Advances in the Genetics of ADHD

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Overview: Advances in the Genetics of ADHD

• Common DNA Variants
  – Genome-wide significant loci
  – Polygenic Risk Scores

• Rare DNA Variants
  – Copy Number Variants
  – Single Nucleotide Variants

• Genetics and Personalized Medicine
  – Is there a Genetic Test for ADHD?
  – Can we Predict ADHD Medication Response?
Mean heritability across 37 studies = 74%
Common DNA Variants

SNP = Single nucleotide polymorphism
GWAS = Genomewide association study
PGC = Psychiatric Genomics Consortium
iPSYCH = Danish Psychiatric Genetics Group
The PGC ADHD/iPSYCH-SSI-Broad collaboration
106 Members, 14 Countries, 5 Continents
ADHD GWAS: 20,183 cases 35,191 controls, 8,151,190 genetic markers

12 genome-wide significant loci
## 12 Genome-wide Significant Loci

<table>
<thead>
<tr>
<th>Chr</th>
<th>Index SNP</th>
<th>Gene</th>
<th>OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rs11420276</td>
<td><strong>ST3GAL3</strong></td>
<td>1.113</td>
<td>2.14 x 10^{-13}</td>
</tr>
<tr>
<td>1</td>
<td>rs1222063</td>
<td><strong>Intergenic</strong></td>
<td>1.101</td>
<td>3.07 x 10^{-8}</td>
</tr>
<tr>
<td>2</td>
<td>rs9677504</td>
<td>SPAG16</td>
<td>1.124</td>
<td>1.39 x 10^{-8}</td>
</tr>
<tr>
<td>3</td>
<td>rs4858241</td>
<td><strong>Intergenic</strong></td>
<td>1.082</td>
<td>1.74 x 10^{-8}</td>
</tr>
<tr>
<td>4</td>
<td>rs28411770</td>
<td>PCDH7</td>
<td>1.09</td>
<td>1.15 x 10^{-8}</td>
</tr>
<tr>
<td>5</td>
<td>rs4916723</td>
<td>LINC00461</td>
<td>0.926</td>
<td>1.58 x 10^{-8}</td>
</tr>
<tr>
<td>7</td>
<td>rs5886709</td>
<td><strong>FOXP2</strong></td>
<td>1.079</td>
<td>1.66 x 10^{-8}</td>
</tr>
<tr>
<td>8</td>
<td>rs74760947</td>
<td>LINC01288</td>
<td>0.835</td>
<td>1.35 x 10^{-8}</td>
</tr>
<tr>
<td>10</td>
<td>rs11591402</td>
<td>SORCS3</td>
<td>0.911</td>
<td>1.34 x 10^{-8}</td>
</tr>
<tr>
<td>12</td>
<td>rs1427829</td>
<td>DUSP6</td>
<td>1.083</td>
<td>1.82 x 10^{-9}</td>
</tr>
<tr>
<td>15</td>
<td>rs281324</td>
<td>SEMA6D</td>
<td>0.928</td>
<td>2.68 x 10^{-8}</td>
</tr>
<tr>
<td>16</td>
<td>rs212178</td>
<td>LINC01572</td>
<td>0.891</td>
<td>7.68 x 10^{-9}</td>
</tr>
</tbody>
</table>

None of these had previously been proposed as ADHD candidate genes.
• A polygenic risk score indexes the number of ADHD risk alleles carried by an individual.

Calculated as \[ S = \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k, \]

\( X_2, \ldots, X_k \) - allele dosages for \( k \) independent markers (SNP-s).
The Polygenic Score is a Molecular Genetic Tease  
(Faraone, Biol Psychiat, 2014)

• It confirms that many common DNA variants are associated with ADHD.  
  – But “many” could mean hundreds, thousands or more.  
  – It cannot tell us which variants are truly associated with the disorder.

• It tells us that about one third of ADHD’s heritability is due to common DNA variants.  
  – We can use polygenic scores to assess genetic overlap among disorders and traits
ADHD Risk Increases with the Polygenic Risk Score

Those in the highest 10% of polygenic risk have five-fold increased risk for ADHD.

...But the PRS is a very weak predictor of who does and does not have ADHD.
ADHD Risk Increases with the Polygenic Risk Score

The finding a significant polygenic background confirms predictions from twin studies suggesting that the diagnosis of ADHD is the extreme of a quantitative trait (e.g., Larsson et al.; Levy et al.; Gjone et al.).
Genetic Correlation Between Males and Females

(Martin et al. In preparation)

Genetic correlations significantly differ from 0 but not from 1
Partitioning SNP Heritability by Functional Annotations

ENRICHMENT = (PROPORTION OF SNP H2)/(PROPORTION OF SNPS)
Partitioning SNP Heritability by Tissue Group

