

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

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Columbia University

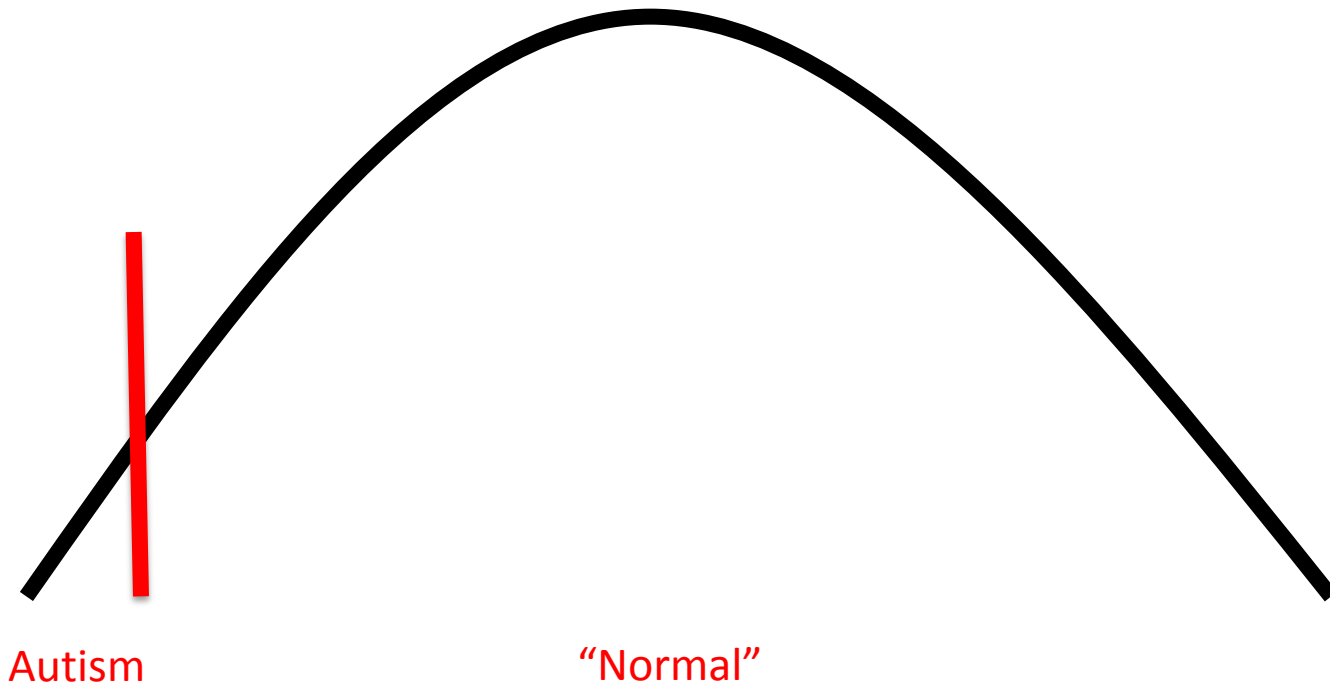
Director of Clinical Research, SFARI/Simons Foundation



# 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

Multiple  
Sclerosis

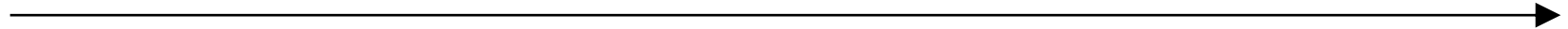
Cancer

Heart Disease

Diabetes

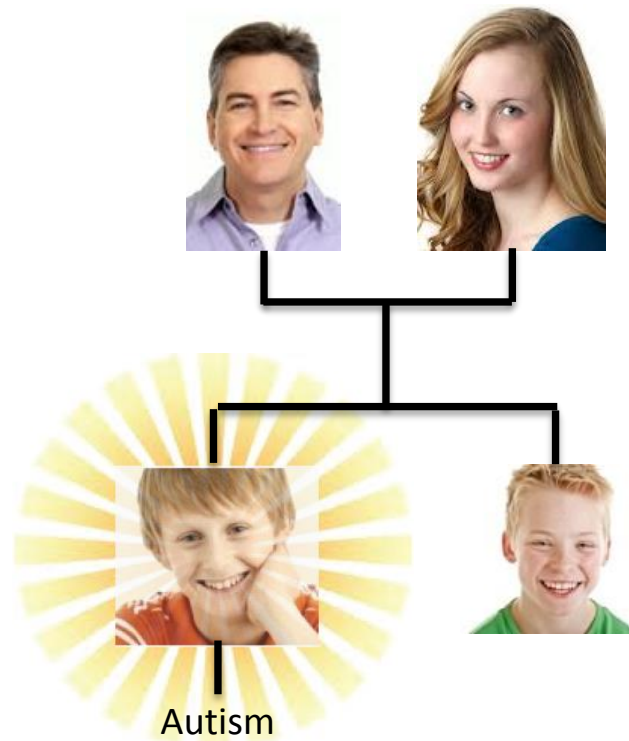
Autism

Psoriasis



Increasing Heritability

# 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 intertwined 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."

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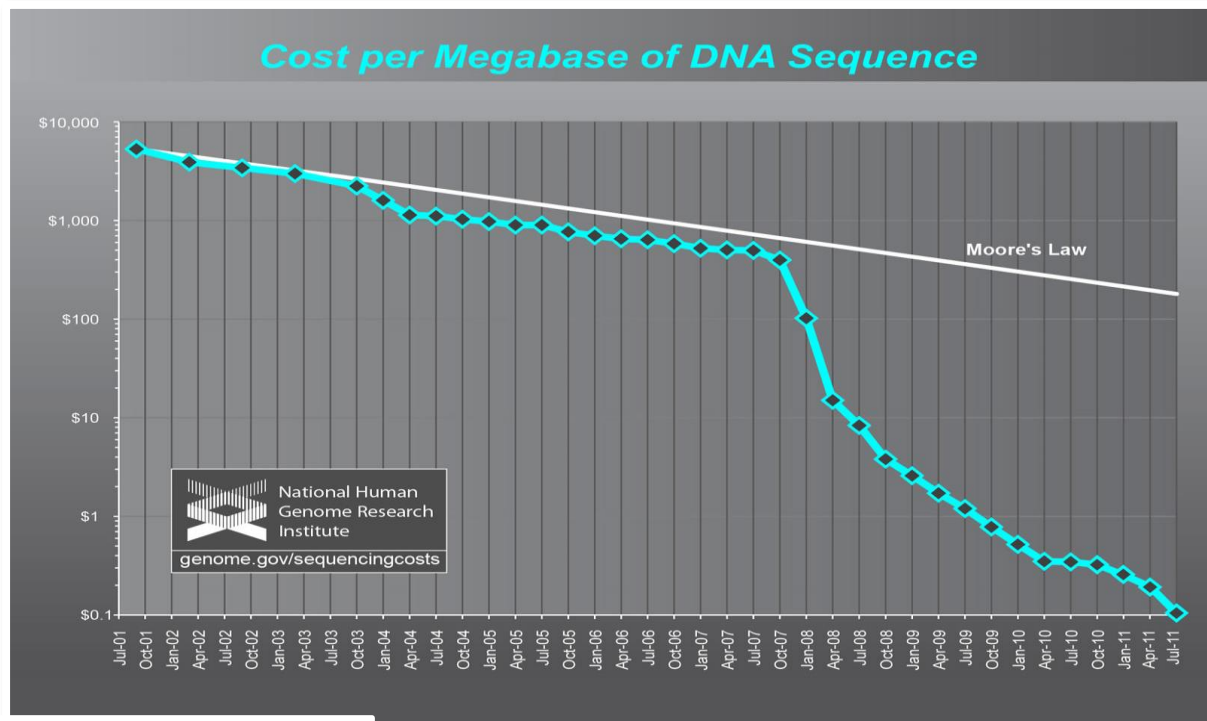
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# Rapidly Decreasing Cost of DNA Sequencing

