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published in
American Journal of Medical Genetics Part B: Neuropsychiatric Genetics
2008

DOI (link to publisher)
10.1002/ajmg.b.30871

document version
Publisher’s PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)

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Brief Research Communication

Parent of Origin Effects in Attention/Deficit Hyperactivity Disorder (ADHD): Analysis of Data From the International Multicenter ADHD Genetics (IMAGE) Program

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There are conflicting reports suggesting that the parental origin of transmitted risk alleles may play a role in the etiology of attention deficit/hyperactivity disorder (ADHD). A recent report by Hawi and colleagues observed a generalized paternal over-transmission of alleles associated with ADHD. This was not replicated in more recent studies. Using data from a large multicenter study we examined the overall and genespecific parent of origin effect in 554 independent SNPs across 47 genes. Transmission disequilibrium and explicit parent of origin test were performed using PLINK. Overall parent of origin effect was tested by Chi-square. There was no overall parent of origin effect in the IMAGE sample ($\chi^2 = 1.82, P = 0.117$). Five markers in three genes, DDC, TPH2, and SLC6A2 showed nominal association ($P < 0.01$) with ADHD combined subtype when restricted to maternal or paternal transmission only. Following the initial report by Hawi and co-workers including this one, found no evidence to support an overall parent of origin effect for markers associated with ADHD. We cannot however, exclude gene-specific parent of origin effect in the etiology ADHD.

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KEY WORDS: ADHD; candidate gene; parent of origin effect


There is considerable evidence to suggest that expression of particular genes can be influenced by their parental origin. The parent of origin effect cannot be explained through inheritance of differences in DNA sequences alone, but requires additional mechanisms to be evoked. These mechanisms are broadly termed “epigenetic inheritance.” Epigenetic inheritance includes stable and heritable alterations of the genetic code, not including change at the DNA sequence. The epigenetic marking of genes altering their expression can be achieved through a number of mechanisms. To date epigenetic modification has been described at the chromatin- and nucleotide-level. The complex packaging of DNA into chromatin and chromosomes is maintained by the histone proteins.

Grant sponsor: NIH; Grant number: R01MH62873.

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Received 28 August 2007; Accepted 4 October 2007

DOI 10.1002/ajmg.b.30659

Published online 28 December 2007 in Wiley InterScience (www.interscience.wiley.com)
Consequently, the histone proteins are integral to the regulation of access to the DNA sequence and therefore the expression of genes maintained within these structures. Modifications of histone proteins can include acetylation, methylation, phosphorylation, and ubiquitination [Jaenisch and Bird, 2003]. However, the most notable epigenetic modification occurs at the nucleotide level through methylation of the nucleotide base cytosine. The methylation of cytosine residues at the gene promoter is thought to decrease the transcriptional activity of a gene [Robertson, 2005]. Imprints are removed during early germ cell development, re-established later in germ cell development or after fertilization, and maintained during embryonic development. “Imprinting” of the gene effectively tells the molecular machinery within the cell to express only one allele in the cell and its progeny. There is evidence to suggest that nearly 80 human genes show mono-allelic expression consistent with imprinting [Jirtle, 2002]. The mechanism underlying the reading of the imprint can involve many aspects of gene expression, and the silencing can be stable throughout the individual’s life [Federman, 2006].

A high proportion of the imprinted genes that have been identified are highly expressed in the central nervous system and serve general housekeeping functions including intracellular signaling, RNA processing and neurotransmitter signaling [Davies et al., 2005]. Interestingly, involvement of imprinting has been suggested for a number of common mental disorders, including autism, bipolar disorder, schizophrenia, and Tourette’s syndrome. The evidence for this has arisen from observed preferential inheritance of risk alleles from either the maternal or paternal line. Imprinting is only one mechanism contributing to these disorders. However, we must also consider the influence of other biological influences such as the in utero maternal environment [Weinberg, 1999].

