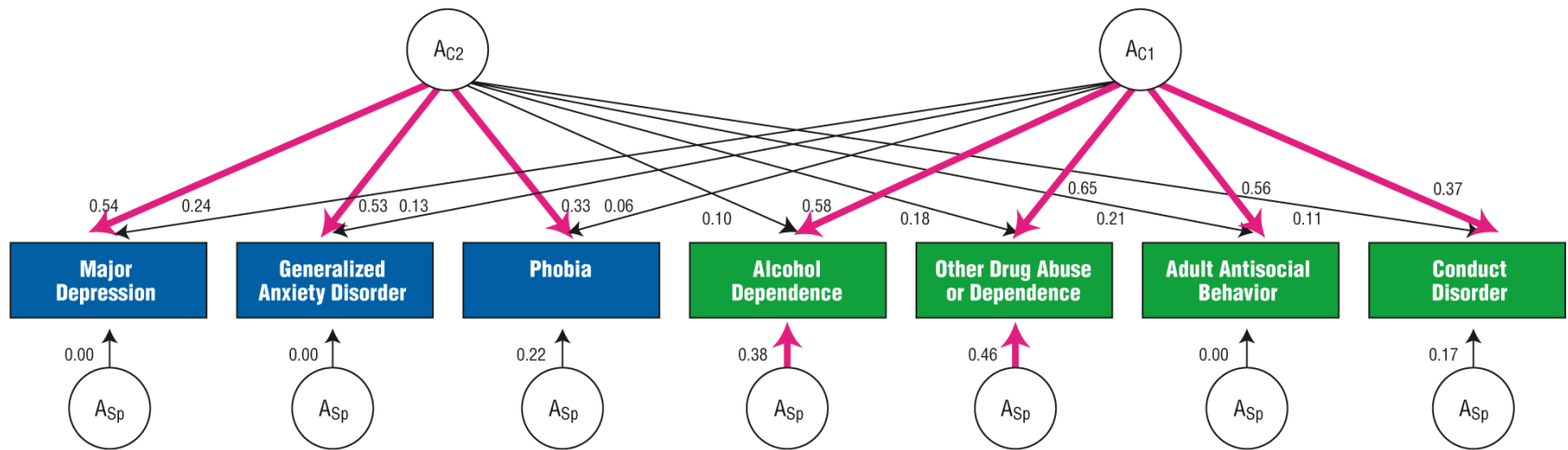# Using the Genetic Architecture of Externalizing Disorders and Behaviors to Aid in Gene Identification

Preliminary Results from the Externalizing Consortium

Peter Barr

10/03/19

VCU

# 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 [11]

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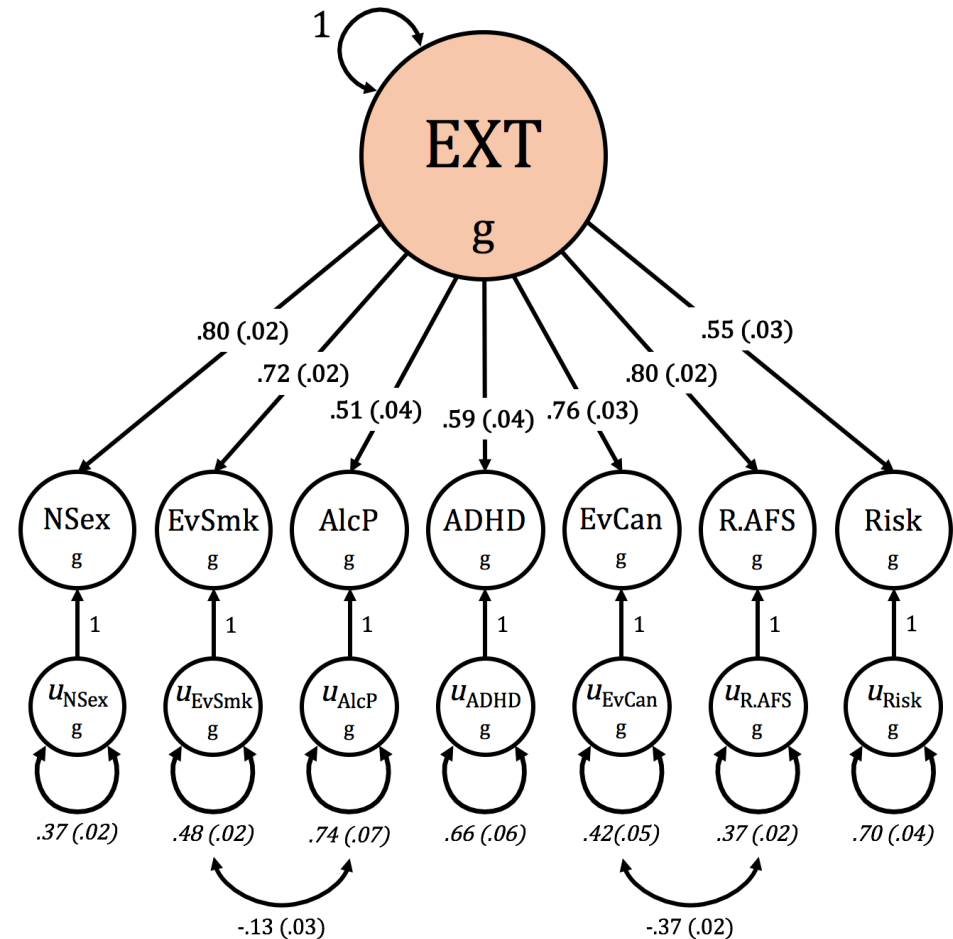
Conclusions

- 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

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

References

1. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychological Medicine. 2015;45(5):1061-72.
2. Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiologic connections among substance dependence, antisocial behavior and personality: Modeling the externalizing spectrum. Journal of Abnormal Psychology. 2002;111(3):411-24.
3. Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Archives of General Psychiatry. 2003;60(9): 929-37.
4. Kendler KS, Myers J. The boundaries of the internalizing and externalizing genetic spectra in men and women. Psychological Medicine. 2013;44(3):647-55.
5. Walters RK, Polimanti R, Johnson EC, McClintick JN, Adams MJ, Adkins AE, . . . Agrawal A. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. Nature Neuroscience. 2018;21(12):1656-69.
6. Kranzler HR, Zhou H, Kember RL, Vickers Smith R, Justice AC, Damrauer S, . . . Gelernter J. Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. Nat Commun. 2019;10(1):1499.
7. Sanchez-Roige S, Palmer AA, Fontanillas P, Elson SL, Adams MJ, Howard DM, . . . Clarke T-K. Genome-Wide Association Study Meta-Analysis of the Alcohol Use Disorders Identification Test (AUDIT) in Two Population-Based Cohorts. American Journal of Psychiatry. 2018:appi.ajp.2018.
8. Pasman JA, Verweij KJH, Gerring Z, Stringer S, Sanchez-Roige S, Treur JL, . . . Vink JM. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. Nature Neuroscience. 2018;21(9):1161-70.
9. Karlsson Linnér R, Biroli P, Kong E, Meddens SFW, Wedow R, Fontana MA, . . . Beauchamp JP. Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. Nature Genetics. 2019;51(2):245-57.
10. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, . . . Neale BM. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nature Genetics. 2019;51(1):63-75.
11. Grotzinger AD, Rhemtulla M, de Vlaming R, Ritchie SJ, Mallard TT, Hill WD, . . . Tucker-Drob EM. Genomic structural equation modeling provides insights into the multivariate genetic architecture of complex traits. Nature Human Behaviour. 2019.

VCU University Relations