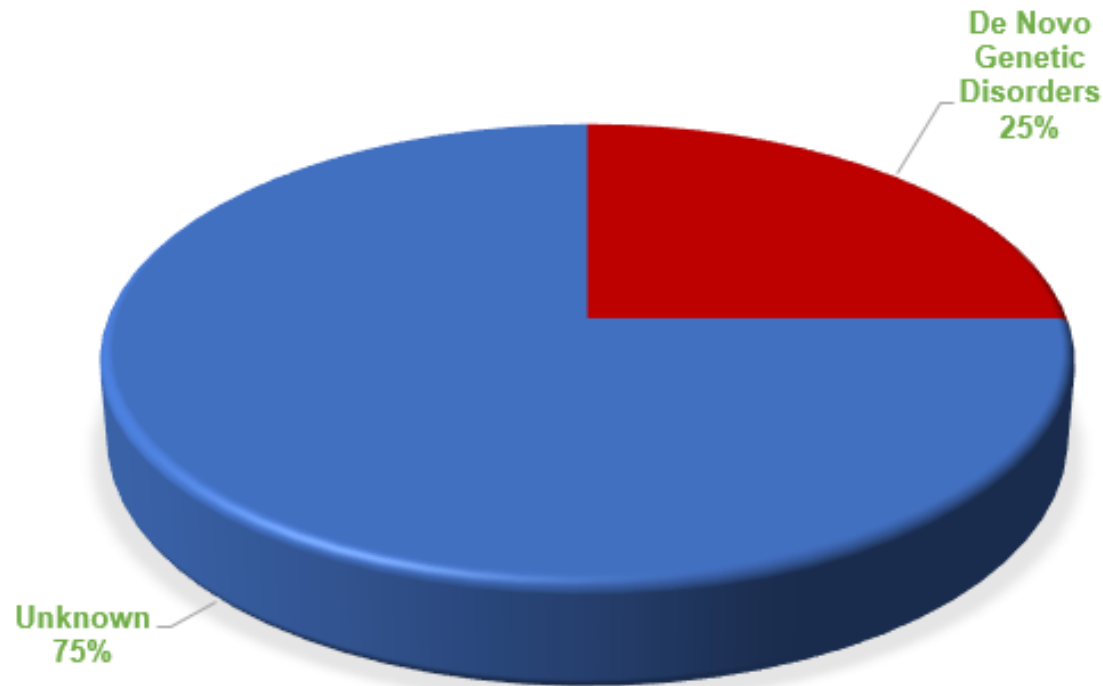




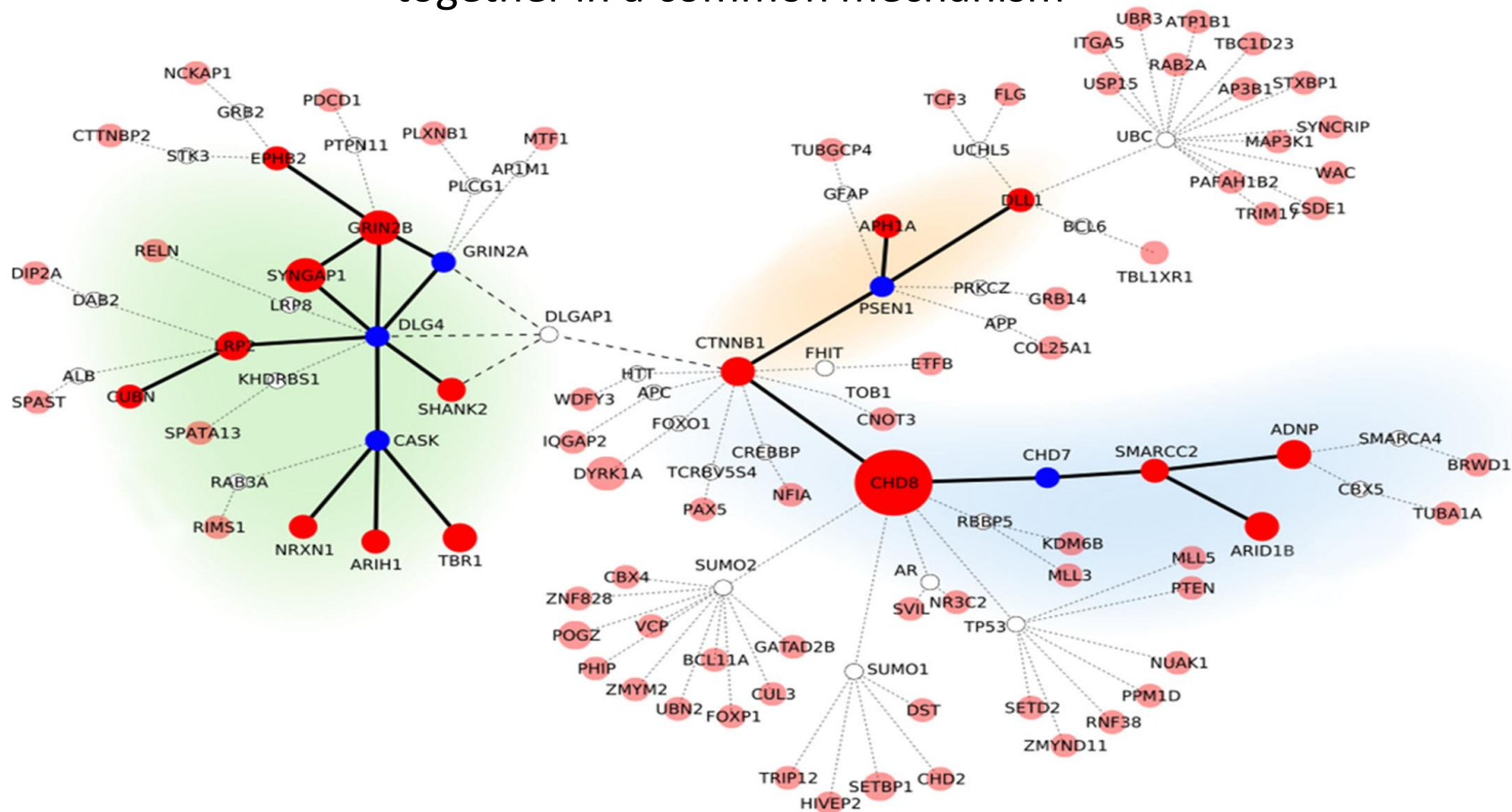
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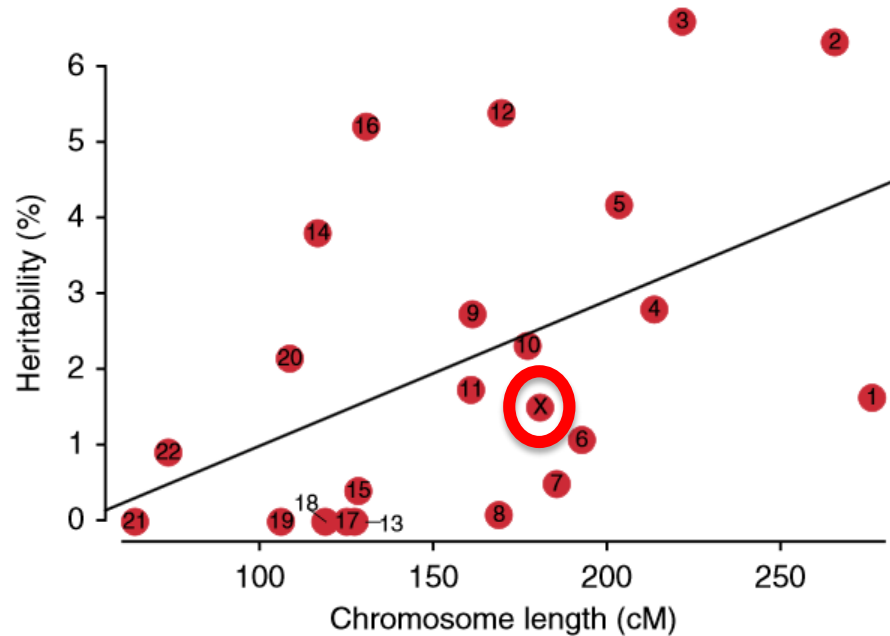
# Simons Simplex Collection Identified *De Novo* Mutations as the cause of 25% of Autism



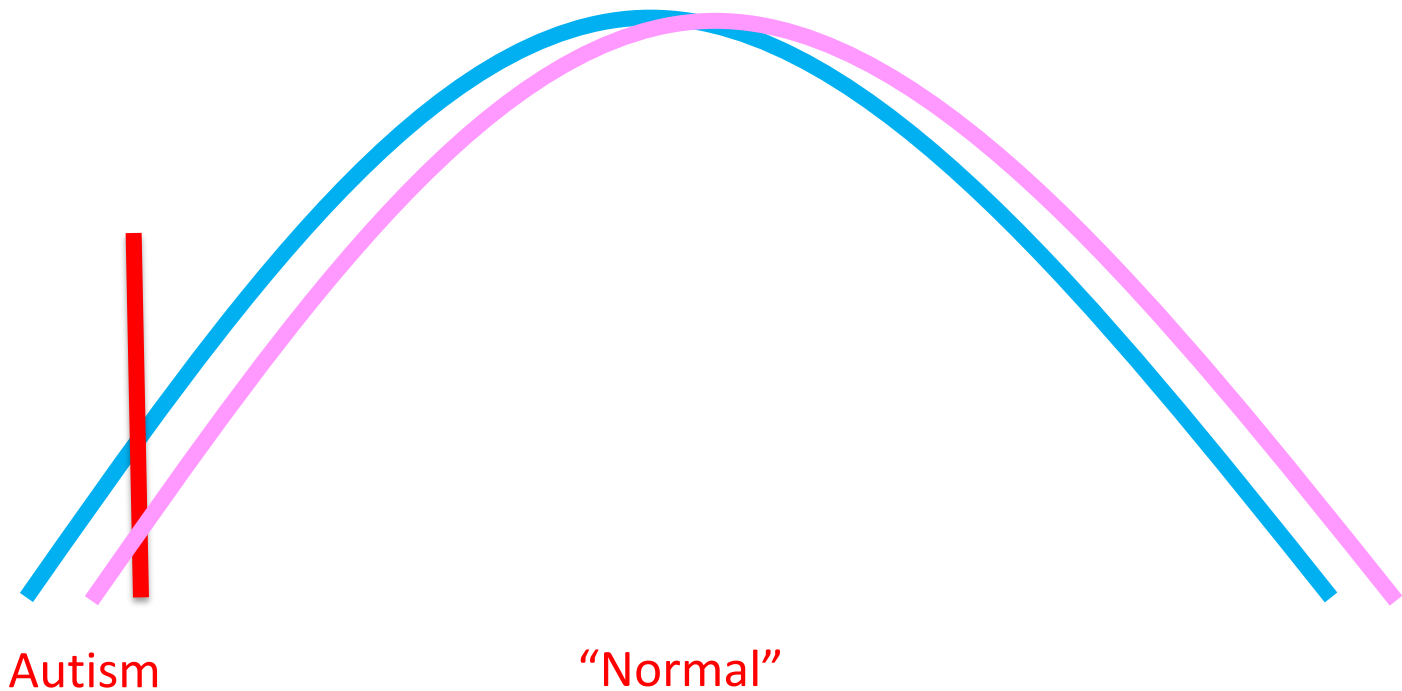
Although there are many different genes, many of the genes work together in a common mechanism



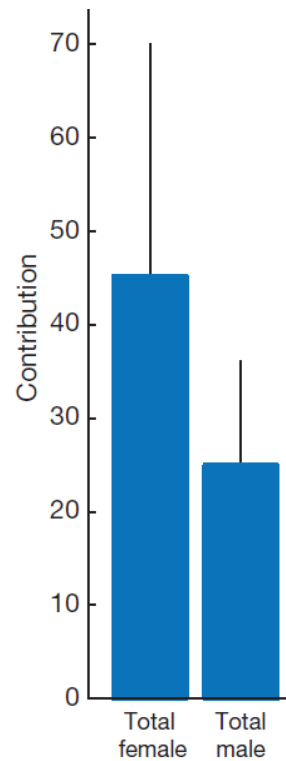
# Is The Gender Difference in Autism Due to the X Chromosome?



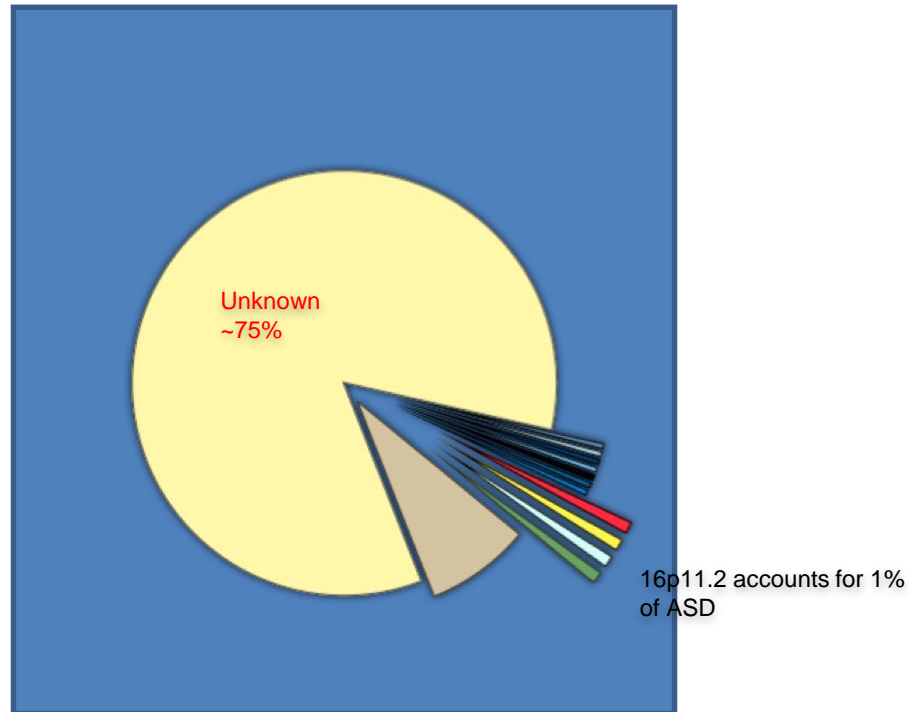
Are Females Protected from Autism?  
If so, is it because of how we raise girls?  
Do girls internalize more and boys externalize?



