Genetic Influences on Attention Deficit Hyperactivity Disorder

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In this article we review behavioral and molecular genetics studies of attention deficit hyperactivity disorder (ADHD). Family, twin, and adoption studies, along with segregation analyses and molecular genetic studies, all support the hypothesis that both genetic and environmental factors contribute to the etiology of ADHD. Despite this strong evidence for the familial transmission of ADHD, the mode of transmission requires further clarification. In addition, because ADHD appears to be genetically heterogeneous, more work is needed to delineate genetically homogeneous subtypes and describe the range of expression of their underlying genotypes.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a condition that onsets in early childhood and is characterized by inattention, and hyperactivity and impulsivity [1]. The disorder is frequently associated with academic underachievement, conduct problems, and substance abuse [2,3••]. Given that it affects 2% to 10% of the population [4], its impact on society in terms of financial cost, stress to families, and disruption in schools is enormous [5].

Since the mid 1960s [6], researchers have examined whether genes play a role in the etiology of ADHD. Despite the fact that the nosology of this disorder has evolved significantly over the past 50 years, studies have consistently shown that ADHD is a familial disorder and that its transmission in families is mediated, at least in part, by genes.

Family Studies

Several studies have examined rates of ADHD among the parents of affected children [7]. With only two exceptions [8,9], early studies of hyperactivity [10,11] and subsequent studies of DSM-III (Diagnostic and Statistical Manual of Mental Disorders, edn 3) attention deficit disorder (ADD), and DSM-III-R ADHD [12–15], support the familial transmission of ADHD and provide evidence for the validity of the diagnosis in adults. Furthermore, in large studies of boys [16] and girls [17] with and without ADHD and their first-degree relatives, relatives of affected probands were at higher risk for ADHD after statistically controlling for gender and generation of relative, intactness of family, and social class. In addition, ADHD probands and their relatives had higher rates of conduct, mood and anxiety disorders than respective controls.

Family studies also provide evidence for the genetic heterogeneity of ADHD. Analyses of independent samples of children with DSM-III ADD [14] and DSM-III-R ADHD [16] suggest that 1) ADHD and major depression share common familial vulnerabilities [18]; 2) ADHD children with conduct [19] and bipolar [20,21] disorders might represent a distinct familial subtype of ADHD; and 3) ADHD is familially independent from anxiety disorders [22] and learning disabilities [23]. Thus, stratification by conduct and bipolar disorders may cleave the universe of ADHD children into more familially homogeneous subgroups.

Although the familial tramsmission of ADHD is consistent with genetic influence, it can also occur as a result of environmental factors that are transmitted from parent to child [24••]. Thus, twin and adoption studies must be used to disentangle genetic from shared environmental influences.

Twin Studies

Twin studies assume that monozygotic [MZ] and dizygotic [DZ] twins reared together share equal amounts of environmental influences but differ in their genetic similarity [24], with MZ twins sharing all of their segregating genes and DZ twins sharing approximately 50%. By this logic, greater similarity of MZ versus DZ twin pairs with regard to a disorder implicates genetic etiology [7,24]. Several twin studies have found genetic influence on hyperactive and inattentive symptoms and minimal impact of the shared environment [25–32]. Depending on the rates and measures employed, the heritability of hyperactivity ranges from 64% to 91% and the heritability of inattention from 39% to 98%. Rhee *et al.* [32] also found that specific genetic and environmental influences were highly similar for boys and girls.

Two of the above studies also examined the genetic contribution to the comorbidity of ADHD and other disorders. Gilger *et al.* [28] found that ADHD and reading disability were genetically independent; however, the existence of a genetically mediated subtype of both disorders could not be ruled out. Evidence from Nadder *et al.* [31] also supports the hypothesis that ADHD and comorbid conduct and oppositional defiant disorder symptoms share genetic risk factors.

Adoption Studies

Adoption studies also implicate genes in the etiology of ADHD. Whereas parents can confer a disease risk to their biologic children via both biologic and environmental pathways, parents of adopted children only confer risk via an environmental pathway [24]. Two early studies found that the adoptive relatives of ADHD children were less likely to have ADHD or associated disorders than the biologic relatives of ADHD children [33,34]. Biologic relatives of children with ADHD also performed more poorly on standardized measures of attention than did adoptive relatives of children with ADHD. [35]. However, conclusions based on these studies are tentative because they did not study the adoptive and biologic relatives of the same children [24].

Segregation Analysis Studies

Segregation analyses provide evidence for genetic transmission by demonstrating that the pattern of illness in families follows the rules of known genetic mechanisms. In an early segregation analysis, Morrison and Stewart [36] concluded that polygenic inheritance was a likely mode of transmission for ADHD. More recent analyses, however, have been consistent with the effect of a single major gene [15,37–41]. Although the results of segregation analyses are compelling, findings are limited by the fact that psychiatric diagnoses are inexact approximations of genetically homogenous phenotypes. Thus, recent technology that allows researchers to examine actual genes provides a more powerful technology for understanding the nature of genetic influence on ADHD.

Molecular Genetics

Although still in their infancy, molecular genetic studies have already implicated several genes as mediating the susceptibility to ADHD [42•]. Researchers have examined candidate genes in dopamine pathways because animal models, theoretic considerations, and the effectiveness of stimulant treatment point to dopaminergic dysfunction in the pathophysiology of this disorder [43•].

A growing number of studies have focused on the dopamine D4 receptor gene (*DRD4*). Several groups have reported an association between ADHD and the 7-repeat allele of *DRD4* [44–49]. Four other groups, however, could not replicate this association [50–53]. It is possible that these negative findings relate to aspects of sampling. For example, Castellanos *et al.* [51] studied individuals with severe ADHD who were in a 3-month day program that was part of a drug-treatment study. Also, Eisenberg *et al.* [53] used a relatively small sample that contained both Ashkenazi and non-Ashkenazi Jews. Nonetheless, it is noteworthy that the agreement across the six positive studies emerged despite the use of different diagnostic systems (DSM-III-R and DSM-IV) and measures of ADHD (rating scales and structured interviews).

Molecular genetics studies of ADHD have also targeted other dopamine-related genes. One population-based association study implicated the A1 allele of the dopamine D2 receptor gene [54] in ADHD. Cook's [55] report of an association between ADHD and the 480-bp allele of the dopamine transporter gene *(DAT*) was replicated in three family-based studies of ADHD [52,56,57] but failed to replicate in two others [50,58]. Finally, Eisenberg *et al.* [59] found an association between the catechol-O-methyltransferase (COMT) polymorphism and ADHD; however, another group found no evidence for linkage between this gene and the disorder.

Conclusions

In sum, results of family, twin, and adoption studies converge with evidence from molecular genetic studies to indicate that genes influence susceptibility to ADHD. In light of the variety of phenotypes studied, including dimensional and categorical measures of inattentive, impulsive/hyperactive and mixed symptoms, the consistency of findings across studies is striking. Notably, two genes (*DRD4* and *DAT*) have already been implicated in the etiology of the disorder; however, their effects are small, suggesting that ADHD is influenced by the combined actions of several genes. Moreover, we know from twin studies that since there are many cases of identical twin pairs in which one has ADHD and the other does not, the environment must also play a role in the etiology of the disorder. Thus, the path between genes and ADHD is likely to be complex and indirect. Rapidly occurring advances in molecular genetics research should set the stage for breakthroughs in our understanding of specific genetic influences on ADHD in the next decade [60••] and, eventually, of the mechanisms by which genes combine and interact with aspects of the social and cultural environment to engender ADHD.

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