Lessons from Three Decades Investigating ADHD Genetics

Stephen V. Faraone, Ph.D.

Distinguished Professor
Departments of Psychiatry & of Neuroscience and Physiology
SUNY Upstate Medical University
@StephenFaraone
## Financial Disclosures (Past 2 Years)

<table>
<thead>
<tr>
<th>Source</th>
<th>Research or CME Funding</th>
<th>Consult Fees</th>
<th>Speakers Bureau</th>
<th>Royalties or IP</th>
<th>In Kind Services</th>
<th>Stock / Equity</th>
<th>Honorarium or expenses for this meeting</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHE Inhibitor Patent</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shire/Takeda</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akili</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vallon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tris</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otsuka</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IronShore</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supernus</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunovion</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genomind</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arbor</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>OnDosis</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lesson 1:

Much of ADHD’s Etiology is Coded in the Genome
Heritability of ADHD
(Faraone & Larsson, Molecular Psychiatry, 2018)

Mean heritability across 38 studies = 74%
Lesson 2:

ADHD & Most Common Forms of Psychopathology are Polygenic
Polygenicity and Genetic Correlations
(Smoller et al., Molecular Psychiatry, 2018)

• Given GWAS data from an individual, we can compute their polygenic risk score for many psychiatric and non-psychiatric disorders.
• These scores can be correlated with one another to compute a genetic correlation.
• The genetic correlation tells us the degree to which two disorders share common DNA variants
ADHD Polygenic Risk in 7,000 Adolescents
(Li, BioRxiv; http://dx.doi.org/10.1101/611897)

• A polygenic risk score indexes the number of ADHD risk alleles carried by an individual.
Genetic Correlation with ADHD Symptoms in the Population

• The EAGLE/QIMR data comprises ADHD parental rating scale scores from 20,464 children and adolescents from the general population.

• Correlation of polygenic score for diagnosis of ADHD and symptoms in the population: \( r_g = 0.97, \ SE = 0.2 \)
Sex Differences in Common Genetic Variants

(Martin et al., Biol. Psychiatry, 2018)

Genetic Correlation between Males and Females:

\[ R_g = 1.2, \ p < 0.000000001 \]
ADHD Polygenic Risk and Functional Outcomes in 7,000 Adolescents
(Li, BioRxiv; http://dx.doi.org/10.1101/611897)
ADHD Polygenic Risk Correlates with Adversity

(Zwicker et al., JCPP, 2019)
Parental Education Correlates with but does not Moderate ADHD Polygenic Risk

(Ostergaard et al., Transl. Psychiat., 2020)
Parental Income Correlates with but does not Moderate ADHD Polygenic

(Ostergaard et al., Transl. Psychiat., 2020)
• The frequency of genetic variants associated with ADHD has steadily decreased since Paleolithic times.
• These findings indicate long-standing selective pressures acting against ADHD risk variants.

Esteller-Cucala et al., Scientific Reports, 2020
Lesson 3:

ADHD Shares its Genetic Etiology with other Psychiatric Disorders
Genetic Correlations among Psychiatric Disorders
(PGC Cross Disorder Group, Cell, 2019)
Genetic Correlations for ADHD & Substance Use Disorders
(Vilar-Ribo et al., 2020, AJMG-B)

Mendelian Randomization Analyses

- Bi-directional causality
- ADHD causes SUD Phenotype

Note: Other causal effects not tested
Causal Modeling of ADHD and Depression

(Riglin et al., Psych Medicine, 2020)

- Used ALSPAC longitudinal, population cohort (N = 8310)
- Childhood ADHD predicted depression in young adulthood
- Mendelian Randomization:
  - Causal effect of ADHD on depression
  - Causal effect of depression of ADHD was only significant for broad definition of depression
Lesson 4:

ADHD Shares Polygenes with Psychological Traits and Medical Conditions
Genetic Correlations with Neuroticism Traits

(Du Rietz et al., Bio Psychiat CNNI, 2017)
Genetic Correlations: Other Traits

(Demontis et al., Nature Genetics, 2018)