# Single Genetic Causes are More Commonly Found in Girls with Autism



# Causes of Autism Spectrum Disorder

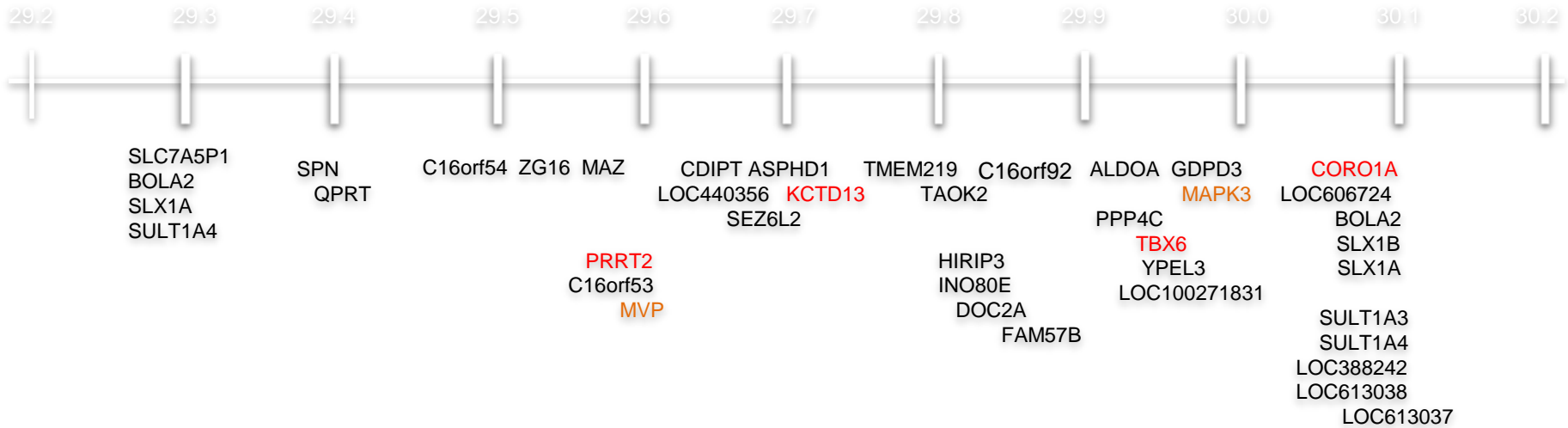






BP4

BP5



# 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 CONNECT

## SIMONS VARIATION IN INDIVIDUALS PROJECT

[Home](#)

[About 16p](#)

[Research Opportunity](#)

### Simons VIP Connect

Linking individuals and their families with Copy Number Variations (CNVs) for support and research opportunities



### 16p11.2 Family Event



This summer, families of children with 16p11.2 deletions and duplications will have the chance to meet one another!

[Learn more ...](#)

### Upcoming Webinars

#### Autism Spectrum Disorders

May 5 @ 1pm EST

Robin Kochel, Ph.D. – Simons VIP Houston

Registration coming soon

### Discussion Boards Available



Join the conversation. Register or log in to connect with other parents.

[Register Now!](#)

### Login

Username

Password

Login

[Forgot login?](#)

### Find us on Facebook



Contact Us

Simons VIP Connect is an online community for individuals with copy number variation (CNV) deletions or duplications and their families. The goal of the community is to allow families to contact each other, provide support and learn more about individuals with CNVs.

### The Goals of Simons VIP Connect

This community was created for individuals with CNVs that may be associated with autism or developmental delay. The community is initially reaching out to individuals with a 16p11.2 deletion or duplication. Over time other targeted CNVs may be added to the community.

### Getting Involved

Registering allows you to connect with other individuals with similar CNVs and to learn about research opportunities.

[Click here to join now!](#)

### Learn More

Are you a clinician or genetic counselor who would like to learn more? Please enter your contact information and the best time and method to contact you below.

Your Name

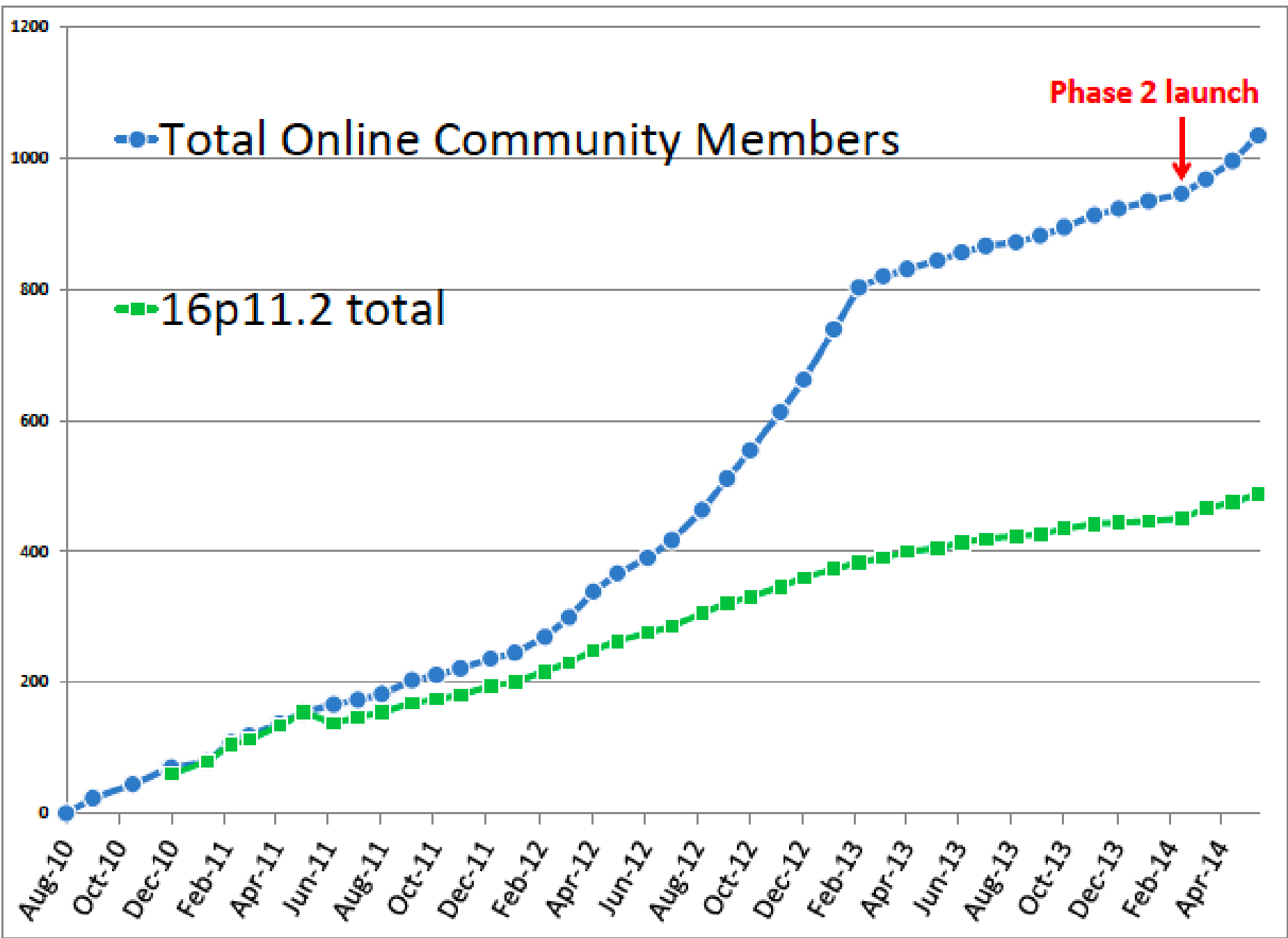
Email Address

Telephone

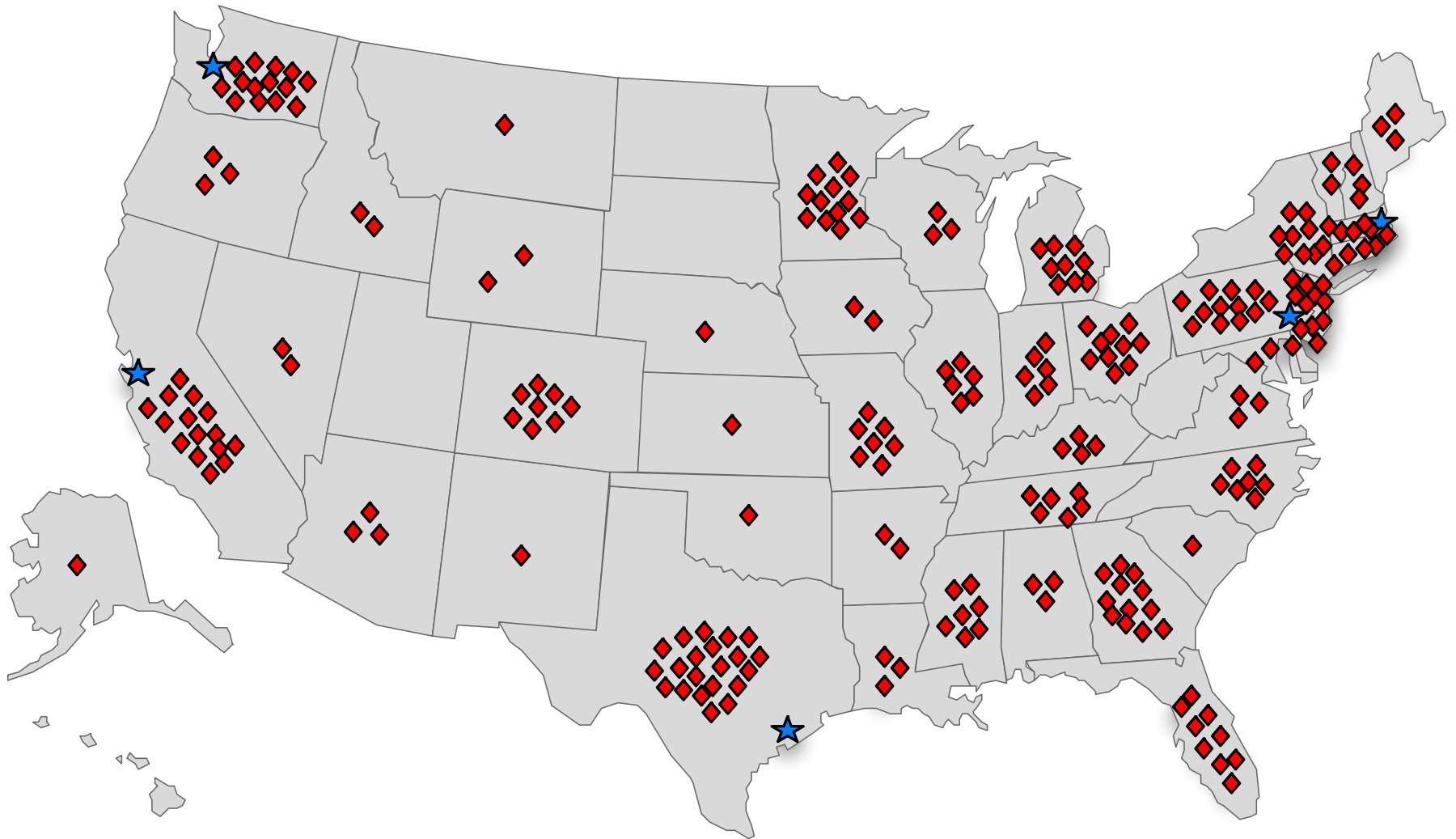
Submit

### Got Brochures?

Help us promote the importance of registering on Simons VIP Connect to your patients. We will mail brochures to your office at no cost.

