Clinical Phenotypes of ASD-Related Genetic Mutations

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Autism spectrum disorder (ASD): a complex collection of phenotypes

- Diagnostic characteristics of ASD
  - Social Communication deficits
  - Repetitive behaviors
- Comorbid conditions “If only it were just the autism!”
  - Intellectual disability
  - ADHD
  - Seizures
  - Sleeping problems
  - Bowel (GI) dysfunction

Importance of ASD Subtypes

- "If you’ve met one child with autism, you’ve met ONE child with autism"
- Many efforts to accurately "subtype" individuals with ASD to identify:
  - Consistent cluster of ASD symptom presentation
  - Medical co-morbidities
  - Recurrence rates
  - Common etiology
  - Targets for intervention
- Made progress in subtyping through genetic research
Background of ASD Genetics
(as told by a clinical psychologist)

Twin studies indicate heritability

Identical (monozygotic) twins
- Share 100% of their DNA
- Share their environment

Fraternal (dizygotic) twins
- Share 50% of their DNA
- Share their environment

If a condition is purely genetic, MZ twins should BOTH be affected

Twin Studies

<table>
<thead>
<tr>
<th></th>
<th>Social/Communication impairments</th>
<th>Autism spectrum</th>
<th>Autism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identical twins</td>
<td>100</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Fraternal twins</td>
<td>60</td>
<td>80</td>
<td>60</td>
</tr>
</tbody>
</table>
Genetic Landscape of Autism in 1977

Unknwon

Genetic Landscape of Autism in 2018

Unknwon

Copy Number Variants

15q11-13, 1q21...

16p11.2

Genetic Syndromes

Fragile X (FMR1), Tuberous sclerosis complex (TSC1 and TSC2)...

Approximately 50% of people with autism

Rare, inherited gene mutations

POGZ, SCN2A...

De novo gene mutations

CHD8, DYRK1A, ADNP, GRIN2B...

Rare, inherited gene mutations

RIMS1, CUL7...

Lessons Learned

• Sample size
  • Need a VERY large sample size to identify very rare mutations that contribute to ASD

• Behavioral testing and research visits were too burdensome for families, relative to results revealed in genetics studies
  • Need ability to tailor testing/questions based on genetic findings
  • Genetics-first approach, dive in with deeper phenotyping
Genetics-First Phenotyping

- Subjects are enrolled with loss-of-function mutation to one of several ASD-related genes of interest identified via:
  - Clinical testing
  - Prior research participation
  - Fly families in to the University of Washington for 2-3 day visit
  - Clinicians are naïve to genetic event during assessment

Genetics-first phenotyping

- Assessments of cognitive, executive fx, memory, motor, processing speed, and language skills
- Autism-related symptomology
- Parent interviews of adaptive functioning, medical and treatment history

- Medical exam, including dysmorphology
- 3D Imaging
- EEG
- Parental phenotyping: cognitive, language, executive fx, ASD-related traits
- Feedback

Genetic Landscape of Autism in 2018

- De novo gene mutations
  - CHD8
  - DYRK1A
  - ADNP
  - GRIN2B
  - POGZ
  - SCN2A
  - Total: 0.84

- Rare, inherited gene mutations
  - RIMS1, CUL7

- Copy Number Variants
  - 15q11-13, 1q21
  - 16p11.2

- Genetic Syndromes
  - Fragile X (FMR1), Tuberous sclerosis complex (TSC1 and TSC2...)

- ~50% of people with autism
Genetic Landscape of Autism in 2018

- De novo gene mutations
  - CHD8
  - DYRK1A
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- Copy Number Variants
  - 15q11-13
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- Genetic Syndromes
  - Fragile X (FMR1)
  - Tuberous sclerosis complex (TSC1 and TSC2)

- ~50% of people with autism

- Unknown gene

- CHD8
  - 0.36%
  - DYRK1A
  - 0.16%
  - ADNP
  - 0.08%
  - GRIN2B
  - 0.08%
  - POGZ
  - 0.08%
  - SCN2A
  - 0.08%
  - Total
  - 0.84%

De novo mutations in CHD8 gene

- Macrocephaly, similar facial features
- Autism spectrum disorder
- Gut motility problems
- Sleep disturbance
- Range of intellectual abilities