There is evidence to suggest that the parental origin of genetic risk factors may play a role in the etiology of attention deficit/hyperactivity disorder (ADHD [MIM143465]). ADHD is typically characterized by inattention, excessive motor activity, impulsivity, and distractibility. Individuals with ADHD have significant impairment in family and peer relations. Moreover, they have difficulties in academic functioning and show high comorbidity with antisocial, mood, anxiety, and substance use disorders. ADHD is a common disorder with a prevalence of European children estimated at between 4.6% [Polanczyk et al., 2007]. Family, twin, and adoption studies strongly support the influence of genetic factors in the etiology of ADHD [Thapar et al., 1999; Asherson, 2004; Faraone et al., 2005]. However, the specific mode of inheritance is unknown.

There have been many association studies examining the role of individual candidate genes in ADHD. Meta-analysis of these data suggests that variation in the genes that code for the dopamine receptors D4 (DRD4) and D5 (DRD5), the 5-hydroxytryptamine (serotonin) transporter (SLC6A4), the serotonin 1B receptor (HTR1B), synaptic protein 25KD (SNAP25) and the dopamine transporter (SLC6A3 (DAT1)) influence susceptibility to ADHD [Faraone et al., 2005]. In examination of putative risk alleles, Hawi and colleagues observed a generalized parent of origin effect in an Irish ADHD study. Using data from genetic variants that showed at least a significant difference in the transmission from the maternal and the paternal line (see Table I). An overall parental origin effect was examined by comparing all maternal and paternal transmissions in the five associated markers. There was no overall parental origin effect in these data ($\chi^2 = 1.82, P = 0.117$). Five additional markers showed association with ADHD-CT when restricted to maternal or paternal transmission only (see Table I). Using the explicit parent of origin test on these SNPs only the dopamine decarboxylase (DDC) linked marker rs11575454 showed a weak parent of origin effect ($P = 0.039$).

Five markers showed an association with ADHD-CT at the unadjusted $P < 0.01$ level. Using the explicit parent of origin test, none show a significant difference in the transmission from the maternal and the paternal lineage (see Table I). An overall parent of origin effect was examined by comparing all maternal and paternal transmissions in the five associated markers. There was no overall parent of origin effect in these data ($\chi^2 = 1.82, P = 0.117$). Five additional markers showed association with ADHD-CT when restricted to maternal or paternal transmission only (see Table II). Using the explicit parent of origin test on these SNPs only the dopamine decarboxylase (DDC) linked marker rs11575454 showed a weak parent of origin effect ($P = 0.039$).
### TABLE I. Summary of Transmission Disequilibrium Test and Parent of Origin Analysis in Markers Showing Nominal Association in the IMAGE Sample at \( P < 0.01 \)

<table>
<thead>
<tr>
<th>CHR</th>
<th>Position</th>
<th>Gene</th>
<th>Marker</th>
<th>GT</th>
<th>Risk</th>
<th>All transmissions</th>
<th>Maternal transmissions only</th>
<th>Paternal transmissions only</th>
<th>Parent of origin effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>144849528</td>
<td>SLC9A9</td>
<td>rs1242075</td>
<td>G/A</td>
<td>G</td>
<td>287 228 6.8 1.3 0.009</td>
<td>150 116 4.35 1.3 0.037</td>
<td>137 113 2.3 1.2 0.129</td>
<td>-0.36 0.716</td>
</tr>
<tr>
<td>3</td>
<td>195339944</td>
<td>HES1</td>
<td>rs4686673</td>
<td>G/A</td>
<td>A</td>
<td>302 239 7.3 1.3 0.007</td>
<td>163 120 6.53 1.4 0.011</td>
<td>139 120 1.4 1.2 0.238</td>
<td>-0.92 0.358</td>
</tr>
<tr>
<td>12</td>
<td>70641446</td>
<td>TPH2</td>
<td>rs1386493</td>
<td>G/A</td>
<td>A</td>
<td>204 150 8.2 1.4 0.004</td>
<td>116 75 8.85 1.6 0.003</td>
<td>90 75.5 1.2 1.2 0.276</td>
<td>-1.25 0.213</td>
</tr>
<tr>
<td>17</td>
<td>4567246</td>
<td>ARBB2</td>
<td>rs7290927</td>
<td>G/A</td>
<td>G</td>
<td>191 67 6.9 1.5 0.009</td>
<td>53 36 3.25 1.5 0.072</td>
<td>48 31 3.7 1.5 0.056</td>
<td>0.16 0.873</td>
</tr>
<tr>
<td>17</td>
<td>35078615</td>
<td>PNMT</td>
<td>rs200173</td>
<td>G/A</td>
<td>A</td>
<td>27 11 6.7 2.5 0.009</td>
<td>16 6 4.55 2.7 0.033</td>
<td>11 5 2.3 2.2 0.134</td>
<td>-0.27 0.790</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All 921 695 32 1.3 1.4E-07</td>
<td>498 353 24.7 1.4 4.3E-06</td>
<td>425 345 8.3 1.2 1.6E-02</td>
<td>0.117*</td>
</tr>
</tbody>
</table>