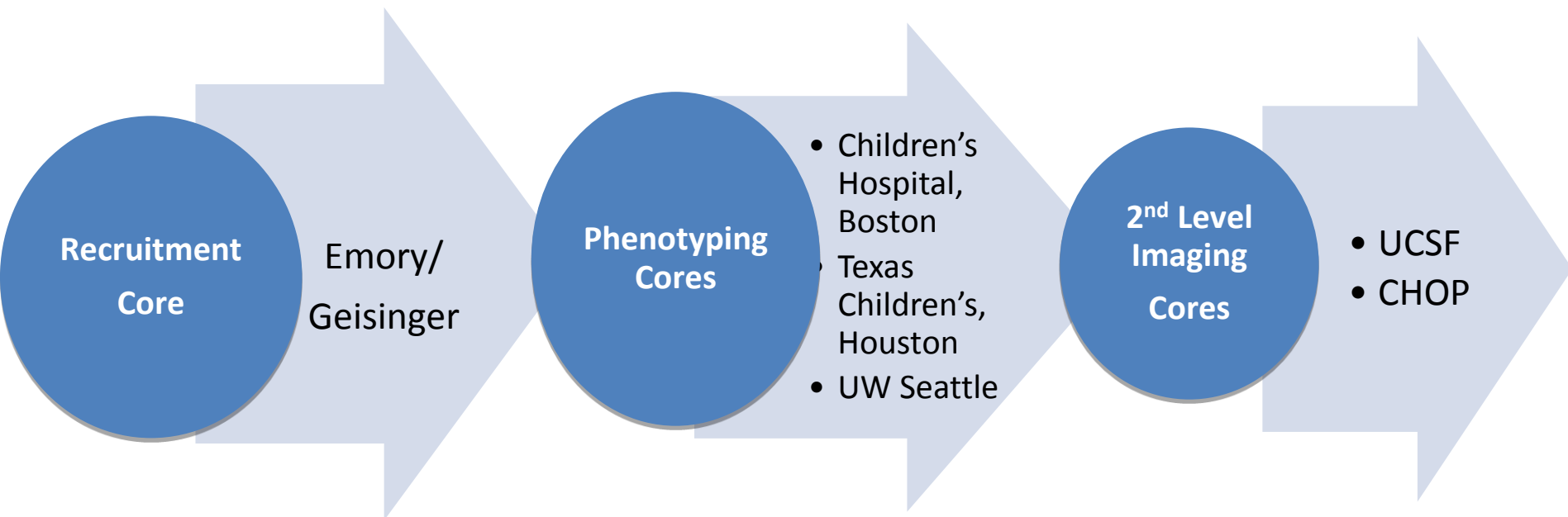


# Simons 'VIP' Connect 'Family' Map



- ★ Data Collection Site
- ◆ Registered 16p11.2 Family (+61 non-US)

# Family Flow



Screening  
Medical records

Multiple day visits  
All family members  
Neurocognitive Testing  
MRI  
Feedback

2 days  
Additional  
neurocognitive  
measures  
fMRI, MEG

# 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
- Observation 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

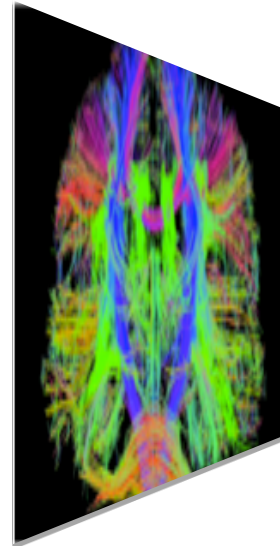
- Delis-Kaplan Executive Function System\*

## Medical\*

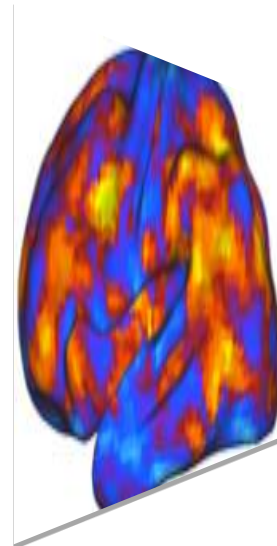
\* Measures done at UCSF and CHOP or Emory

# 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

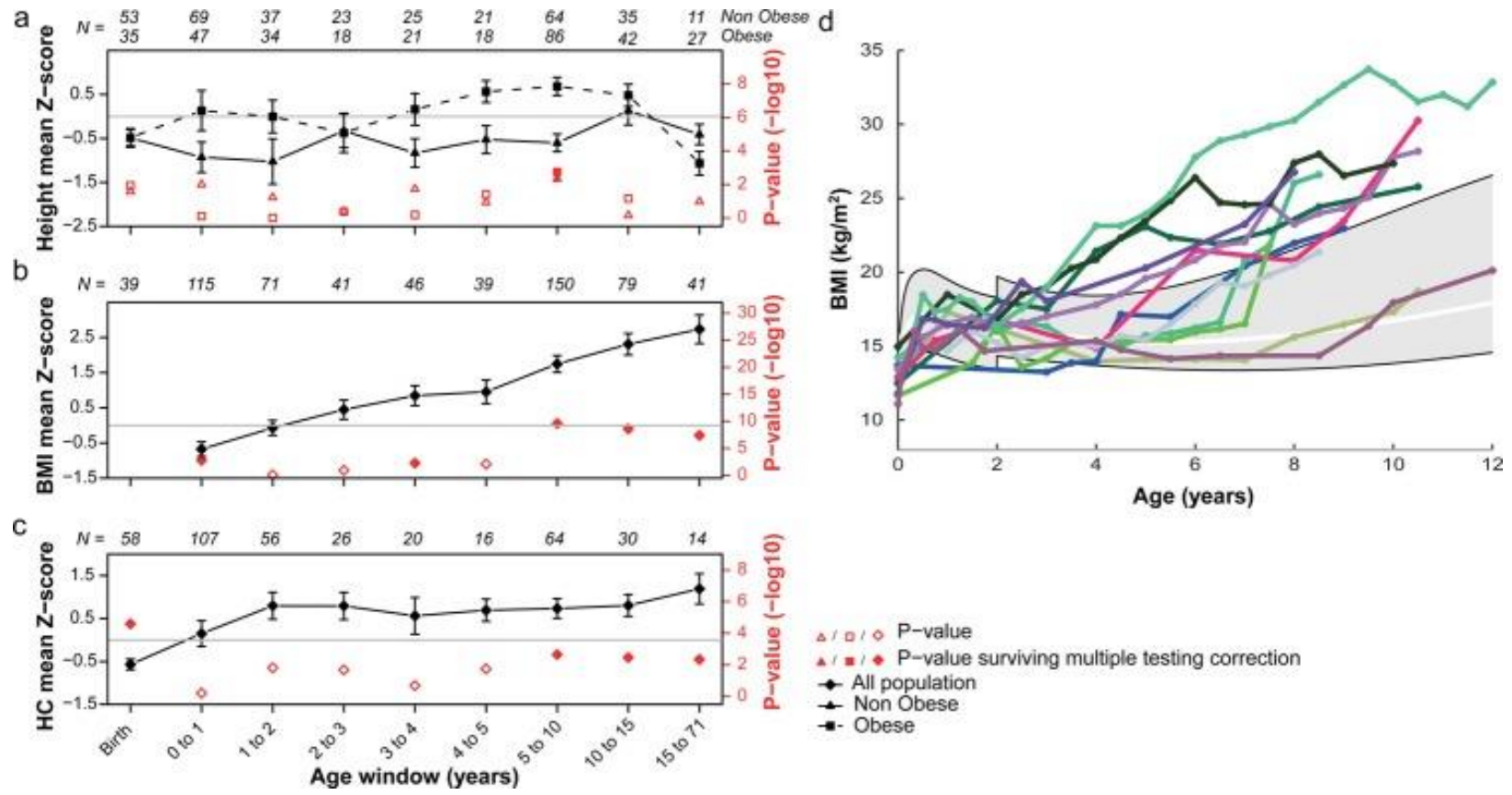


Hunter





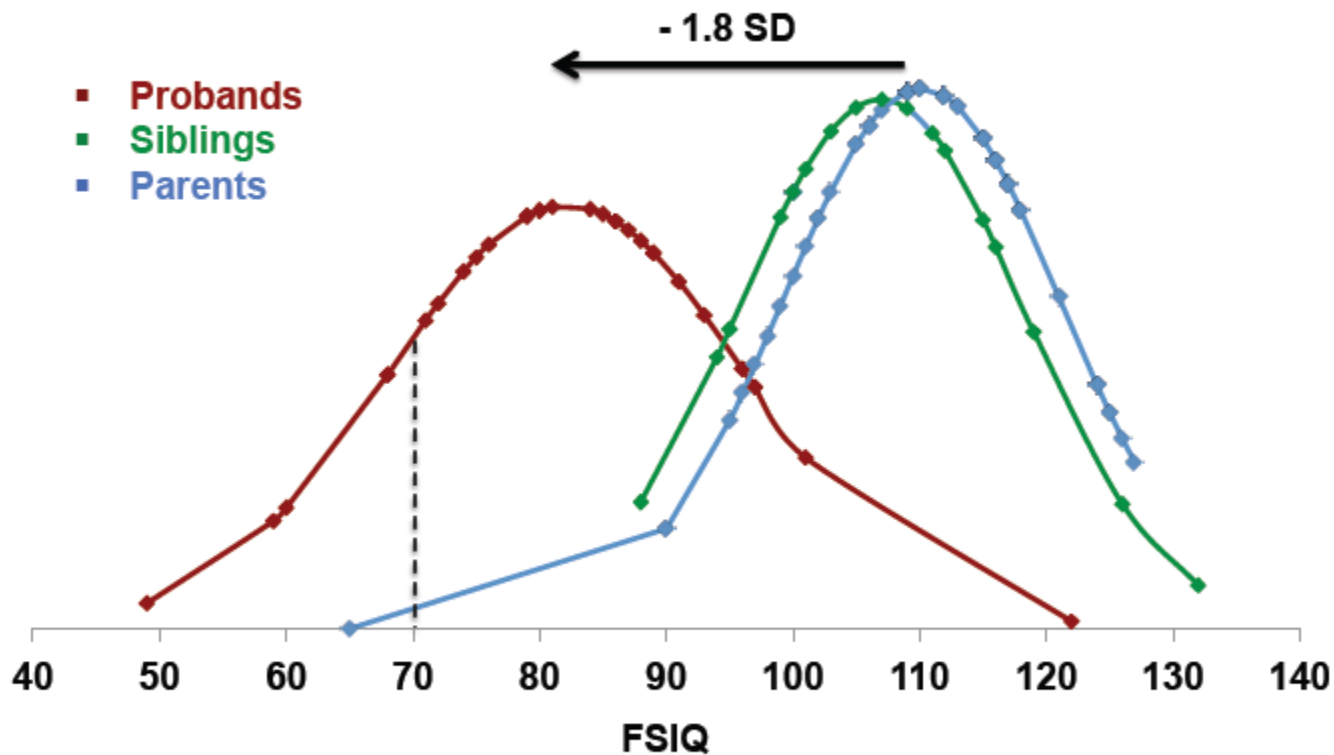
# BMI increases over time in 16p11.2 deletion carriers