Annotations

\[ P = 5.23 \times 10^{-5} \]

\[ P = 0.005 \]
Genetic Correlations Across Psychiatric Disorders
(Verneri et al, submitted)
These findings confirm predictions from many, many family and twin studies that ADHD share parts of its genetic etiology with several other disorders (too many to cite!).
Genetic correlations between Psychiatric and Neurologic Disorders
(Verneri et al, submitted)
Genetic Correlations for ADHD and Personality
(Verneri et al, submitted)
Rare DNA Variants

CNV = Copy number variant
SNV = Single nucleotide variant
Burden of Large (>500kb) Rare Copy Number Variants (CNVs) in ADHD

Average Number of CNVs per Subject

- **Elia 2012**
  - Control: N=8220
  - ADHD: N=2488

- **Lionel 2011**
  - Control: N=2357
  - ADHD: N=248

- **Yang 2012**
  - Control: N=898
  - ADHD: N=969

- **Mick 2012**
  - Control: N=735
  - ADHD: N=1844

- **Stergiakouli 2012**
  - Control: N=727
  - ADHD: N=5081

- **Williams 2011**
  - Control: N=896
  - ADHD: N=2455

- **Williams 2010**
  - Control: N=410
  - ADHD: N=1156

- **P-values**
  - Stergiakouli 2012: P=.02
  - Williams 2010: P=.0009
Pathway Analysis of CNVs: Significant Enrichment of Glutamate Network
(Elia et al., Nature Genetics, 2011)

\[ P = 4.38 \times 10^{-10} \]
Pathway Analysis of CNVs: Significant Enrichment of Glutamate Network
(Elia et al., Nature Genetics, 2011)

These findings have led to a clinical trial of a drug to treat ADHD patients with glutamate pathway mutations (Hakonarson et al.)

$P = 4.38 \times 10^{-10}$
ADHD CNVs Enriched in Genes with Schizophrenia and Autism *de novo* SNVs
(Thapar et al. Molec Psych, 2016)

<table>
<thead>
<tr>
<th>Gene set</th>
<th>Genes</th>
<th>CNVs &gt;500 kb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>SCZ (NS)</td>
<td>611</td>
<td>5.4 × 10⁻⁴</td>
</tr>
<tr>
<td>SCZ (LoF)</td>
<td>87</td>
<td>0.33</td>
</tr>
<tr>
<td>AUT (NS)</td>
<td>2726</td>
<td>0.019</td>
</tr>
<tr>
<td>AUT (LoF)</td>
<td>538</td>
<td>0.026</td>
</tr>
</tbody>
</table>

AUT, autism; CNV, copy number variant; Del, deletion; Dup, duplication; LoF, loss of function; NS, non-synonymous; SCZ, schizophrenia
Top pathways in pooled meta-analysis with most significant enrichment for ADHD case CNV hits among CNVs >500 kb

(Thapar et al. Molec Psych, 2016)

<table>
<thead>
<tr>
<th>Pathway name</th>
<th>Pathway ID</th>
<th># Genes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6-mediated signalling events</td>
<td>NCI:62</td>
<td>82</td>
<td>$1.33 \times 10^{-11}$</td>
</tr>
<tr>
<td>TGF-β receptor signalling</td>
<td>NCI:95</td>
<td>44</td>
<td>$4.90 \times 10^{-11}$</td>
</tr>
<tr>
<td>Defence response to virus</td>
<td>GO:51607</td>
<td>147</td>
<td>$7.02 \times 10^{-8}$</td>
</tr>
<tr>
<td>Respiratory electron transport</td>
<td>REACT:1019</td>
<td>81</td>
<td>$1.98 \times 10^{-7}$</td>
</tr>
<tr>
<td>Organonitrogen compound catabolic process</td>
<td>GO:1901565</td>
<td>893</td>
<td>$9.08 \times 10^{-7}$</td>
</tr>
<tr>
<td>Transmembrane transporter activity</td>
<td>GO:22857</td>
<td>902</td>
<td>$9.10 \times 10^{-7}$</td>
</tr>
<tr>
<td>Citric acid (TCA) cycle and respiratory electron transport</td>
<td>REACT:1240</td>
<td>118</td>
<td>$1.16 \times 10^{-6}$</td>
</tr>
<tr>
<td>Carbohydrate derivative catabolic process</td>
<td>GO:1901136</td>
<td>747</td>
<td>$2.19 \times 10^{-6}$</td>
</tr>
<tr>
<td>Ligand-gated ion channel activity</td>
<td>GO:15276</td>
<td>136</td>
<td>$2.33 \times 10^{-6}$</td>
</tr>
<tr>
<td>Methyltransferase activity</td>
<td>GO:8168</td>
<td>201</td>
<td>$3.19 \times 10^{-6}$</td>
</tr>
<tr>
<td>Small thymus</td>
<td>MGI:706</td>
<td>199</td>
<td>$4.15 \times 10^{-6}$</td>
</tr>
<tr>
<td>Transmembrane transport</td>
<td>GO:55085</td>
<td>1124</td>
<td>$5.22 \times 10^{-6}$</td>
</tr>
<tr>
<td>Ion-gated channel activity</td>
<td>GO:22839</td>
<td>300</td>
<td>$5.29 \times 10^{-6}$</td>
</tr>
</tbody>
</table>
Rare Single Nucleotide Variants and ADHD
(Hawi et al., Molec Psych, 2016)