- Ever vs never smoked ($P=4\times10^{-16}$)
- Cigarettes smoked per day ($P=1\times10^{-05}$)
- Former vs Current smoker ($P=7\times10^{-05}$)
  - Lung cancer ($P=6\times10^{-10}$)
  - Lung cancer (all) ($P=3\times10^{-07}$)
  - Squamous cell lung cancer ($P=5\times10^{-05}$)
- Age of first birth ($P=4\times10^{-61}$)
- Number of children ever born ($P=9\times10^{-17}$)
- Age at Menopause ($P=2\times10^{-04}$)
- Mothers age at death ($P=6\times10^{-07}$)
- Fathers age at death ($P=7\times10^{-06}$)
- Parents age at death ($P=4\times10^{-05}$)
- Insomnia ($P=4\times10^{-11}$)
- Rheumatoid Arthritis ($P=1\times10^{-04}$)
Association of Polygenic Risk and BMI
(Du Rietz et al., Bio Psychiat CNI, 2017)

$P = 4.5 \times 10^{-129}$
Narcolepsy PRS Predict ADHD Symptoms in Youth from the General Population
(Takahashi, Transl. Psychiat., 2020)
Lesson 5:

Genomewide Significant Findings Implicate Genes and Regulatory Elements Expressed in Brain
Partitioning Polygenic Risk by Tissue Group

Annotations

- LOG10(P_ENRICHMENT)

- Adrenal/Pancreas
- Central Nervous...
- Cardiovascular
- Connective bone
- Gastrointestinal
- Immune/Hematopoietic
- Kidney
- Liver
- Skeletal Muscle

P = 5.23 x 10^-5

P = 0.005
Functional Annotations Implicates Epigenetic Effects

ENRICHMENT = (PROPORTION OF SNP H2)/(PROPORTION OF SNPS)

P = 8.49E-10*

P = 0.008

P = 0.004

P = 0.005

P = 0.005
Lesson 6:

ADHD in Childhood and ADHD in Adulthood Share Many Polygenes
Common Genetic Variants Mostly the Same for Childhood and Adult ADHD
(Rovira et al., Neuropsychopharm, 2020)

\[ h^2_{SNP} = 0.20 \]
\[ (SE = 0.023) \]

\[ h^2_{SNP} = 0.21 \]
\[ (SE = 0.025) \]

Genetic Correlation
\[ R_g = 0.81 \]
\[ (0.08) \]
\[ P-Value = 5.1235e-21 \]
Genetic Correlations with Other Traits the Same for Childhood and Adult ADHD

(Rovira et al. submitted)
Lesson 7:

What is the Pathway Towards Actionable Genomic Information?
Can We Use DNA to Make Psychiatric Diagnoses?

- No
- Current polygenic risk scores are not sufficiently accurate for use in the clinic
- Accuracy may improve as samples get larger, more sophisticated algorithms are applied and other data sources (transcriptome, epigenome imaging) are combined
The new molecular genetic data will, hopefully, put an end to debates about psychiatric comorbidity.

We now know that most psychiatric disorders are correlated with one another at the level of DNA.

Diagnosticians should expect “pervasive comorbidity”
- ADHD can co-occur with many disorders
- Multiple comorbidities are to be expected in some patients
What About Drug Development?

• Theoretically, genetic studies might identify new targets for drugs with novel mechanisms of action.

• These targets, however, may be most important early in development and would be relevant for prevention, not treatment.

• We have many targets to choose from, which suggests that multi-target therapies may be needed.
Summary: Lessons From ADHD Genetics

- ADHD has a strong genetic component
- Most forms of ADHD have a polygenic etiology
- ADHD shares DNA risk variants with other disorders
- Genetic risk for ADHD predicts psychological traits and medical outcomes.
- The genetic risk for ADHD is expressed in the brain
- ADHD in childhood and adulthood share polygenic risk
- Diagnostic practice should incorporate comorbidity assessments

www.mghcme.org
Thanks for Listening!

Free CME: www.adhdinadults.com

MyADHD Blogs: www.linkedin.com/in/stephenfaraone

Tweets: @StephenFaraone

8th World Congress on ADHD
From Child to Adult Disorder
6 – 9 May 2021