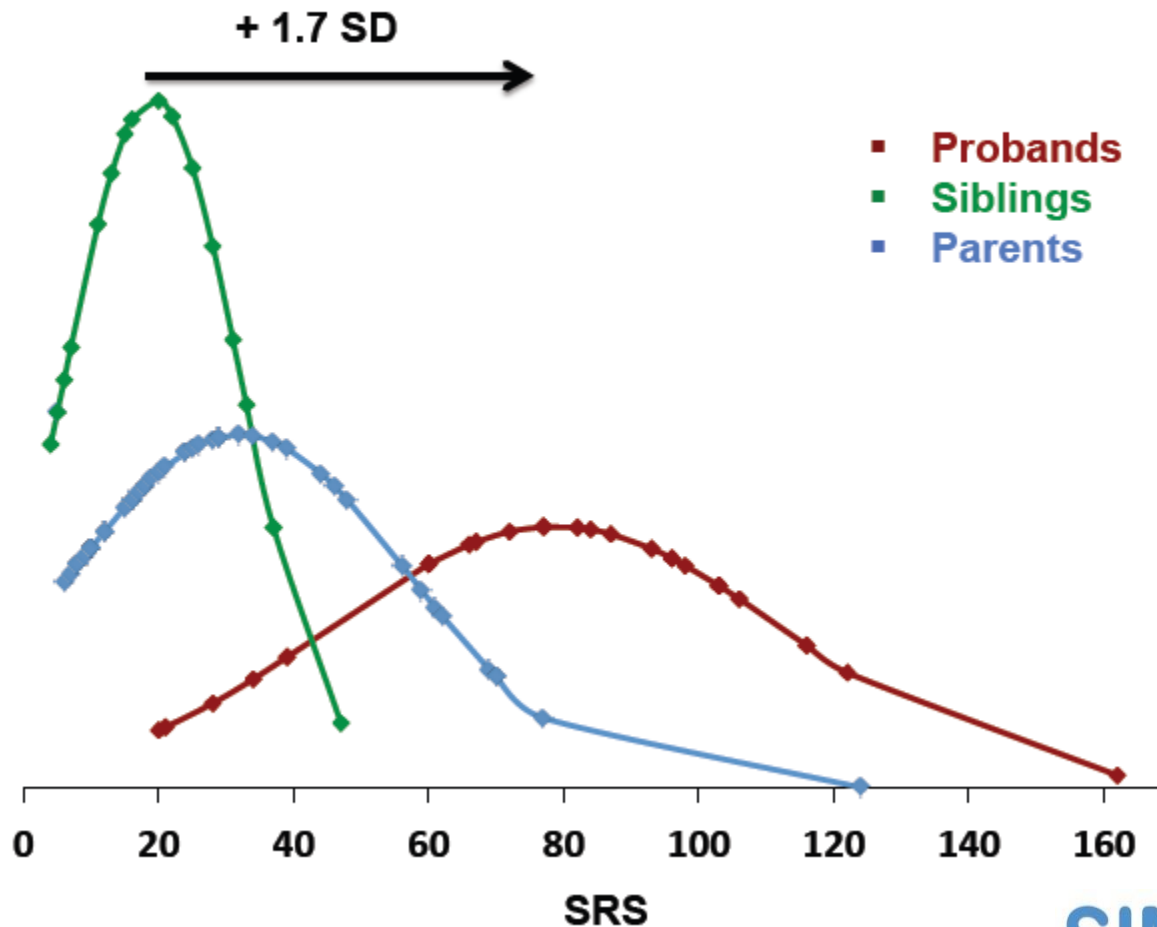
# 16p11.2 deletion carriers: neurological phenotype

Neurological features		Probands			Relatives	All
		Questionnaire N=76	Full assessment N=54	Literature N=65 <sup>+</sup>	N=38	N=233 (%)
Seizures <sup>1</sup>	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	

# 16p11.2 deletion carriers have IQs $\sim 2$ SD lower than their family members



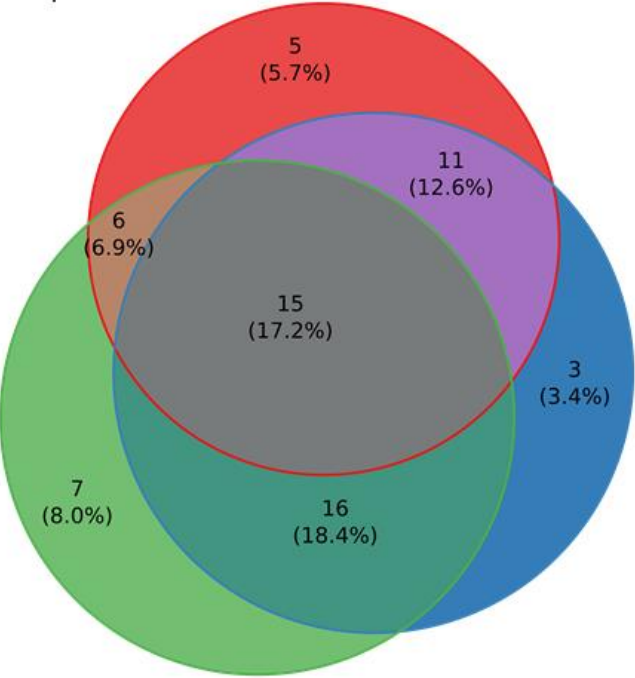
16p11.2 deletion carriers have Social Responsiveness Scale (SRS)  $\sim 2$  SD higher than their family members



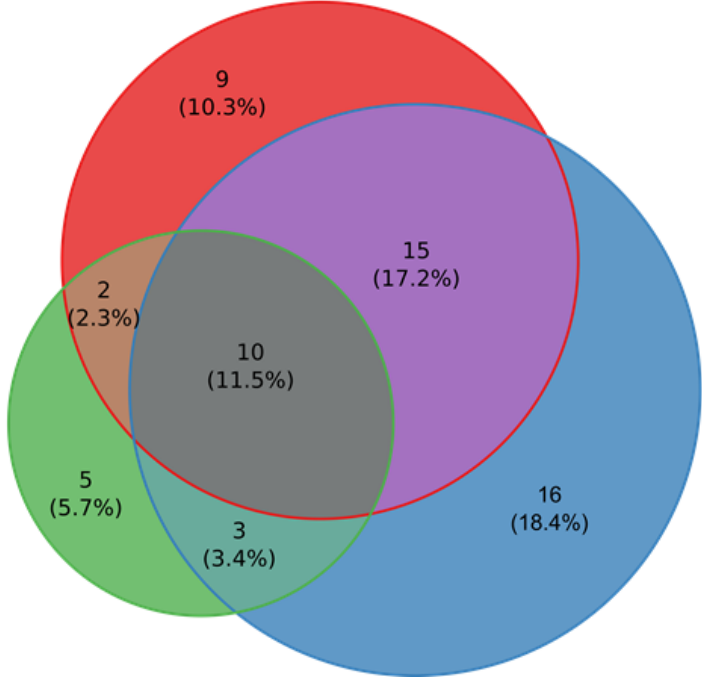
# Diagnostic Profile: 16p11.2 Deletion

## 23% have ASD

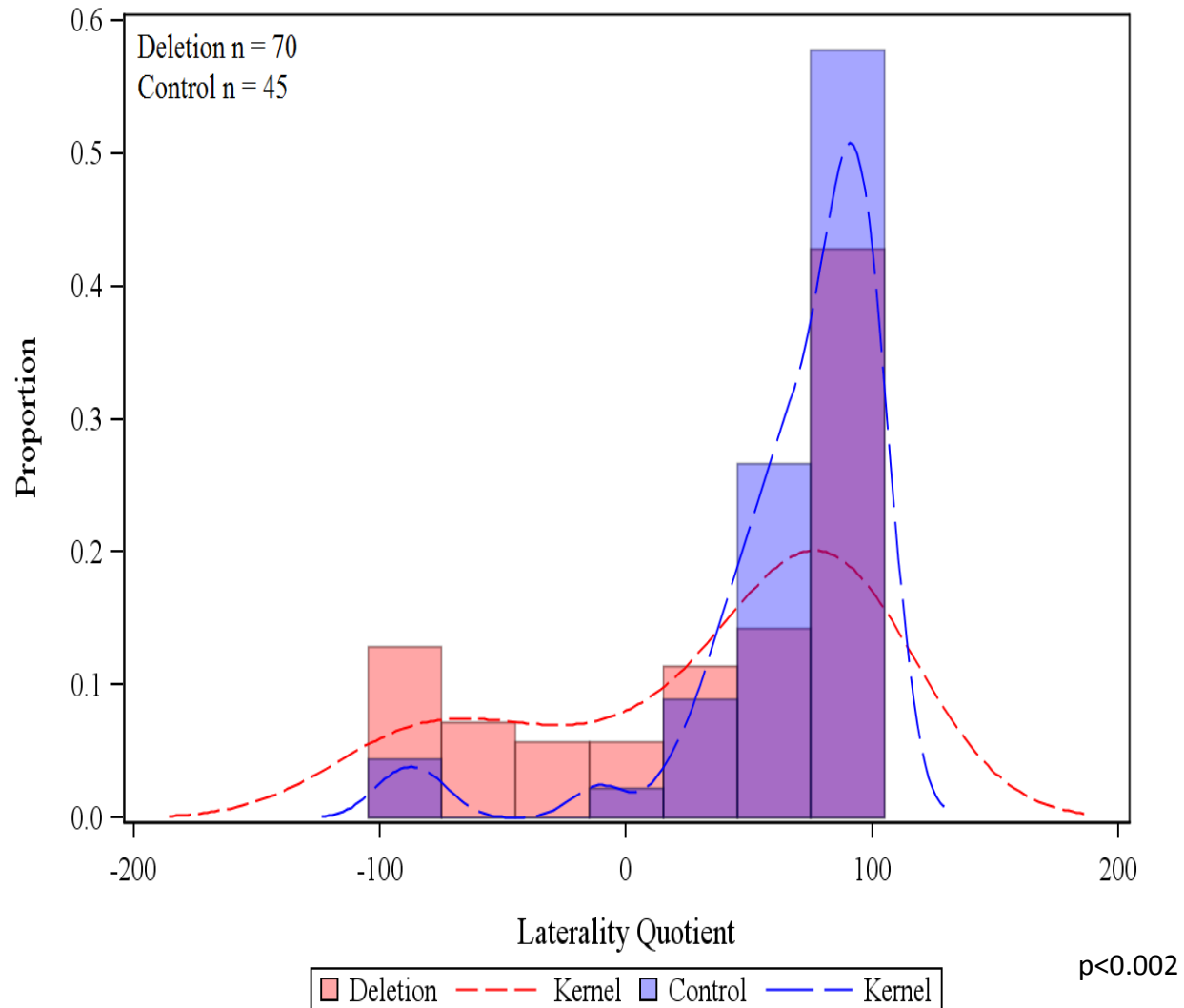
- Expressive and Mixed Receptive-Expressive Language Disorder
- Phonological Disorder
- Developmental Coordination Disorder



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



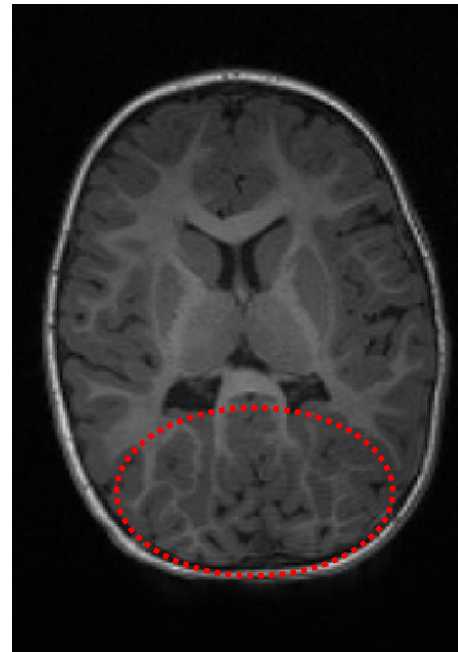
# Deletion carriers are less likely to be right handed