Next generation sequencing
152 youth with ADHD and 188 controls
Red line is Bonferroni corrected for 117 candidate genes
Only BDNF was significant with novel variants identified
Rare Single Nucleotide Variants and ADHD (Zayats et al., Trans Psych, 2016)

- Exome chip analysis of 1846 adults with ADHD and 7519 controls
- 152 youth with ADHD and 188 controls
- Four coding SNVs had Bonferroni significance of $p < 0.000008$
  - 6q22.1 locus implicates NT5DC1 and COL10A1
  - SEC23IP
  - PSD
  - ZCCHC4
- Results suggest that signal transduction molecules are involved in the etiology of ADHD
More Evidence for CNVs and SNVs in the Etiology of ADHD

- Increased burden of CNVs in adult ADHD (Ramos-Quiroga et al., J Psych Res, 2014)
- Rare CNVs in PARK2 (Jarick et al., Molec Psych, 2014)
- Exome sequencing
  - 26 de novo SNVs; 3 de novo CNVs (Leandro de Araujo Lima et al., Sci Rep, 2016)
  - Sporadic ADHD: 8 de novo missense SNVs; no de novo CNVs (Kim et al. AJMG-B, 2017)
Genetics and Personalized Medicine
Molecular Genetics & Diagnosis
Pharmacogenetics: Can We Predict Drug Pharmacokinetics from DNA Variants? (Froelich, McGough & Stein, CNS Drugs, 2010)

- Rare CES1 variants in poor metabolizers of methylphenidate
- 20% of Caucasians are poor metabolizers for amphetamine due to DNA variants at CYP2D6
- CYP3A4 variants may explain ancestry group differences in amphetamine metabolism.
- CYP2D6 and atomoxetine Ultra-rapid metabolizers:
  - 10% Caucasians; 3% African-Americans
Pharmacogenetics: Can We Predict Drug Response from DNA Variants?
(Meyer et al., Molecular Psychiatry, 2017)

- Pharmacodynamics: DNA Variants and Clinical Response of ADHD symptoms to Methylphenidate
  - Meta-analysis of variants in 6 genes from 50 studies of ADHD youth

<table>
<thead>
<tr>
<th>Gene</th>
<th>Odds Ratio</th>
<th>P-value</th>
<th>Heterogeneity</th>
<th>Pub. Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPHN3</td>
<td>1.1</td>
<td>NS</td>
<td>.70</td>
<td>No</td>
</tr>
<tr>
<td>DRD4</td>
<td>1.7</td>
<td>.003</td>
<td>.13</td>
<td>No</td>
</tr>
<tr>
<td>SLC6A2</td>
<td>2.9</td>
<td>.002</td>
<td>.32</td>
<td>No</td>
</tr>
<tr>
<td>SLC6A3</td>
<td>1.4</td>
<td>.009</td>
<td>.00001</td>
<td>Yes</td>
</tr>
<tr>
<td>COMT</td>
<td>1.4</td>
<td>.0001</td>
<td>.53</td>
<td>No</td>
</tr>
<tr>
<td>ADRA2A</td>
<td>1.7</td>
<td>.0001</td>
<td>.9</td>
<td>No</td>
</tr>
</tbody>
</table>
Pharmacogenetics of ADHD: Is it Clinically Useful?

- Effects of DNA variants on drug metabolism are strong and thus, theoretically useful
  - But fast and slow metabolizers can be detected via slow titration in clinical practice
- Effects of DNA variants on the response of ADHD symptoms to methylphenidate are real but weak. Predictive value is low
- Ultimately, to conclude that pharmacogenetically guided treatment is better than treatment as usual, we need randomized, controlled clinical trials.
Summary: Gene finding in ADHD
(Faraone et al., Nature Rev Dis Primers, 2015)

- **22q11.2 deletion syndrome**
  - Jacobsen syndrome (deletions of end of 11q)
  - Turner’s syndrome (X0)
  - Klinefelter’s syndrome (XXY)

- **16p13.11**
  - 15q11-13 region containing nicotinic α-7 acetylcholine receptor subunit gene
  - Rare point mutations expected from sequencing studies

- **Monoamine system genes**
  - Neurite outgrowth genes

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**Graph: Effect size vs Allele frequency**

- **High** Rare chromosomal anomalies
- **Low** Common variants explain about 40% of heritability

- **Effect size**
  - Very rare
  - Rare
  - Low

- **Allele frequency**
  - Common
  - Rare
  - Very rare
Summary: Parsing the Etiology of ADHD

- Environment & Error
- Common SNPs
- Rare Variants & G*E
Thanks for Listening!

Free CME: www.adhdinadults.com

My ADHD blogs: bit.ly/Farao