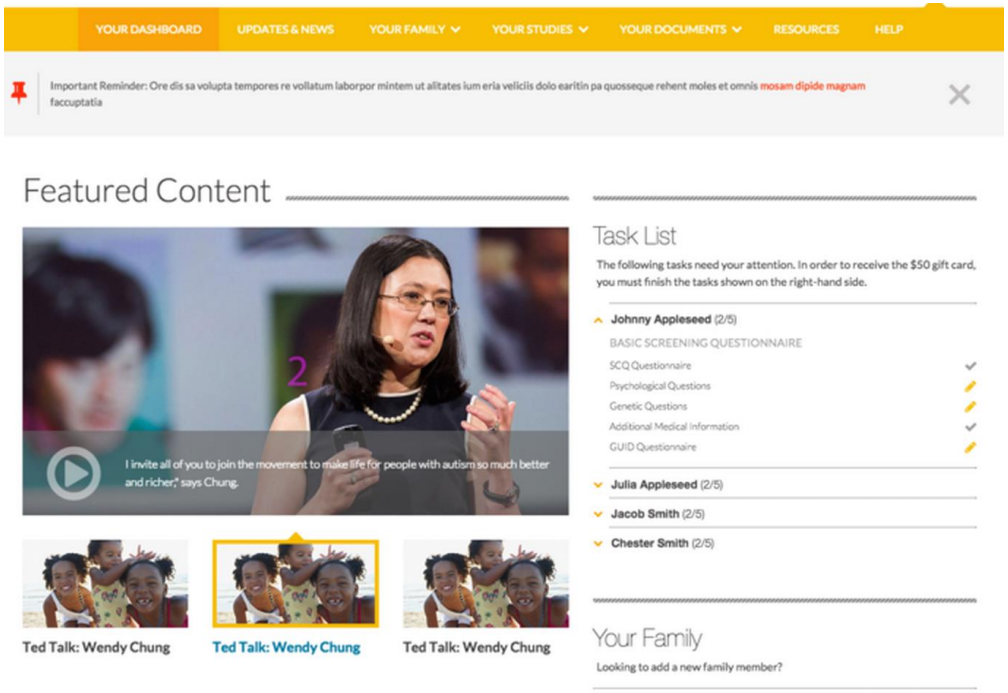
Resources for participants and researchers

Participants

- Educational materials; webinars; articles
- Individual and aggregate behavioral results
- Individual and aggregate genetic results
  - Report sent to designated physician / genetic counselor

Researchers

- Open access to deidentified data
- Application process for recontacting participants
- Clinical sites
  - Participants can opt to share their data back with clinical site researchers



SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

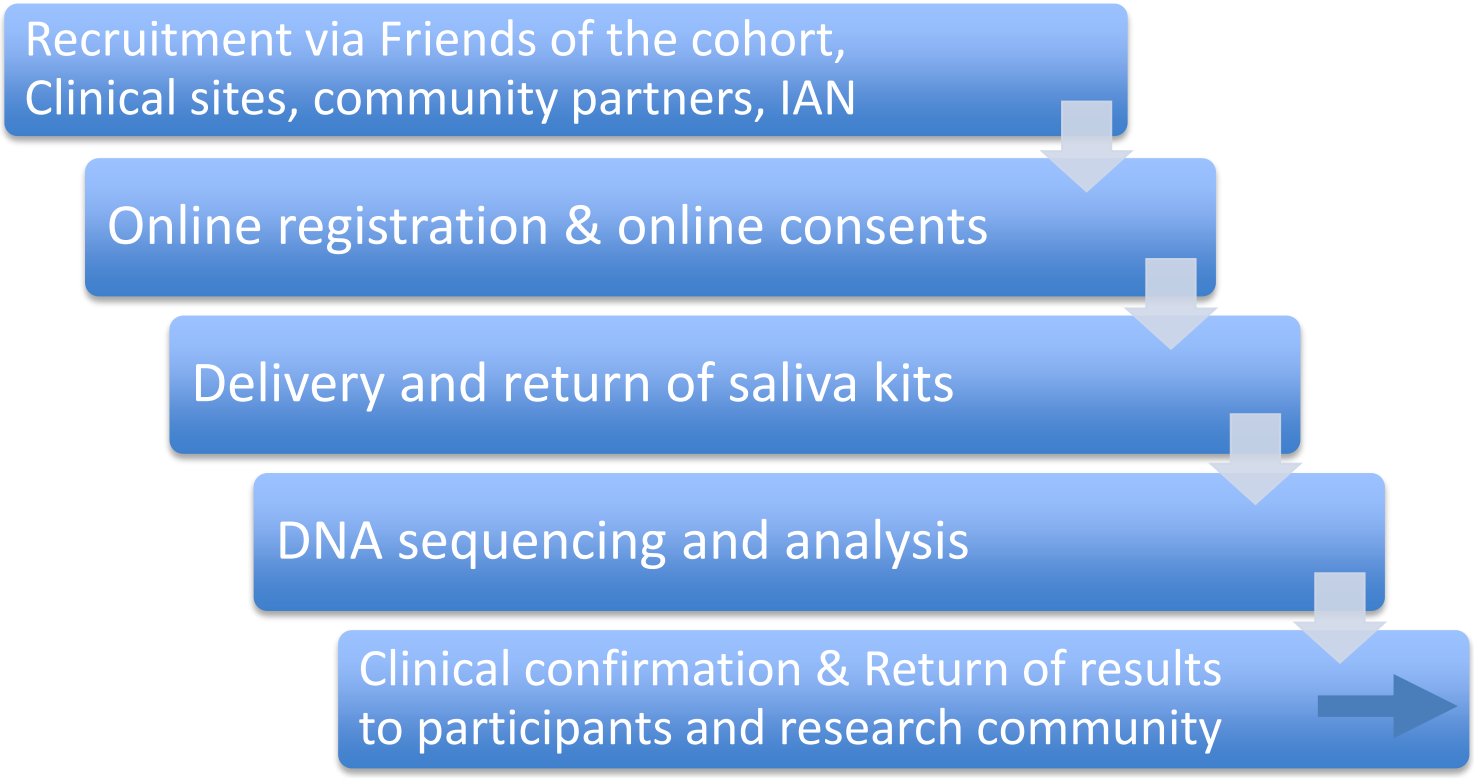
Genetics for pilot phase

- All samples to be received into a CLIA lab and DNA extraction performed
- All exome production to take place in a research setting
- Bioinformatics pipeline to pull all variants to be sent for clinical confirmation to be done at SFARI or outsourced
- Genetic results for pre-defined list of genes returned to participant-designated physician or genetic counselor

Timeline

Pilot: December 2015 - February 2016

Recruit 500 individuals with autism and their biological parents to evaluate:



SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Conclusion

- Autism is not a single disorder but is a spectrum
- Autism is more common in males
- The causes of autism are many, and genes play an important role
- There are other causes besides genes, but they are harder to define
- We are beginning to understand the molecular basis of autism and to develop methods of early diagnosis with positive effects of early intervention

Simons VIP Study Team

Overall oversight (*Columbia, Simons Foundation*)

Chung Spiro Tiernagel Bowe Fischbach

Geisinger

Ledbetter Lese-Martin Faucett Smith-Packard Martin

Psychological/psychiatric testing (*Harvard*):
Sites: *Harvard, UW Seattle, Baylor*

Hanson Bernier Kochel

Neurology and Neuroimaging (UCSF):
Structural: *Harvard, UW Seattle, Baylor*

Sherr Buckner Roberts Grant Aylward Hunter Steinman Spence Ramocki Poduri

Neuroimaging

Nagaraian Mukherjee

Statistical core (*Columbia*)

Vaughan Chen

Biospecimens (*Rutgers, Simons*)

Tischfield Sheldon Benedetti Packer

Informatics (*Prometheus*)

Voccola Jensen

SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT

National autism cohort staff

Wendy Chung
Dir. Clinical Research

Pamela Feliciano
Senior Scientist

Amy Daniels
Project Manager

Stephen Zukin
Dep. Dir. Clinical Research

LeeAnne Green Snyder
Clinical Research Scientist

Jennifer Tjernagel
Project Manager, VIP

Casey White-Lehman
Project Manager, SSC

Karen Walton-Bowen
Clinical Operations

Hana Zaydens
Administrative Assistant

Rick Remington
Outreach Manager

Julie Manoharan
Project Coordinator

Vincent Myers
Research Assistant

Alex Lash
Chief Informatics Officer

Alpha Amatya
Sr. Software Engineer

Richard Marini
Sr. Software Engineer

Martin Butler
Software Engineer

Andrei Salomatov
Bioinformatics Engineer

Natalia Volfovsky
Analytics Manager

Ron Edgar
Informatics Consultant

Chris Rigby,
Informatics Consultant