Genetic heterogeneity of autism spectrum disorders

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.
Neuropsychiatric disorders have a negative impact on fecundity

Ramifications:
Common and low frequency variants can be plentiful at very low effect sizes (OR < 1.1)

Large effect alleles must be extremely rare

From: Fecundity of Patients With Schizophrenia, Autism, Bipolar Disorder, Depression, Anorexia Nervosa, or Substance Abuse vs Their Unaffected Siblings
Common variants of very small effect act additively across the genome

Biological insights from 108 schizophrenia–associated genetic loci

- Polygenic risk for schizophrenia predicts case control status in independent samples
- Estimated polygenic risk mediates ~20% of family history effect in the Danish registry data (Agerbo et al., JAMA Psych 2015)
Similar story with rare variation

Natural selection prevents strong alleles from achieving any measurable population frequency

Rare mutations fall across 100s of genes and strong alleles are removed by natural selection…
Therefore 10000s of exomes / genomes required to discover rare associated variants

Beneficial exception: de novo mutations easy to find and can have large effects

Slide courtesy of Mark Daly
Following recent discovery: two types of genetic instruments

Polygenic risk

- Continuously distributed and present in everyone to some degree

De novo variation

- A binary variable: presence/absence of a *de novo* variant from a class associated with disease risk
ASDs’ genetic influences span the frequency spectrum

To what extent are these average contributions consistent across all ASDs?

Gaugler et al. 2014
De novo variation plays a significant role in neurodevelopmental disorders

### Table: Mutation Type vs. Observed vs. Expected de novo events per exome

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Observed de novo events per exome</th>
<th>Expected de novo events per exome</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synonymous</td>
<td>0.263</td>
<td>0.274</td>
<td>0.179</td>
</tr>
<tr>
<td>Missense</td>
<td>0.707</td>
<td>0.620</td>
<td>1.33E-11</td>
</tr>
<tr>
<td>PTV</td>
<td>0.145</td>
<td>0.086</td>
<td>8.61E-32</td>
</tr>
</tbody>
</table>

n = 3982 families
De novo rate and IQ in ASDs

The genetic architecture of ASDs overlaps with that of other neuropsychiatric disorders in a manner dependent on proband cognitive ability and case severity.

Robinson, Neale, Hyman, Curr Opinion Pediatrics 2015
Common variant risk for ASDs and other neuropsychiatric disorders is comparatively neurologically gentle

The genetic correlation between ASDs and general population IQ is estimated at 0.2 - 0.4 (more risk -> higher IQ)

No common variant association between ASDs and epilepsy

Bulik-Sullivan and Finucane et al. 2015
1a Randomly Selected Trios

- Mothers
  Mean PRS = A

- Fathers
  Mean PRS = B

- Offspring
  Mean PRS = \((A+B)/2\)

1b Trios Selected for High Height in Offspring

- Mothers
  Mean PRS = A

- Fathers
  Mean PRS = B

- Offspring
  Mean PRS = \((A+B)/2 + n\)

The diagram illustrates the distribution of PRS values for height, showing how offspring with high PRS values are selected for further study.
Update on contributing *de novo* variants (ASDs)

1) **Protein Truncating Variants** (6.5% cases : 2% controls)

2) **Deletions** including a constrained gene and/or 500kb+ (3.1% cases : 0.6% controls)

3) **Duplications** larger than 500kb (1.6% cases : 0.6% controls)

4) **Missense Variants**

We observe high impact *de novo* variants in approximately 15% of ASD cases and 4% of controls

Jack Kosmicki, Emilie Wigdor, Kaitlin Samocha
Rate of CDNVs Increases with Number of Adverse Neurological and Developmental Events

Event Count: Delayed Walking, Seizures, and Intellectual Disability

- Control Rate of CDNVs: 0 (N=1,476) OR=3.15 p=3.88E−10
- 1 (N=719) OR=4.53 p=5.33E−15
- 2 (N=134) OR=10.18 p=6.94E−23
- 3 (N=16) OR=15.05 p=9.08E−10

Common Polygenic and Rare De Novo Variation Act Additively in CDNV Carriers to Influence ASD Risk (N=201)

- ASD: p=6.76E−03
- SCZ: p=9.24E−03
- EA: p=0.63

Average Polygenic Risk Score (Standard Deviations on the Average Parent Distribution)
When risk-contributing genetic factors are reasonably orthogonal, extreme scores aren’t required to create a rare outcome.
Understanding autism

Understanding the biology of autism – both negative and potentially positive elements – requires a comprehensive approach that articulates and interprets all genetic components of all types and penetrances.

15% of cases carry severe de novo mutation; highly enriched for ID, seizures.

Polygenic risk
Thanks

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