Bernier, Stessman, Gerdts, et al. (2014) Cell

Significant genotypes associated with disruptive mutations in CHD8

CHD8 clinical features:
- Macrocephaly, hypertelorism, gastrointestinal (GI) and sleep disturbances

Bernier, Stessman, Gerdts, et al. (2014) Cell
De novo mutations in ADNP gene

- Mild to severe intellectual disability
- Autism spectrum disorder
- Vision impairment
- Motor delays
- Feeding problems
- Macrocephaly, similar facial features
**ADNP biomarker**

- 81% of ($n=45/55$) children with ADNP mutations had a nearly full set of teeth at 11-12 months old, including molars
  - Premature tooth eruption as a potential early diagnostic biomarker
  - Not seen in any other syndrome
  - Adnp-deficient mice showed similar teeth abnormalities

Gozes, Sermone et al. (2017), Translational Psychiatry

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**Distinct DYRK1A syndromic facial features**

Earl, Gerdts et al. (2017); van Bon, et al. (2016) Mol Psychiatry

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**Foot and ear anomalies**

Earl, Gerdts et al. (2017)
Is the *DYRK1A* phenotype distinct from idiopathic autism?

Frequency of *DYRK1A* groups who present with >5 of these features greater than that of idiopathic ASD group. Fisher’s exact test, *p* < 0.001

GRIN2B clinical phenotype

(n = 19), 17 months - 16 years

<table>
<thead>
<tr>
<th>Developmental and Psychiatric Diagnoses</th>
<th>Medical and physical features</th>
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<tbody>
<tr>
<td>• 95% had significant motor and language delays</td>
<td>• Physical</td>
</tr>
<tr>
<td>• Of those evaluated:</td>
<td>• This stature (BMI underweight: 89%)</td>
</tr>
<tr>
<td>– 90% had ASD diagnosis</td>
<td>• Large unremarkable facial features</td>
</tr>
<tr>
<td>– 100% met criteria for Global Developmental Delay or Intellectual Disability or Mild to Severe</td>
<td>• Normal head circumference (84%)</td>
</tr>
<tr>
<td>– 36% diagnosed w/ ADHD</td>
<td>• Medical</td>
</tr>
<tr>
<td></td>
<td>• Hypotonia (74%)</td>
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<td></td>
<td>• Feeding difficulties, including GI tube (61%)</td>
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<td></td>
<td>• Vision Problems (43%)</td>
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<td>• GI Problems: GERD (58%) and constipation (42%)</td>
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<td></td>
<td>• Recurrent and frequent otitis media (47%)</td>
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<td></td>
<td>• Sleep Difficulties (50%)</td>
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<tr>
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<td>• History of seizures (57% + 21% suspected seizures)</td>
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<td></td>
<td>• EEG abnormalities (37%)</td>
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</table>

GRIN2B clinical phenotype

(n = 19), 17 months - 16 years

*compared to idiopathic ASD control group
GRIN2B behavioral features

Behavioral Observations

• Social exuberance, friendly, outgoing, despite ASD-related impairments
• Social Responsiveness Scale, 2nd Edition:
  • Significant group effects for the SRS-2 Social Motivation domain, but non-significant differences on other domains
  • SRS-2 Social Motivation subscale scores in the average-mild range for GRIN2B

What’s in it for the families?

Knowing the genetic diagnosis...

• Helps to understand long-term prognosis and helps families set expectations
• Provides information about recurrence
• Connects families to a community
• Might lead to changes in medical care
• Ends the ‘diagnostic odyssey’
• May provide precision medicine opportunities
• Majority of ASD families say genetic test results were moderately to extremely helpful

Chen, et al (2017); Genet Med
New RARE Clinic: Launched!

- Rare Autism-Related Genetic Consultation Clinic
  - Short-term consultation clinic to evaluate children with certain genetic mutations related to ASD
    - Psychology (Jen G), speech and language (Jim M), and pediatrics (Jen M)
    - Based on child's needs, we may help set up appointments with other providers
  - 3 to 4 appointments in a single day, including team feedback
    - Provide clinical impressions and individualized treatment recommendations
    - Information known about particular genetic event

What about Precision Medicine?

"An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."

-- NIH Genetics Home Reference
What about Precision Medicine?

- Precision Medicine is not a new concept
- BUT…we have new tools that will help us develop even more precise therapies!
- Animal models show promising results for several compounds specific to particular mutations: setting the stage for clinical trials

Thank you: Families! And Bernier Lab