*Test statistic derived from \( \chi^2 \) of total maternal and paternal transmissions.

### TABLE II. Summary of Transmission Disequilibrium Test and Parent of Origin Analysis in Markers Showing Nominal Association From Maternal-Only or Paternal-Only Transmissions in the IMAGE Sample at \( P < 0.01 \)

<table>
<thead>
<tr>
<th>CHR</th>
<th>Position</th>
<th>Gene</th>
<th>Marker</th>
<th>GT</th>
<th>Risk</th>
<th>All transmissions</th>
<th>Maternal transmissions only</th>
<th>Paternal transmissions only</th>
<th>Parent of origin effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>50322022</td>
<td>DDC</td>
<td>rs11575454</td>
<td>G/C</td>
<td>C</td>
<td>21 9 5 2.3 0.028</td>
<td>12 1 9 12 0.002</td>
<td>9 8 0.1 1.1 0.808</td>
<td>-2.1 0.039</td>
</tr>
<tr>
<td>7</td>
<td>50381415</td>
<td>DDC</td>
<td>rs1466163</td>
<td>G/A</td>
<td>A</td>
<td>160 129 3 1.2 0.068</td>
<td>69 70 0 1 0.932</td>
<td>92 60 6.8 1.5 0.009</td>
<td>1.9 0.062</td>
</tr>
<tr>
<td>12</td>
<td>70641446</td>
<td>TPH2</td>
<td>rs1386493</td>
<td>G/A</td>
<td>A</td>
<td>204 150 8 1.4 0.004</td>
<td>116 75 9 1.6 0.003</td>
<td>90 76 1.2 1.2 0.276</td>
<td>-1.2 0.213</td>
</tr>
<tr>
<td>17</td>
<td>79712221</td>
<td>TPH2</td>
<td>rs17110747</td>
<td>G/A</td>
<td>G</td>
<td>175 134 5 1.3 0.020</td>
<td>100 66 7 1.5 0.008</td>
<td>76 69 0.3 1.1 0.560</td>
<td>1.4 0.164</td>
</tr>
<tr>
<td>16</td>
<td>54252607</td>
<td>SLC6A2</td>
<td>rs3785143</td>
<td>G/A</td>
<td>A</td>
<td>130 95 5 1.4 0.020</td>
<td>56 51 0 1.1 0.629</td>
<td>75 44 8.1 1.7 0.004</td>
<td>1.6 0.105</td>
</tr>
</tbody>
</table>
To date a number of reports have described markers showing a parent of origin effect in ADHD. As mentioned above, three studies have examined overall parent of origin effects in ADHD [Hawi et al., 2005; Kim et al., 2007; Laurin et al., 2007a]. Additional gene-specific parent of origin effects has been observed for BDNF [Kent et al., 2005], DDC [Hawi et al., 2001], GNAL [Laurin et al., 2007b], HTR1B [Hawi et al., 2002], SLC6A4 [Hawi et al., 2005; Banerjee et al., 2006], SNAP25 [Mill et al., 2004], TPH2, DRD4, DRD5, and SLC6A3 [Hawi et al., 2005]. In a post-hoc analysis we tested whether markers examined in more than one study showed evidence of a parent of origin effect (see Table IV). Briefly, seven SNP markers across seven genes have been examined in the IMAGE and at least one other study. No evidence of a parent of origin effect was observed for any of the tested markers.

