The International Multisite ADHD Genetics Project

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IMAGE Sites

- Switzerland (CH)
- Belgium (BE)
- Holland (NL)
- England (EN)
- Ireland (IR)
- Spain (ES)
- Israel (IL)
- Germany (DE)
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Note: Original QTL design based on advice from Prof Sham and from Shaun Purcell

Supported by NIH grant R01MH62873 to S. Faraone
Overview of Attention Deficit Hyperactivity Disorder

- A disorder of inattention, hyperactivity and impulsivity
- Onsets in childhood
- Impairs academic performance, social functioning and occupational performance
- Affects 8 to 12% of youth worldwide
Bradley: benzedrine helps hyperactive children

US Surgeon General: lack of resources a “public crisis in mental health”

CDC: ADHD a serious public health problem

Methylphenidate indicated for behavioral disorders in children

DSM IV revises criteria to include 3 subtypes of ADHD

DSM III-R re-emphasizes hyperactivity

DSM III ADD emphasizes attention

FDA approves methylphenidate for depression and nacolepsy

ADHD symptoms described in medical literature as MBD

DSM II Hyperkinetic Reaction

Dr. George Still describes DMC syndrome in Lancet

ADHD symptoms described in medical literature as MBD
Is ADHD an “American Disorder”?
(Faraone et al., World Psychiatry, 2003)
Concurrent Validity: Structural Neuroimaging
Brain Structures with Largest ADHD Effects
(Valera, Faraone, et al., Biological Psychiatry, 2006)

Right Cerebral Volume
N = 3
P < .001

Right Globus Pallidus
N = 3
P < .05

* Splenium
N = 6
P < .001

Cerebellar Vermis
N = 3
P < .01

Right Prefrontal Cortex (gray)
N = 3
P < .05

Posterior Inferior Vermis
N = 5
P < .001

** Left Prefrontal Cortex (gray)
N = 3
P < .05

* Witelson and O’Kusky methods combined. Also significant with Witelson only (N = 4). ** Pub bias.
ADHD Has a Substantial Genetic Component
(Faraone et al., Biological Psychiatry, 2005)

Mean Heritability of ADHD=.76
Adoption Study of ADHD
(Sprich et al., JAACAP 2000)

% ADHD in Relative

- Siblings
  - Biologic
  - Adoptive
  - Control

- Parents
  - Biologic
  - Adoptive
  - Control
ADHD is a Genetically Complex Disorder
(Faraone et al., Biological Psychiatry, 2005)

- FB: HTR1B (G861C)
- CC: S LC6A4 (5HTTLPR long)
- FB: SNAP25 (T1065G)
- FB: DBH (Taql A)n
- FB: S LC6A3 (VNTR, 10-repeat)
- FB: DRD5 (CA repeat, 148 bp)
- CC: DRD4 (VNTR, 7-repeat)
- FB: DRD4 (VNTR, 7-repeat)

Odds Ratio
ADHD is an Environmentally Complex Disorder
(Banerjee, Middleton & Faraone, Acta Pediatrica, in press)

- Pregnancy and Delivery Complications
- Exposure to Toxins
  - mercury, manganese, lead
  - polychlorinated bi-phenyls
- Fetal exposure to alcohol
- Fetal exposure to maternal smoking
- Chaotic family environments
- Low social class
Overview of IMAGE Study
(Kuntsi et al., Beh Brain Functions, 2006)

• Ascertain a Large Sample of Families Suitable for Quantitative Trait Mapping
  • Families identified from proband diagnosed with DSM-IV Attention Deficit Hyperactivity Disorder, Combined type
  • Proband assessed clinically
• Apply Quantitative Trait Linkage and Association Mapping to ADHD
  • Probands and all siblings assessed with quantitative trait measures of ADHD
• DNA collected from all family members and sent to Rutgers University Cell and DNA Repository
ADHD as a Quantitative Trait

- Quantitative measures of ADHD are highly heritable (Faraone et al., Bio Psych, 2005)
- Mathematical modeling of twin data suggest the diagnosis of ADHD is the extreme expression of a trait that varies quantitatively in the population (Gjone et al. 2006; Levy et al., 1997)
Inclusion Criteria for Probands

