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
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?

Autism

“Normal”
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 Cole 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 plumped it on the piano in front of him.

Over the years, the truth of how my husband became a singer is so entwined 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 Strodt, 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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Rapidly Decreasing Cost of DNA Sequencing
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

- Unknown: ~75%
- 16p11.2 accounts for 1% of ASD
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
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.

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.

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

Recruitment Core
- Emory/Geisinger

Phenotyping Cores
- Children’s Hospital, Boston
- Texas Children’s, Houston
- UW Seattle

2nd Level Imaging Cores
- UCSF
- CHOP

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

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*

Adaptive Behaviors
- Vineland

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

Medical*

* Measures done at UCSF and CHOP or Emory
Neuroimaging

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

<table>
<thead>
<tr>
<th>Neurological features</th>
<th>Questionnaire N=76</th>
<th>Full assessment N=54</th>
<th>Literature N=65*</th>
<th>Relatives N=38</th>
<th>All N=233 (%)</th>
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<tbody>
<tr>
<td><strong>Seizures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>6</td>
<td>9</td>
<td>11</td>
<td>3</td>
<td>52 (22.3%)</td>
</tr>
<tr>
<td>Generalized</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Tone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Spasticity/Hyperreflexia</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>38 (16.3%)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>9</td>
<td>6</td>
<td>11</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Gait, coordination, movements disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dysmetria</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gait disorder/ataxia</td>
<td>5</td>
<td>18</td>
<td>0</td>
<td>1</td>
<td>45 (19.3%)</td>
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<tr>
<td>Paroxysmal movements disorder (chorea, athetosis, tremor)</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Cranial nerve anomaly</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left abducens nerve aplasia</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td>Unilateral facial palsy</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
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</tbody>
</table>
16p11.2 deletion carriers have IQs ~2 SD lower than their family members
16p11.2 deletion carriers have Social Responsiveness Scale (SRS) ~2 SD higher than their family members.
Diagnostic Profile: 16p11.2 Deletion
23% have ASD
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

Brain Volume (cm$^3$)

* *
Cortical Surface Area is Increased in 16p11.2 Deletion Carriers
Imaging Brain Signals

![Graph showing Latency (ms) for different cases.](image)
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
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

- Individual genetic results about cause of child’s ASD: 73.29% (609)
- Printable results or summary document of surveys to share: 54.27% (451)
- Monetary compensation up to $50: 42.12% (350)
- Notifications about additional research: 36.10% (300)
- Access to a genetic counselor to walk through results: 29.12% (242)
## Top Three Informational Resources To Provide

<table>
<thead>
<tr>
<th>Resource</th>
<th>Percentage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to autism-specific educational apps and websites</td>
<td>61.01%</td>
<td>507</td>
</tr>
<tr>
<td>Articles about latest findings in autism research</td>
<td>42.48%</td>
<td>353</td>
</tr>
<tr>
<td>Local / regional listings of autism service providers</td>
<td>38.15%</td>
<td>317</td>
</tr>
<tr>
<td>Interactive webinars on the latest findings in autism</td>
<td>31.65%</td>
<td>263</td>
</tr>
<tr>
<td>Ways to connect individuals and families with others</td>
<td>30.20%</td>
<td>251</td>
</tr>
</tbody>
</table>
How did we get here?

<table>
<thead>
<tr>
<th>Qualitative Interviews: Adults with ASD &amp; Parents (n=29)</th>
<th>Quantitative Survey 1: Adults with ASD &amp; Parents (n=496)</th>
<th>SAB Member Feedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feedback from Scientific Community, Parents, Adults w/ASD (n=263)</td>
<td>Quantitative Survey 2: 100 Adults with ASD &amp; 900 Parents</td>
<td>Interactions with various groups with similar missions</td>
</tr>
</tbody>
</table>
Anyone w/ a professional diagnosis of autism & their family members (biological mom, dad, unaffected siblings)

Clinical sites (ASD clinical research centers)

Advocacy & Community-based organizations

Interactive Autism Network

Community at large (national media campaign)
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?

1. Register online
2. Consent online to share data
3. Consent online to DNA analysis
4. Enter basic information about family structure
5. Complete surveys
6. Provide saliva
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
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
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:

- Recruitment via Friends of the cohort, Clinical sites, community partners, IAN
- Online registration & online consents
- Delivery and return of saliva kits
- DNA sequencing and analysis
- Clinical confirmation & Return of results to participants and research community

NATIONAL LAUNCH
APRIL 2016
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  Tiemagel  Bowe  Fischbach

Geisinger:
Ledbetter  Lese-Martin  Faucett  Smith-Packard  Martin

Psychological/psychiatric testing (Harvard):
Sites: Harvard, UW Seattle, Baylor
Hanson  Bernier  Kochel  Sherr  Buckner  Roberts  Grant  Ayiward  Hunter  Steinman  Spence  Ramocki  Poduri

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

Neuroimaging
Nagarajan  Mukherjee  Vaughan  Chen

Statistical core (Columbia)

Biospecimens (Rutgers, Simons)
Tischfield  Sheldon  Benedetti  Packer

Informatics (Prometheus)
Voccola  Jensen

SIMONS VIP
VARIATION IN INDIVIDUALS PROJECT