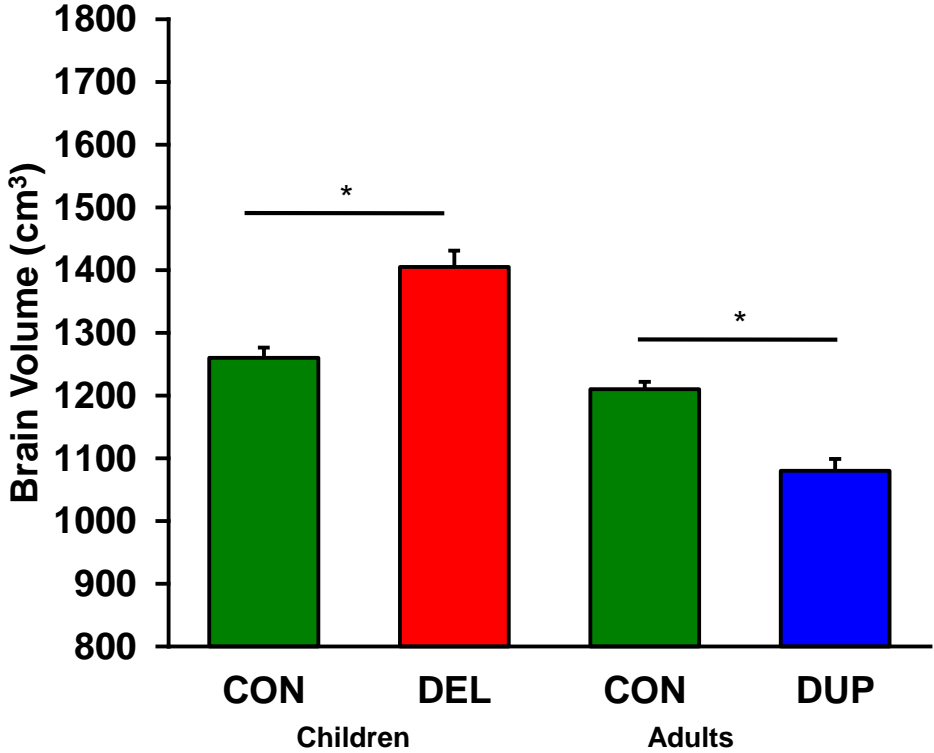
Chiari I Malformation



Polymicrogyria

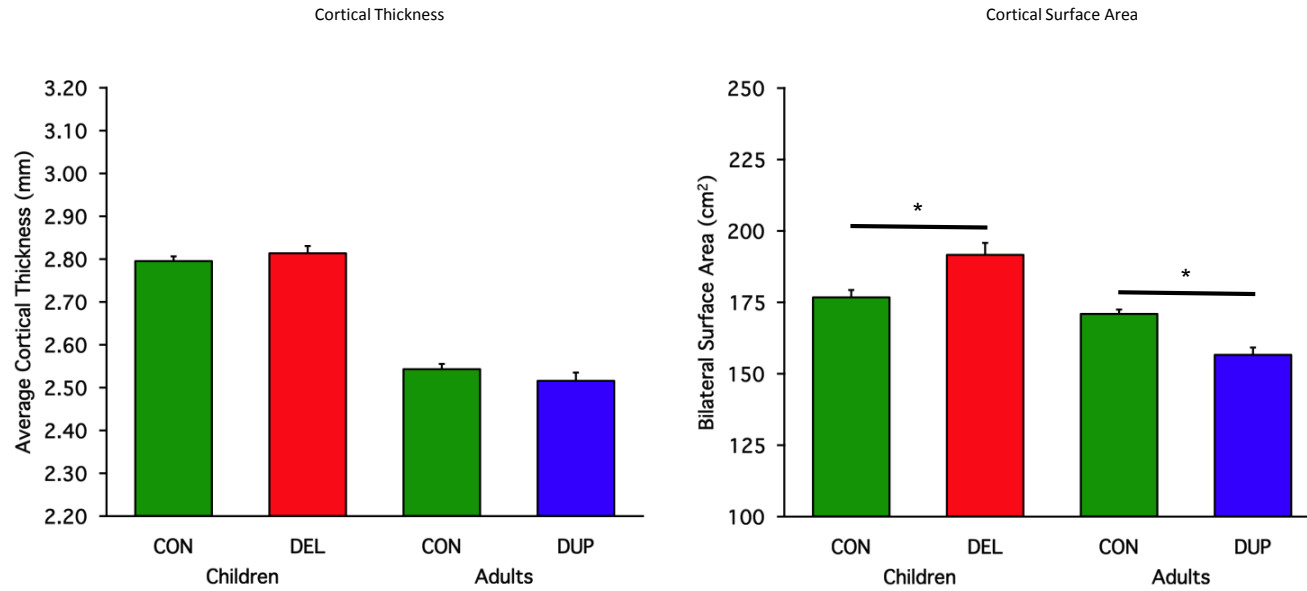


# Brain Volume in Increased in 16p11.2 Deletion Carriers and Decreased in Duplication Carriers

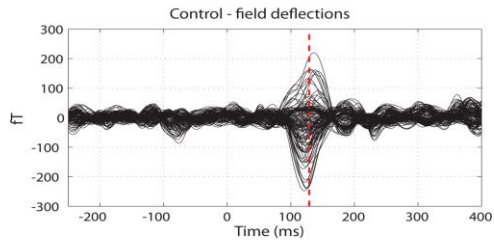
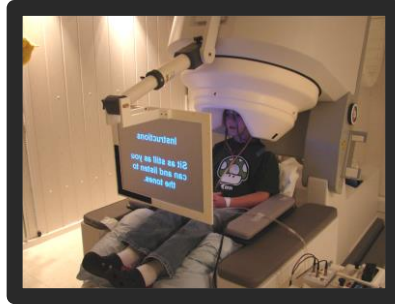




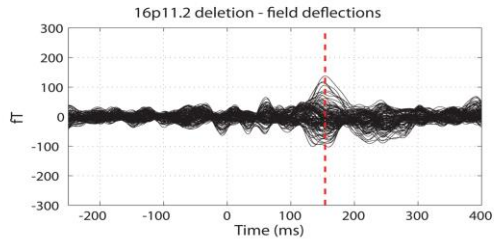
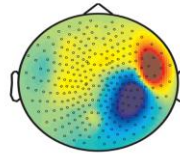
# Cortical Surface Area is Increased in 16p11.2 Deletion Carriers



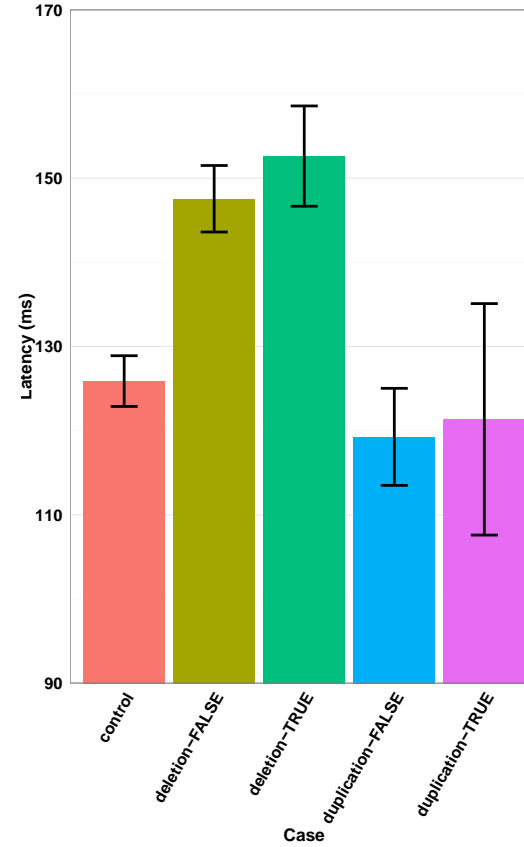
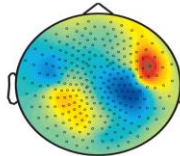
# Imaging Brain Signals



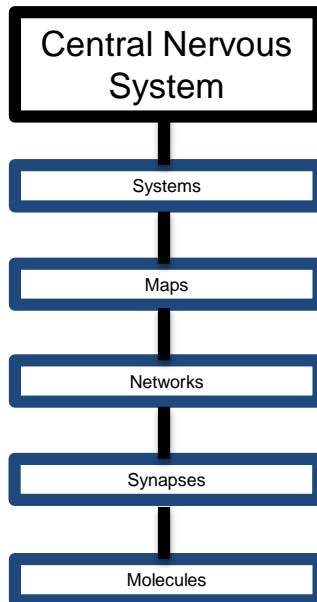
Control - M100 topography



16p11.2 deletion - M100 topography



# Understanding the genetics of autism informs brain function

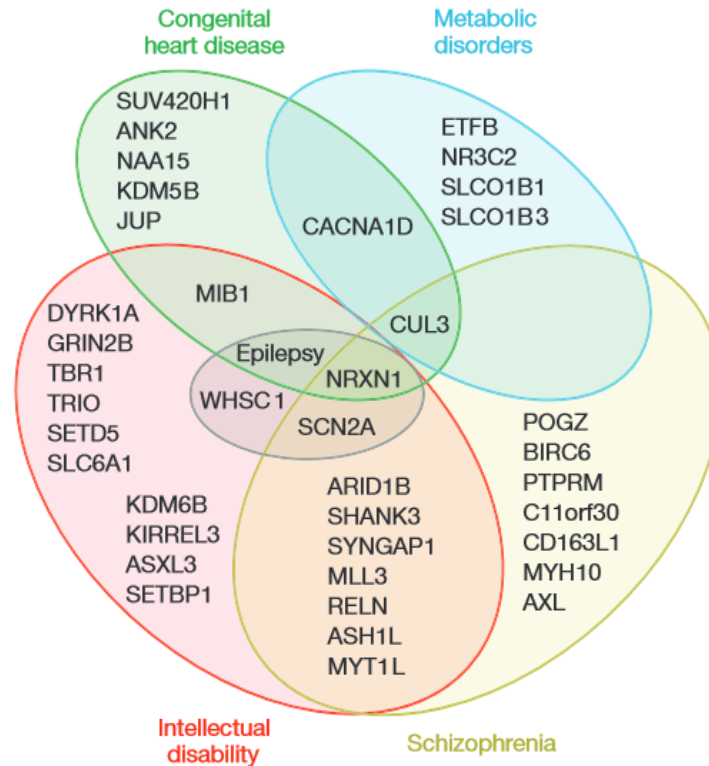


Churchland & Sejnowski  
1992

# 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

# 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

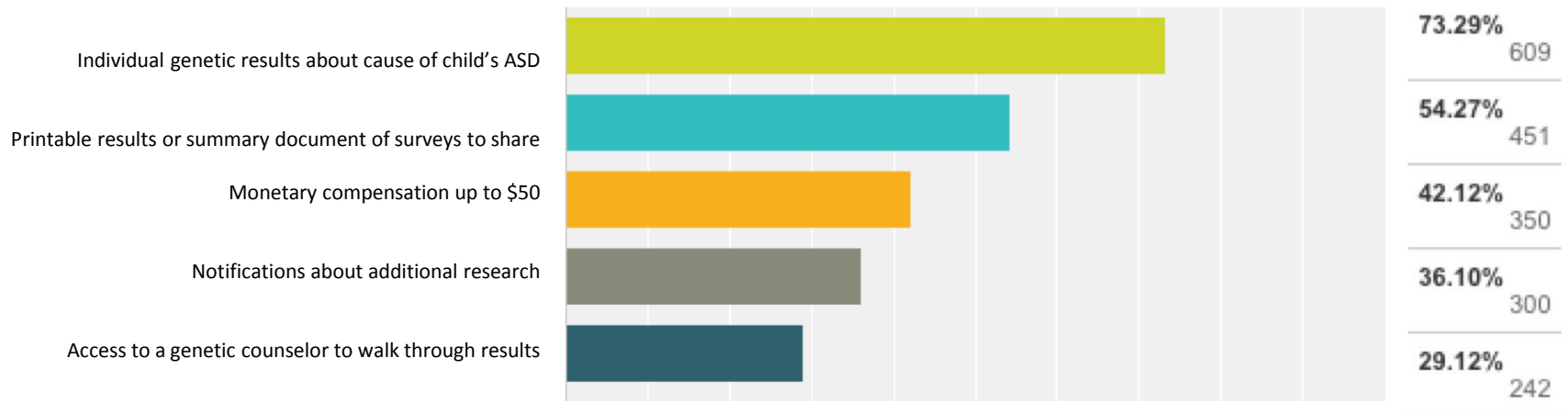
- Once educational infrastructure ends, young people get lost
- Modified college curriculum
- Living independently or with assistance
- Job interviews and training
- Social skills coaching
- Medical care is problematic