- European-Caucasian ethnicity
- Referred to ADHD specialty clinic
- Met criteria for DSM-IV combined type ADHD (lower prevalence ~3%)
  - 6 of 9 symptoms of inattention
  - 6 of 9 symptoms of hyperactivity-impulsivity
- Both parents and one or more sibling available for study
- No autism, epilepsy, IQ<70, brain disorder or genetic disorder known to mimic ADHD
Why Study ADHD in Europe

- Existing network of ADHD investigators
- Prevalence and features of ADHD similar around the world
- Heritability of ADHD similar around the world
- No evidence of heterogeneity of candidate gene effect sizes across America, Europe, Brazil & China
- Assessment instruments had been translated
Assessment Measures

- Probands diagnosis of ADHD by interview
  - Parental Account of Children's Symptoms
  - Designed for reliable cross-national studies
- Probands and Siblings measured for quantitative ADHD traits
  - Conners' Rating Scales-Revised
  - Strengths and Difficulties Questionnaire
  - Twin data: hierarchical factor model yields composite index with estimated heritability of 79%
- Parents not assessed
Subjects with DNA and Clinical Data

- **Total Sample**
  - 1,227 families with 6,130 members
  - Mean of 5 members per family

- **Families to be genotyped by GAIN program**
  - GAIN decided to limit sample to trio families in which the DNA source for all family members was a blood sample. Buccal samples were eliminated

- **Final sample:** 858 trio families

- **With 5,800 SNP linkage scan we may be able to reconstruct WGA genotypes in siblings** (Abecasis, HapMap3 Meeting, 2006)
Subtypes of ADHD
Co-morbidity by subtype for probands
<table>
<thead>
<tr>
<th>Main milestones for IMAGE sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidate gene scan in stage I sample: April 2006</td>
</tr>
<tr>
<td>N=776 combined type probands</td>
</tr>
<tr>
<td>Affected sibling pair + QTL linkage analysis: December 2006</td>
</tr>
<tr>
<td>N=1,200 families</td>
</tr>
<tr>
<td>Whole genome association through GAIN initiative</td>
</tr>
</tbody>
</table>
## Nominal and gene-wide significance levels

(Brookes et al, Molec Psychiat, 2006)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Nominal P-value</th>
<th>T</th>
<th>NT</th>
<th>OR</th>
<th>Global P-value</th>
<th>P_SUM Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPH2</td>
<td>0.003</td>
<td>207</td>
<td>151</td>
<td>1.37</td>
<td>0.036</td>
<td>0.106</td>
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<tr>
<td>ARRB2</td>
<td>0.004</td>
<td>103</td>
<td>66</td>
<td>1.56</td>
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<td>0.209</td>
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<tr>
<td>DAT1</td>
<td>0.005</td>
<td>349</td>
<td>278</td>
<td>1.26</td>
<td>0.119</td>
<td>0.014</td>
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<tr>
<td>PNMT</td>
<td>0.008</td>
<td>70</td>
<td>42</td>
<td>1.67</td>
<td>0.012</td>
<td>0.024</td>
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<tr>
<td>SLC9A9</td>
<td>0.01</td>
<td>74</td>
<td>46</td>
<td>1.61</td>
<td>0.485</td>
<td>0.114</td>
</tr>
<tr>
<td>NET</td>
<td>0.012</td>
<td>133</td>
<td>95</td>
<td>1.4</td>
<td>0.349</td>
<td>0.786</td>
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<tr>
<td>ADRB2</td>
<td>0.013</td>
<td>210</td>
<td>162</td>
<td>1.3</td>
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<td>0.485</td>
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<tr>
<td>HES1</td>
<td>0.016</td>
<td>300</td>
<td>244</td>
<td>1.23</td>
<td>0.076</td>
<td>0.096</td>
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<td>ADRA1A</td>
<td>0.017</td>
<td>283</td>
<td>229</td>
<td>1.24</td>
<td>0.443</td>
<td>0.387</td>
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<tr>
<td>PER2</td>
<td>0.017</td>
<td>31</td>
<td>15</td>
<td>2.07</td>
<td>0.124</td>
<td>0.419</td>
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<tr>
<td>MAOA</td>
<td>0.02</td>
<td>175</td>
<td>134</td>
<td>1.31</td>
<td>0.082</td>
<td>—</td>
</tr>
<tr>
<td>SNAP25</td>
<td>0.035</td>
<td>155</td>
<td>120</td>
<td>1.29</td>
<td>0.529</td>
<td>0.198</td>
</tr>
<tr>
<td>DDC</td>
<td>0.039</td>
<td>161</td>
<td>126</td>
<td>1.28</td>
<td>0.537</td>
<td>0.597</td>
</tr>
<tr>
<td>FADS2</td>
<td>0.039</td>
<td>284</td>
<td>237</td>
<td>1.2</td>
<td>0.389</td>
<td>0.727</td>
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<tr>
<td>SYP</td>
<td>0.045</td>
<td>180</td>
<td>114</td>
<td>1.25</td>
<td>0.034</td>
<td>—</td>
</tr>
<tr>
<td>CHRNA4</td>
<td>0.05</td>
<td>116</td>
<td>88</td>
<td>1.32</td>
<td>0.503</td>
<td>0.663</td>
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<tr>
<td>HTR1E</td>
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<td>53</td>
<td>1.42</td>
<td>0.509</td>
<td>0.214</td>
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<tr>
<td>DRD4</td>
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<td>34</td>
<td>20</td>
<td>1.7</td>
<td>0.199</td>
<td>0.321</td>
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</tbody>
</table>
### Replication dataset