In conclusion, in this report we showed parent-specific associations with ADHD-CT \((P < 0.01)\) for five independent markers linked to three genes, namely DDC, TPH2, and SLC6A2 (see Table II). Assuming all of the 554 markers are independent and a type 1 error of 1% we would expect to observe 11 associations from both the paternal and maternal transmissions by chance alone. This would suggest that these observations may be due to chance alone.

However, previous data from analysis of DDC show that the association signals are stronger from the paternal chromosome in ADHD [Hawi et al., 2001] and bipolar affective disorder [Borglum et al., 2003]. DDC is located on chromosome 7p11, 27kb from GRB10 (encoding growth factor receptor-bound protein 10), that has been demonstrated to be imprinted in various human and mouse tissues. Imprinting of GRB10 is partial with tissue and isoform specificity [Blagitko et al., 2000]. Since imprinted genes are often found in clusters regulated by imprinting centers the DDC gene locus may also be imprinted. The direct examination of the imprinting status of the DDC gene shows evidence of asynchronous replication, a phenomenon suggestive of imprinting. However, SNP expression analysis shows biallelic expression of transcribed DDC SNPs in various human and mouse tissues, which is counter-indicative of imprinting [Hitchins et al., 2002]. The imprinting status of DDC is therefore not conclusive but does not exclude the possibility of partial or tissue and developmental phase specific imprinting for this gene. Tph1, the mouse homologue to human TPH1, shows some evidence of paternal imprinting in the mouse cerebellum using a custom murine chromosome 7 microarray [Buettner et al., 2004]. However, there is evidence to suggest that Tph1 is not expressed in the brain, and that the tryptophan hydroxylase in the brain is generated from Tph2 [Walther et al., 2003]. It would therefore be prudent to further examine the human TPH2 gene in cerebellum and other brain regions to examine potential imprints. Moreover, paternal imprinting of the TPH2 gene would support the association with ADHD stemming from transmission from the maternal chromosomes observed in this study.

Two markers showed an explicit parent of origin effect, namely markers linked to FADS2 and ADRBK2. However, it is important to consider that the significance of these findings is driven not only by an over-transmission of a putative risk allele from one parent but a combined under-transmission of the risk allele from the other parent. This would suggest conflicting selection at the maternal and paternal chromosome as opposed to a one-way selection bias as observed for DDC, TPH2, and SLC6A2 described above.

Data from the Irish ADHD study presented by Hawi et al. [2005] suggested that the risk alleles for ADHD are, in general,
preferentially transmitted via the paternal chromosome. In three follow-up studies, including data presented here, no evidence to support an overall parent of origin effect for markers associated with ADHD was found. We cannot, however, exclude gene-specific parent of origin effects in the etiology ADHD.

### ACKNOWLEDGMENTS

The IMAGE project is a multisite, international effort supported by NIH grant R01MH62873 to S.V. Faraone. Site Principal Investigators are Philip Asherson, Tobias Banaschewski, Jan Buitelaar, Richard P. Ebstein, Stephen V. Faraone, Michael Gill, Ana Miranda, Fernando Mulas, Robert D. Oades, Herbert Roevers, Aribert Rothenberger, Joseph Sergeant, Edmund Sonuga-Barke, and Hans-Christoph Steinhausen. Senior co-investigators are Margaret Thompson, Pak Sham, Peter McGuffin, Robert Plomin, Ian Craig and Eric Taylor. Chief Investigators at each site are Rafaela Marco, Nanda Rommelse, Wai Chen, Henrik Uebel, Hanna Christiansen, Ueli Mueller, Cathelijne Buschgens, Barbara Franke, Lamprini Psychogiou. We thank all the families who kindly participated in this research.

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