Genetics of Childhood Disorders: XX. ADHD, Part 4: Is ADHD Genetically Heterogeneous?

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Reviews of the literature leave no doubt that genes influence the etiology of attention-deficit/hyperactivity disorder (ADHD) (Faraone et al., 1998). Notably, twin studies show the heritability of ADHD to be about 0.80, indicating that the effect of genes is substantial. These genetic epidemiological studies have motivated molecular genetic studies of ADHD that have produced intriguing but conflicting results (Faraone and Biederman, 1998). Researchers have focused on genes in dopamine pathways because animal models, theoretical considerations, and the effectiveness of stimulant treatment implicate dopaminergic dysfunction in the pathophysiology of the disorder. Two genes that have been intensively studied are the dopamine transporter gene (DAT) and the dopamine D4 receptor gene (DRD4). Some studies of these genes strongly suggest that they influence susceptibility to ADHD. There are, however, several negative studies for each gene.

The inconsistent results from molecular genetic studies could mean that rather than being a unitary disorder, ADHD comprises several disorders having different genetic and nongenetic etiologies. If this were so, then the power to detect genetic effects would be small and we would expect to observe an inconsistent pattern of replication. What, then, is the evidence for genetic heterogeneity in ADHD? In the next column in this series, Todd will review the evidence for genetic heterogeneity based on the type of ADHD symptoms seen in twin pairs. This column focuses on evidence suggesting 2 other clinical features that may be useful for parsing the genetic heterogeneity of ADHD: psychiatric comorbidity and long-term outcome.

Epidemiological studies have documented high rates of psychiatric comorbidity among children with psychiatric disorders. These data confirm the adult epidemiological literature that suggests that comorbidity is the rule rather than the exception for psychiatric disorders. Researchers and clinicians have known for decades about ADHD’s comorbidity with conduct disorder (CD) and learning disabilities. More recently, researchers have documented its comorbidity with mood and anxiety disorders.

To examine the familial heterogeneity of ADHD, my colleagues and I have tested competing hypotheses about the association of ADHD with other psychiatric disorders. Our analyses from independent studies of DSM-III attention deficit disorder (ADD) and DSM-III-R ADHD suggested that ADHD with CD or bipolar disorder (BPD) may be a distinct familial subtype of ADHD (Faraone et al., 1998). Stratification of ADHD patients by the presence of CD and/or BPD appears to cleave the universe of ADHD children into familial homogeneous subtypes. Put simply, there seem to be 2 types of ADHD families: those in which CD and/or BPD occur comorbidly with ADHD and those in which ADHD occurs without these disorders.

We have also shown that ADHD and major depression share common familial vulnerabilities, but our data cannot separate distinct familial types of ADHD based on the presence of depression in the family. Instead, depression seems to be a nonspecific manifestation of the familial predisposition to ADHD. Whereas CD or BPD appears to be a marker for genetic heterogeneity in ADHD, with different subforms having different familial (and presumably genetic) causes, major depression appears to be a marker of phenotypic heterogeneity. In ADHD families, it is one of several manifestations of the genes that cause ADHD.

In contrast to our findings for CD, BPD, and depression, our data suggest that anxiety disorders and learning disabilities are not good candidates for resolving either genetic or phenotypic heterogeneity. These disorders are only weakly associated with ADHD in families, which suggests that they do not share genetic causes with ADHD. Notably, a meta-analysis of several studies supports the above conclusions about depression (Faraone and Biederman, 1997), but more work is needed to reach similar conclusions regarding anxiety disorders and learning disabilities.

Many groups have reported systematic differences between the families of ADHD children with and without CD. For example, compared with other ADHD children, fathers of ADHD+CD children have a high prevalence of substance abuse, depression, childhood CD, and adult antisocial personality disorder. Notably, Szatmari et al. (1993) confirmed the familial coaggregation of ADHD and CD in a population-based epidemiological family study, as did Silberg et al. (1996) in a population-based twin study. The latter investigators concluded that their results were consistent with the existence of a biologically based group of children who manifest both ADHD and conduct disturbances.

These studies of ADHD+CD are compelling, but they did not address whether BPD is also associated with the ADHD+CD phenotype. Our meta-analysis documented a
ADHD is highly familial and thus may be more strongly influ-
enced by genes compared with remitting ADHD. To summarize, prior work suggests 2 clinical features that
might be useful for parsing the genetic heterogeneity of
ADHD: comorbidity with CD or BPD and persistence of
ADHD into adolescence. These inferences about genetic hetero-
genosity are limited by the fact that much of the data are from
family studies, which cannot disentangle genetic from environ-
mental sources of familial transmission (Faraone et al., 1999).
We need twin studies of genetic heterogeneity to show whether
genes mediate differences among these putative subtypes.

This column’s discussion of genetic heterogeneity adopts a
categorical as opposed to a dimensional view of the nature of
ADHD. A categorical view sees ADHD as a distinct condi-
tion. In contrast, a dimensional view sees ADHD as a con-
tinuous trait. Some people have no or few ADHD symptoms,
while others have moderate or severe ADHD symptoms. In a
dimensional framework, the clinical category of ADHD is
seen as resulting from the imposition of an arbitrary threshold
on the continuous dimension of ADHD symptoms. Despite
the importance of categories for clinical work, we must rec-
ognize that a dimensional view might also explain the appar-
ten genetic heterogeneity of the disorder. Population-based
twin studies suggest that the clinical syndrome of ADHD is
influenced by the same set of genes that influences the expres-
sion of subclinical forms of the disorder (Levy et al., 1997).
They support the idea that there is a set of genes that influence
ADHD symptoms. People with many of these genes develop
ADHD, people with few are asymptomatic, and those in
between show some ADHD symptoms but do not meet diag-
nostic criteria for the disorder. Could it be possible that
ADHD with CD or BPD is simply a genetically severe form
of ADHD? Could the same be said of persistent ADHD?

Ultimately, these questions must await large-scale molecular
 genetic studies for their answers. Meanwhile, the identifica-
tion of highly familial subtypes of ADHD could prove useful for
researchers seeking to optimize the statistical power of genetic
association and linkage studies. Statistical power increases with
the magnitude of risk ratios computed by dividing the prev-
ance of a disorder among biological relatives by the prev-
ance in the population. Table 1 shows the risk ratios of
ADHD in relatives when different subtypes of ADHD are
 used to select families (see Faraone et al., 2000, for details).

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Parents</th>
<th>Siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>5.4</td>
<td>4.0</td>
</tr>
<tr>
<td>ADHD and CD or BPD</td>
<td>8.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Persistent ADHD</td>
<td>19.7</td>
<td>17.2</td>
</tr>
<tr>
<td>Persistent ADHD and CD or BPD</td>
<td>25.3</td>
<td>26.2</td>
</tr>
</tbody>
</table>

Note: ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; BPD = bipolar disorder.
Because these risk ratios increase dramatically with narrower definitions of ADHD, these narrower definitions may prove useful for selecting cases for molecular genetic studies.

WEB SITES OF INTEREST
http://members.aol.com/BevKPrice/HTML/title.html
http://www.add.org/

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