#### Stage II (n = 383)

<table>
<thead>
<tr>
<th>Gene</th>
<th>rs ID</th>
<th>Type</th>
<th>P value</th>
<th>T</th>
<th>NT</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPH2</td>
<td>rs1843809</td>
<td>Intron 5</td>
<td>0.044</td>
<td>65</td>
<td>90</td>
<td>0.72</td>
</tr>
<tr>
<td>SLC9A9</td>
<td>rs9832471</td>
<td>5' to gene</td>
<td>0.03</td>
<td>29</td>
<td>15</td>
<td>1.93</td>
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<tr>
<td>SLC6A3</td>
<td>rs11564750</td>
<td>5' to gene</td>
<td>0.008</td>
<td>54</td>
<td>30</td>
<td>1.80</td>
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<tr>
<td>HTR1E</td>
<td>rs7751022</td>
<td>5'UTR/Intron</td>
<td>0.0004</td>
<td>36</td>
<td>12</td>
<td>3.00</td>
</tr>
</tbody>
</table>

#### Stage I + II (n = 1,159)

<table>
<thead>
<tr>
<th>Gene</th>
<th>rs ID</th>
<th>Type</th>
<th>P value</th>
<th>T</th>
<th>NT</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPH2</td>
<td>rs1843809</td>
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<td>0.2493</td>
<td>248</td>
<td>223</td>
<td>1.11</td>
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<tr>
<td>SLC9A9</td>
<td>rs9832471</td>
<td>5' to gene</td>
<td>0.001</td>
<td>103</td>
<td>61</td>
<td>1.69</td>
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<tr>
<td>SLC6A3</td>
<td>rs11564750</td>
<td>5' to gene</td>
<td>0.001</td>
<td>181</td>
<td>124</td>
<td>1.46</td>
</tr>
<tr>
<td>HTR1E</td>
<td>rs7751022</td>
<td>5'UTR/Intron</td>
<td>0.0005</td>
<td>111</td>
<td>65</td>
<td>1.71</td>
</tr>
</tbody>
</table>
The 10-3 haplotype is associated with ADHD in UK and Taiwanese populations

(Brookes et al., Arch Gen Psych, 2006)
Stage I + II IMAGE sample: Replication of 10-3 haplotype association

(Asherson et al., Molec Psych, in press)

Global $p = 0.02$, haplotype specific $p = 0.002$
Restrictions on Data Use

- DNA and clinical data have been sent to NIMH data repositories, which govern their release and use.
- Consent forms restrict use:
  - for studies of ADHD & associated features
  - for researchers approved by NIMH
- Consents allow same access for academic and industry users.
ADHD Samples Available Through the ADHD Molecular Genetics Network

- The ADHD MGN is an international group of researchers that has met yearly for 7 years thanks to an NIMH conference grant.
- Among 31 laboratories having DNA and ADHD phenotype data, there are (excluding IMAGE data):
  - 2,300 sibling pair families
  - 4,060 additional nuclear families
  - 3,913 additional ADHD cases
  - 12,209 non-ADHD controls
  - 1,221 ADHD cases with methylphenidate response data

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