# What is the goal of the new Simons Foundation cohort?

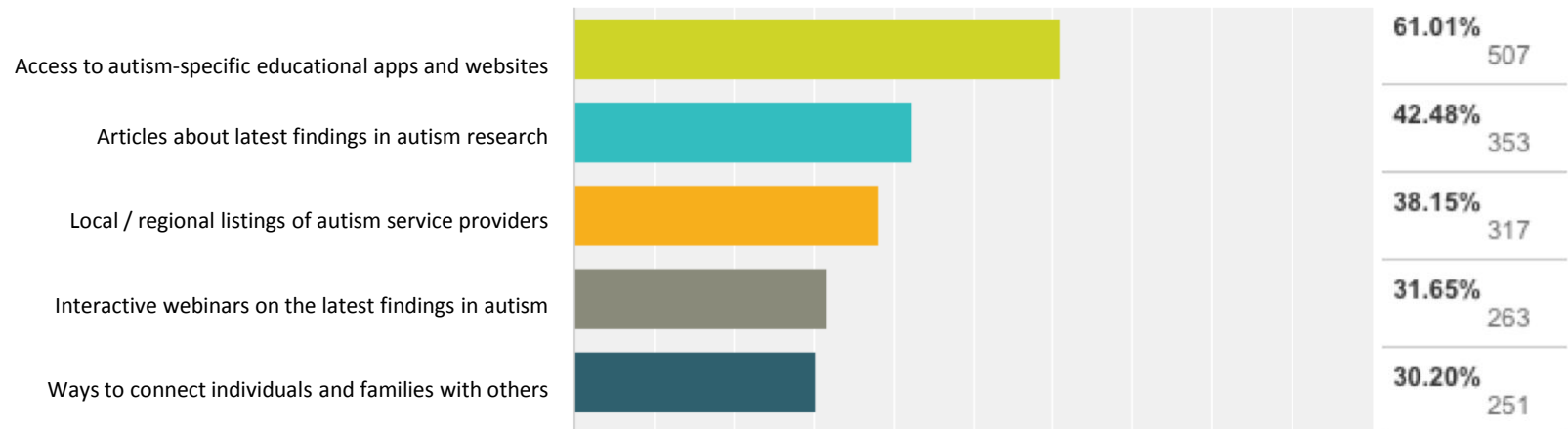
To **recruit, engage and retain** a community of **50,000 individuals with ASD and their family members** in the United States to:

- 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**



**Feedback from  
Scientific Community,  
Parents, Adults  
w/ASD  
(n= 263)**

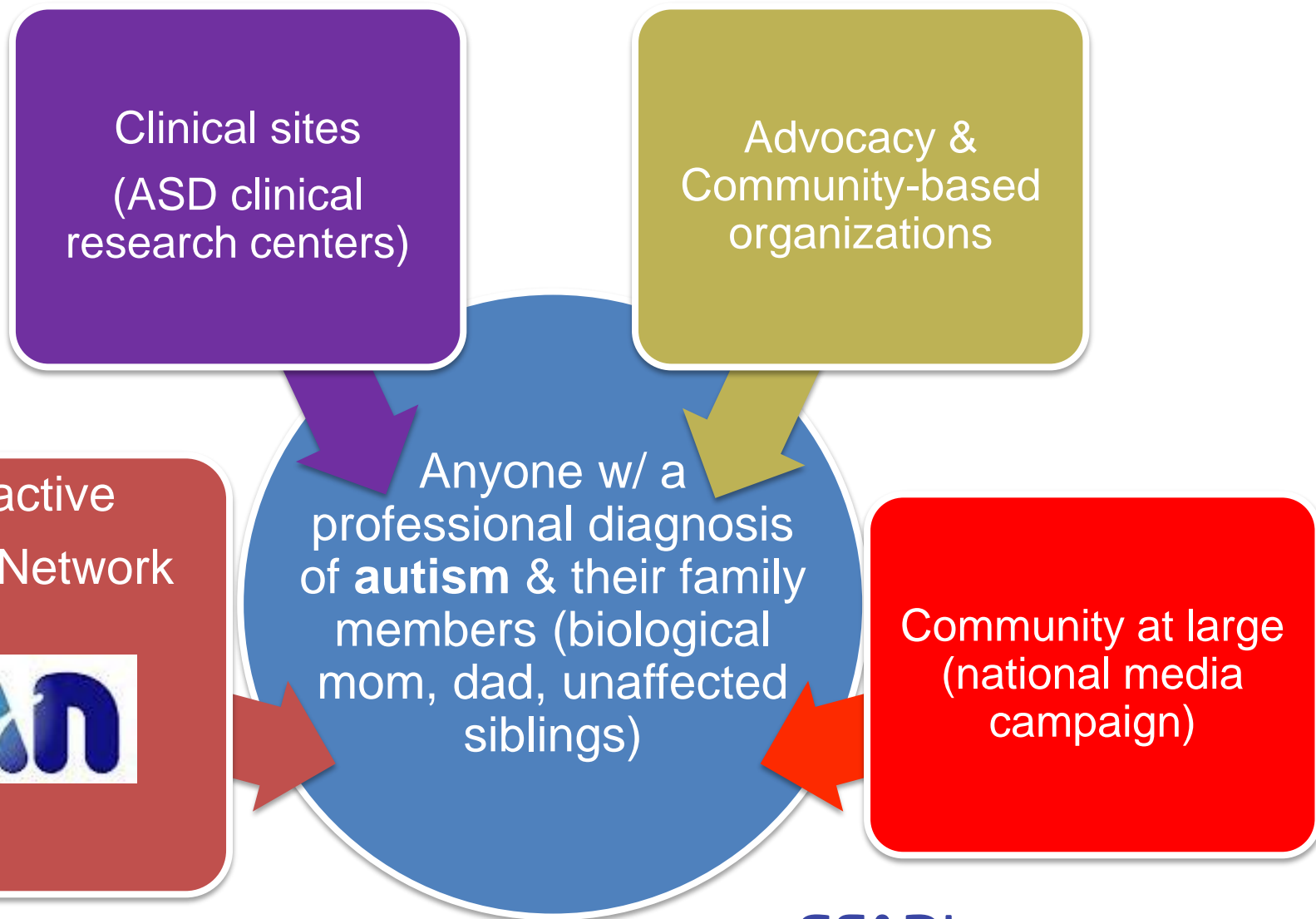


**Quantitative Survey 2:  
100 Adults with ASD &  
900 Parents**



**Interactions  
with various groups  
with similar missions**

# Recruitment

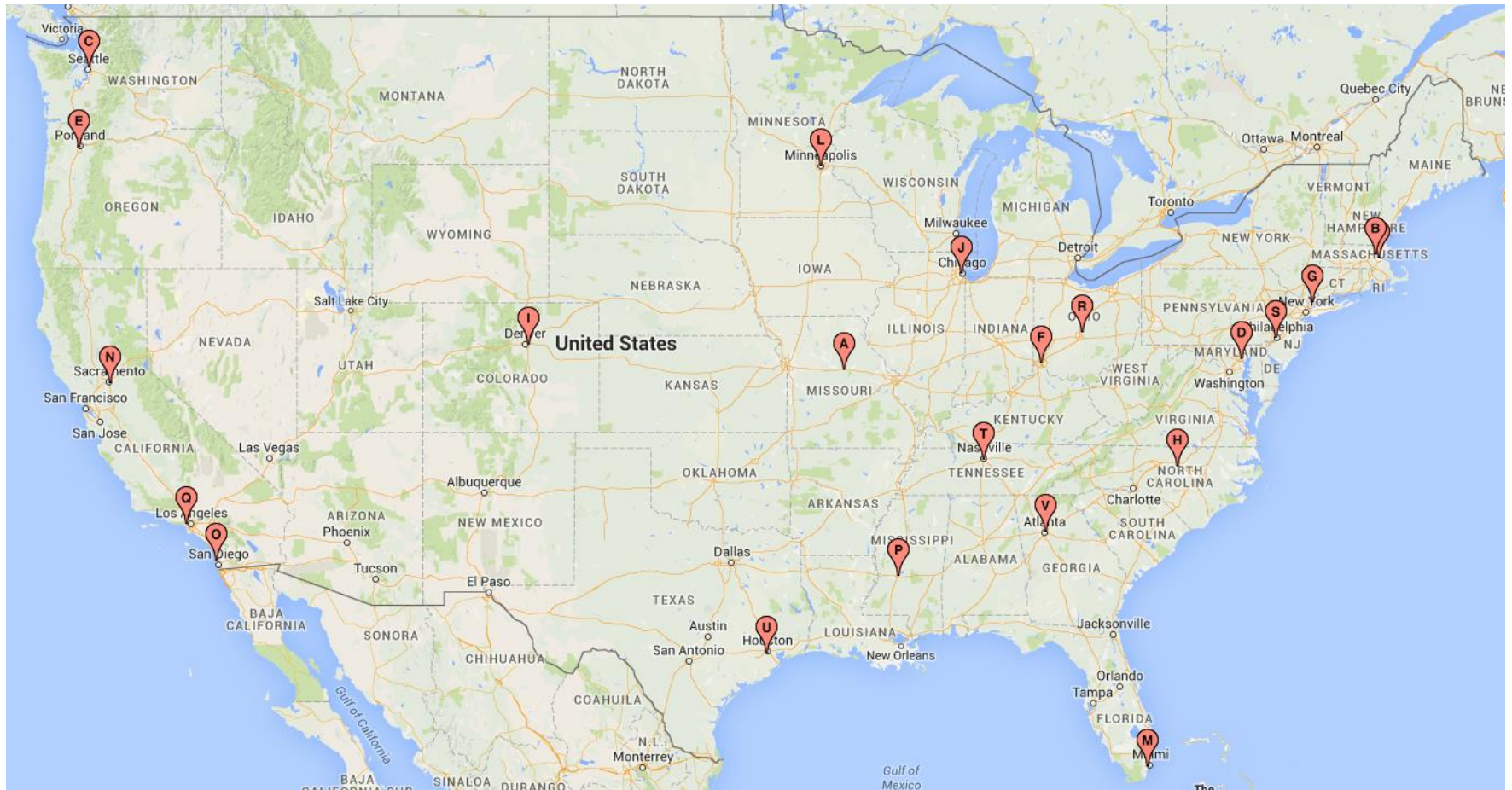


# Recruitment sources for the cohort: Interactive Autism Network (IAN)



- 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



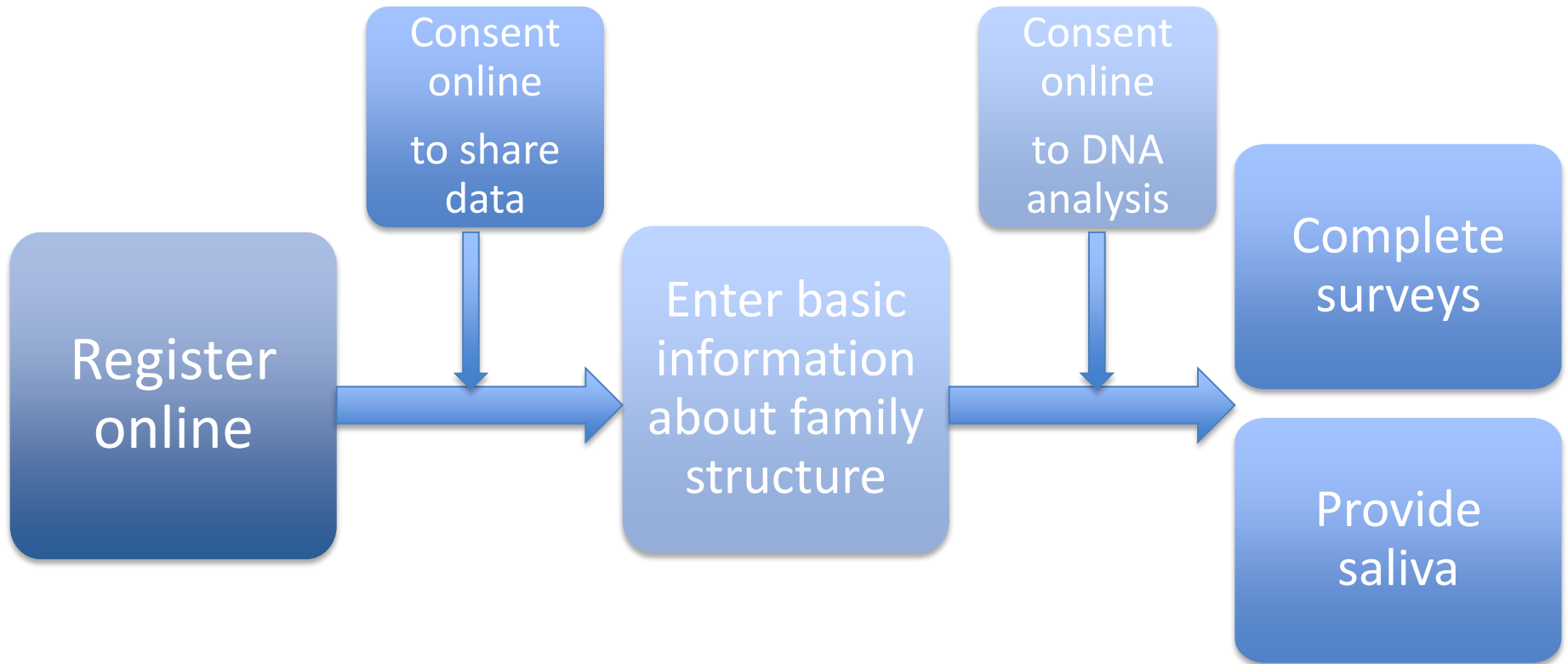


# Recruitment sources for the cohort: Community-based organizations

- 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

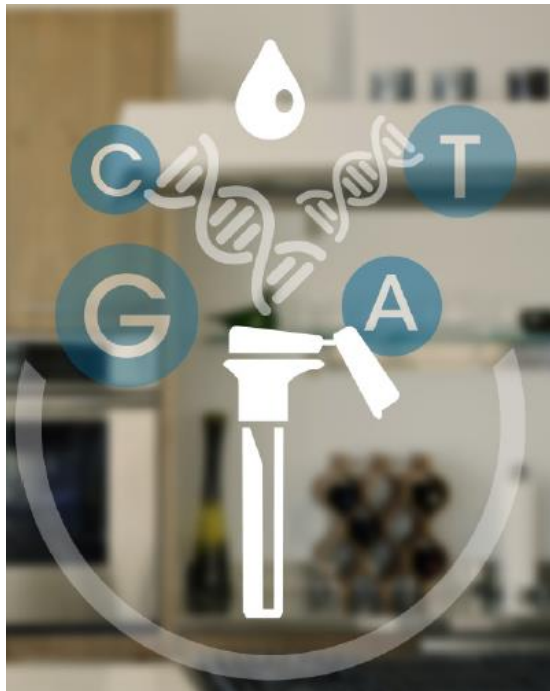


# How will families participate in the cohort?




# 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




## WHY DO YOU NEED MY FAMILY'S DNA?

Autism is known to have a strong genetic component. While we've identified some specific genes already, more research is needed to find other genetic contributors to autism.



## WHOSE DNA DO YOU NEED?



**an individual with autism**      **a biological parent** of an individual with autism      **a sibling** (unaffected with autism) of an individual with autism

The SPARK team would like DNA from the individual with autism, their biological parents, and from a sibling closest in age to the individual with autism (if there is a sibling). In families where there is more than one individual with autism, the SPARK team would like DNA from all siblings (unaffected and affected) and the biological parents. The quality of genetic analyses that we are able to perform increases when we have DNA from both biological parents and we are more likely to discover changes in genes that are related to an individual's autism when we have DNA from both parents.

## WHAT IS THE PROCESS FOR SUBMITTING MY FAMILY'S DNA TO SPARK?

- Once consent is provided, a saliva kit will be shipped to your family at no cost.
- Eligible individuals in your family will be asked to provide a 1 mL (or approximately one-fifth of a teaspoon) amount of saliva. If any individuals are not able to spit, a special kit that will allow a caregiver to assist in saliva collection by using a sponge that will absorb saliva from his/her mouth will be provided.
- The kit will also contain a pre-paid shipping box for you to mail the collected saliva back to us at no cost.



**STEP 1** You consent to share your genetic data

**STEP 2** A saliva kit is mailed to you

**STEP 3** You spit into the kit and mail it back

**STEP 4** Your spit is analyzed and stored

**STEP 5** You may be contacted about results

# 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

The screenshot shows a user dashboard with a yellow navigation bar at the top containing links for 'YOUR DASHBOARD', 'UPDATES & NEWS', 'YOUR FAMILY', 'YOUR STUDIES', 'YOUR DOCUMENTS', 'RESOURCES', and 'HELP'. Below the navigation bar is a red pin icon and an 'Important Reminder' message in a light gray box. The main content area is divided into two columns. The left column is titled 'Featured Content' and features a large video player showing a woman speaking, with a play button icon and a subtitle: 'I invite all of you to join the movement to make life for people with autism so much better and richer,' says Chung. Below the video are three smaller thumbnails of the same video, each labeled 'Ted Talk: Wendy Chung'. The right column is titled 'Task List' and contains a message: 'The following tasks need your attention. In order to receive the \$50 gift card, you must finish the tasks shown on the right-hand side.' Below this message is a list of tasks for three users: Johnny Appleseed (2/5), Julia Appleseed (2/5), Jacob Smith (2/5), and Chester Smith (2/5). Each task has a dropdown arrow and a progress indicator (yellow bar). The bottom of the dashboard has a section titled 'Your Family' with the text 'Looking to add a new family member?'.

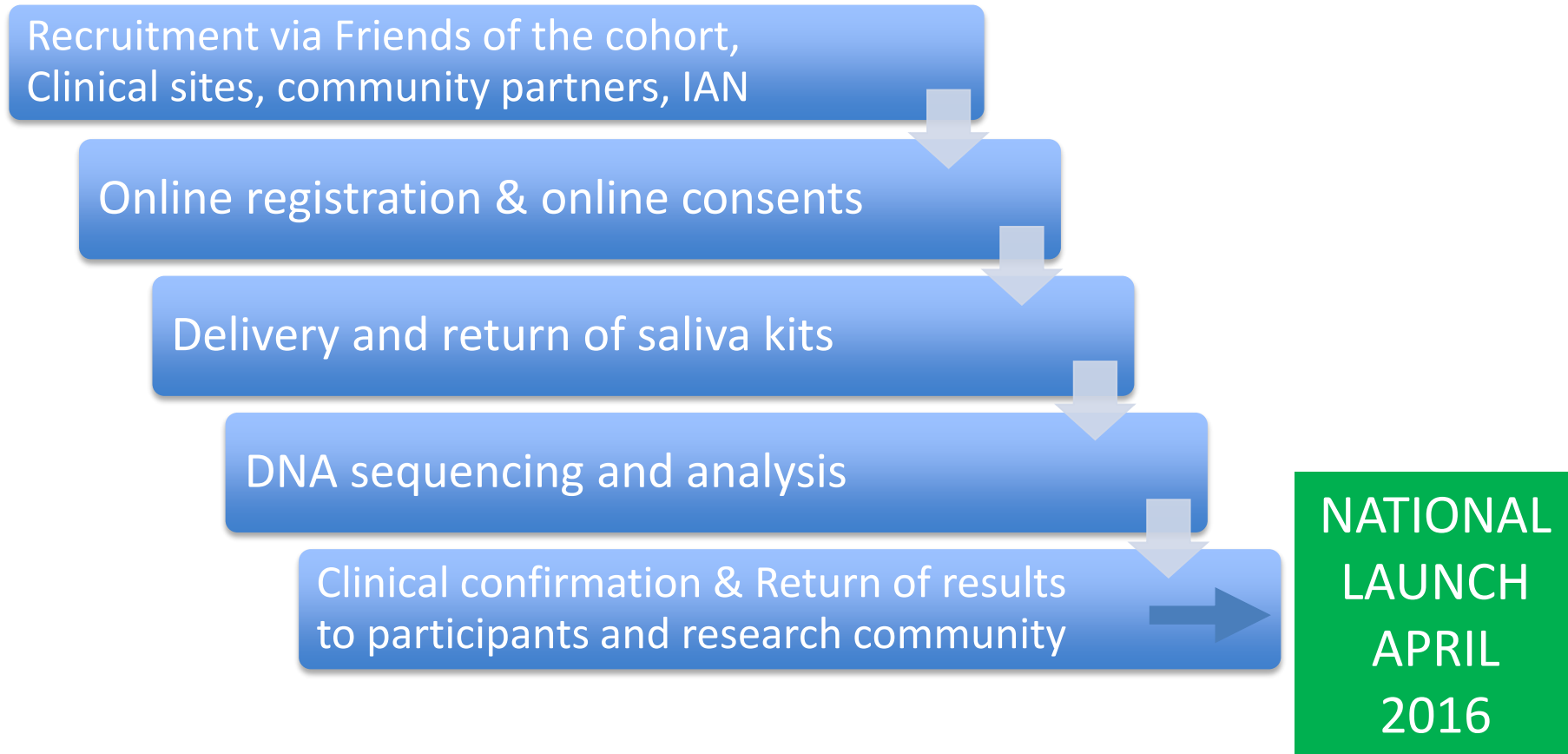
# Genetics for pilot phase

- 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:



# 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 Bemier Kochel



Sherr Buckner Roberts



Grant Aylward



Hunter Steinman



Spence



Ramocki



Poduri

## Neurology and Neuroimaging (UCSF):

Structural: Harvard, UW Seattle, Baylor

## Neuroimaging



Nacarajan Mukherjee

## Statistical core (Columbia)



Vaughan Chen

## Biospecimens (Rutgers, Simons)



Tischfield Sheldon Benedetti Packer

## Informatics (Prometheus)



Voccola Jensen



# National autism cohort staff



Wendy Chung  
Dir. Clinical Research



Pamela Feliciano  
Senior Scientist



Amy Daniels  
Project Manager



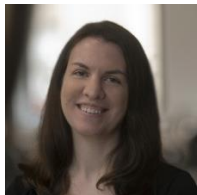
Stephen Zukin  
Dep. Dir. Clinical Research



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



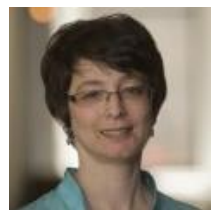
Richard Marini  
Sr. Software Engineer



Martin Butler  
Software Engineer



Andrei Salomatov  
Bioinformatics Engineer



Natalia Volfovsky  
Analytics Manager



Ron Edgar  
Informatics Consultant

Chris Rigby,  
Informatics Consultant