Using the Genetic Architecture of Externalizing Disorders and Behaviors to Aid in Gene Identification

Preliminary Results from the Externalizing Consortium

Peter Barr
10/03/19
Genetics of Alcohol Use Disorders (AUD)

- AUD is a moderately heritable traits (~50%) ¹
  - Strong genetic overlap with traits related to behavioral under-control ²
  - Generally referred to as the externalizing spectrum
  - Includes other substance misuse, antisocial behaviors, risk-taking, and personality characteristics ²,³
- Externalizing factor is highly heritable (~81%) ²
  - Explains 74-80% of the genetic influence on AUD and 62-74% of the genetic influence on other SUD ⁴
GWAS of Externalizing Traits

• Multiple GWAS of Externalizing traits:
  – Problematic Alcohol Use $^{5,6,7}$
  – Lifetime Cannabis Use $^8$
  – General risk tolerance $^9$
  – ADHD $^{10}$

• Single phenotype GWAS ignore the shared genetic etiology of these traits on the externalizing spectrum.
The Externalizing Consortium: Modeling Externalizing using Genomic SEM

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>N total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>53,293</td>
</tr>
<tr>
<td>Age at first sexual intercourse</td>
<td>357,187</td>
</tr>
<tr>
<td>Alcohol problems</td>
<td>150,640</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>1,232,091</td>
</tr>
<tr>
<td>General risk tolerance</td>
<td>390,934</td>
</tr>
<tr>
<td>Lifetime cannabis use</td>
<td>186,875</td>
</tr>
<tr>
<td>Number of sexual partners</td>
<td>336,121</td>
</tr>
</tbody>
</table>
Conclusions

• Results indicate a single latent factor for Externalizing:
  – ~580 Independent GWS loci
  – Estimated sample size of 1.5 million individuals

• Next steps:
  – Replication using top SNPS and PRS
  – Exploratory analyses of PRS with a broad range of phenotypes
Acknowledgments

- Richard Karlsson-Linnér
- Travis Mallard
- Sandra Sanchez-Roige
- Danielle M. Dick*
- Paige Harden*
- Philipp Koellinger*
- Abe Palmer*
- Arpana Agrawal
- Joel Gerlenter
- Daniel Gustavson
- Hank Kranzler
- Irwin Waldman
- Other members of the Externalizing Consortium

- Funding:
  - NIAAA: R01AA015416

- Cohorts:
  - Psychiatric Genomics Consortium
  - 23andMe
  - UK Biobank
  - Million Veterans Program
  - BioVU
  - COGA
  - Add Health
References