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

STEPHEN V. FARAONE, PH.D.

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 familially homogeneous subgroups. 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

link between ADHD and BPD by showing an increased prevalence of ADHD among children of BPD parents and an increased prevalence of BPD among relatives of ADHD children. Moreover, our family data show that ADHD, CD, and BPD tend to be transmitted together in families (Faraone et al., 1998). Although no other groups have examined the familial association between ADHD, BPD, and CD, there are reports indicating high levels of comorbidity in youth between ADHD and BPD and between CD and BPD.

Studies of long-term outcome provide another window on clinically meaningful variability in ADHD that may have implications for genetic heterogeneity. Several medium- and long-term follow-up studies have examined the natural history of ADHD. Despite methodological variability in sample characteristics, diagnostic criteria, age of subjects, assessment instruments, and the frequency and timing of follow-up reassessments, these studies have consistently documented that only a subgroup of children with ADHD have a disorder that persists into adolescence and young adulthood (Barkley, 1998). Could there be biological and, perhaps, genetic differences between persistent and remitting forms of ADHD?

Several studies suggest that genes influence persistent ADHD more than they influence remitting ADHD (Faraone et al., 2000). A prospective 4-year follow-up study found that by mid-adolescence, 85% of boys with ADHD continued to have ADHD while 15% had remitted. The prevalence of ADHD among parents was 16.3% for the persistent ADHD probands and 10.8% for the remitted ADHD probands. For sibs, the respective prevalence rates were 24.4% and 4.6%. These data suggest that children with persistent ADHD have a more familial form of ADHD than those whose ADHD remits by adolescence.

Two retrospective studies provided additional evidence for the increased familiality of persistent ADHD. One showed that children of parents with childhood-onset ADHD were at high risk for meeting diagnostic criteria for ADHD: 84% of the adults with ADHD who had children had at least 1 child with ADHD and 52% had 2 or more children with ADHD. The 57% rate of ADHD among children of adults with ADHD was much higher than the more modest 15% risk for ADHD in siblings of children with ADHD. These findings were consistent with a prior *DSM-III*–based study which found that 41% of siblings of adult ADD probands had ADHD compared with none of the non-ADD comparison siblings.

Another retrospective study compared children with ADHD and ADHD adolescents who retrospectively reported childhood onset. It found that the relatives of adolescent probands had higher rates of ADHD compared with the relatives of child probands. Thus, a prospective study of children and retrospective studies of adolescents and adults all suggest that persistent ADHD is highly familial and thus may be more strongly influenced 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* heterogeneity are limited by the fact that much of the data are from family studies, which cannot disentangle genetic from environmental 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 condition. In contrast, a dimensional view sees ADHD as a continuous 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 recognize that a dimensional view might also explain the apparent 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 expression 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 diagnostic 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 identification 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 prevalence of a disorder among biological relatives by the prevalence 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 1
Relative Risk Ratios for ADHD Phenotypes

Phenotype	Parents	Siblings
ADHD	5.4	4.0
ADHD and CD or BPD	8.9	5.0
Persistent ADHD	19.7	17.2
Persistent ADHD and CD or BPD	25.3	26.2

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

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Dr. Faraone is Associate Professor of Psychology in the Department of Psychiatry, Harvard Medical School at the Massachusetts Mental Health Center, Boston.

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Correspondence to Dr. Lombroso, Child Study Center, Yale University School of Medicine, 230 South Frontage Road, New Haven, CT 06520; e-mail: Paul.Lombroso@Yale.edu.

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