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Genetic Influences in Childhood-Onset Psychiatric Disorders: Autism and Attention-Deficit/Hyperactivity Disorder

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Unlike such psychiatric disorders as depression, schizophrenia, and bipolar illness, which generally have their onset in adulthood, there are a few psychiatric disorders in which onset in childhood is part of the diagnostic criteria. Two of these childhood-onset conditions, autistic disorder (AD) and attention-deficit/hyperactivity disorder (ADHD), illustrate both the behavioral heterogeneity that makes diagnosis a challenge and the potential of genetic analysis in the study of normal and abnormal behaviors. AD, while rare, is probably the best-validated psychiatric disorder in childhood (Rutter and Schopler 1988), whereas ADHD is the most common such disorder. These two conditions illustrate the diversity of behavioral phenotypes yet also exemplify some common aspects of the childhood-onset conditions.

AD, previously called “infantile autism,” “childhood autism,” and “Kanner autism,” is a pervasive developmental disorder with onset by 3 years of age. AD is defined as a triad of social relating and communication impairments, with restricted, repetitive, or stereotyped behaviors (American Psychiatric Association 1994). AD is rare, affecting ~5/10,000 individuals, with a male:female ratio of 4:1 (reviewed in Smalley et al. 1988). Neurological involvement is indicated by the high frequency of mental retardation (~75% of cases), seizures (15%–30% of cases), and electroencephalographic abnormalities (20%–50% of cases) (Rossi et al. 1995; Bailey et al. 1996).

The etiology of AD is unknown. There is no consistent biochemical marker for AD, although ~25% of subjects show hyperserotonemia (Cook and Leventhal 1996). No pharmacological intervention is available that ameliorates all aspects of this condition. Positive findings in drug studies generally show a reduction in behavioral

symptoms such as aggression, anxiety, and obsessive-compulsive behaviors but little or no improvement in social relating or communication (Campbell et al. 1996). Recent studies of drugs targeting serotonin activity have shown both impressive success in the behavioral symptoms described above and a moderate improvement in social relating and communication (Gordon et al. (1993; McDougle et al. 1996). Further study using controlled trials to clarify the efficacy of this class of drugs in the treatment of AD is needed.

A genetic basis for AD was suggested in the original paper, by Leo Kanner in 1943, describing this condition. Kanner (1943, p. 250) defined autism as “an innate inability to form the usual, biologically provided affective contact with people.” Despite this early suggestion that genetic factors underlie autism, a lengthy period of time followed during which autism was thought to arise from environmental causes (reviewed in DeMyer et al. 1981). Over the past several decades, investigations using traditional methods of behavioral genetic analysis (see Sherman et al. 1997 [in this issue]) have supported a significant role for genetic influences in autism.

The sibling recurrence risk of AD is 3%–5%, suggesting a sibling lambda (λ) of 60–100. Twin studies suggest that genes underlie this familiarity, since the range for the MZ concordance rate is 69%–98%, and the DZ concordance rate is similar to the sibling recurrence risk (Bailey et al. 1996). Family and twin studies do not support the possibility that a single major gene underlies AD (Jorde et al. 1991). Recurrence risks are substantially lower than expected under single-gene inheritance, and patterns of relative risk across relative classes suggest multiplicative gene action with perhaps as few as three or four underlying genes (Pickles et al. 1995).

Family and twin data show that a variety of behavioral and psychiatric symptoms occur with greater frequency among relatives of autistic probands than among relatives of controls. However, the boundaries of the AD phenotype remain poorly defined. A “broader phenotype” has been proposed, to include milder deficits in social functioning (e.g., poor friendships), stereotyped behaviors, speech and language deficits, as well as anxiety and mood disorders (Folstein and Rutter 1977;

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DeLong and Dwyer 1988; Piven et al. 1990, 1991; Bolton et al. 1994; Smalley et al. 1995).

If relatively common susceptibility genes interact in the pathogenesis of autism, then their expression, when not in concert with other susceptibility genes, is likely to manifest in milder or alternative ways. Evidence in support of this hypothesis comes from recent candidate-gene studies in AD. Cook et al. (in press) have found a significant association between a haplotype at the serotonin receptor locus (*5HTT*) and AD, using family-based controls. Previously, an association between an allele at *5HTT* and anxiety in the general population had been reported (Lesch et al. 1996). These data suggest that an allelic variant at *5HTT* may contribute to the underlying genetic susceptibility to autism and may be expressed among nonautistic relatives as an anxiety disorder. Replication of this finding is needed, with careful evaluation of the genotype status of the relatives considered to be affected with the broader phenotype.

Linkage investigations in AD, using nonparametric approaches, are underway in many groups. Hallmeyer et al. (1996) excluded a significant proportion of the X chromosome as a candidate for containing a gene of major effect in autism. At present, collaborative genome scans in affected sibling pairs are underway, with sample sizes starting to reach numbers needed to detect susceptibility genes with small effect. Reports of candidate-gene investigations are numerous, but most of these use population-based case controls, which may lead to spurious associations as a result of stratified sampling. As described by Sherman et al. (1997), methodological improvements, such as the use of family-based case controls in candidate-gene studies, have permitted localization of disease genes for complex traits. At present, three candidate genes, *HRAS* (Herault et al. 1993, 1994; Comings et al. 1996), *5HTT* (Cook et al., in press), and an extended HLA haplotype (Daniels et al. 1995; Warren et al. 1996), are suggested as playing a role in AD, on the basis of either multiple population-based studies or a family-based case-control study. Replication studies are needed to validate the putative associations reported to date.

AD is a heterogeneous disorder both clinically and in terms of etiology. Approximately 15%–37% of cases of AD have a comorbid medical condition, including 5%–14% with a known genetic condition or chromosomal anomaly (Rutter et al. 1994; Gillberg and Coleman 1996). Significant associations at a phenotypic level may reflect (a) disruptions in a common neurobiological pathway, (b) common susceptibility genes, or (c) genes in linkage disequilibrium. The four most common associations include fragile X, tuberous sclerosis, 15q duplications, and untreated phenylketonuria (reviewed in Smalley et al., in press). A major susceptibility gene has been excluded in the fragile X region, but other chromo-

somal locations are under investigation. A careful delineation of the gene-brain-behavior pathways for these rarer genetic conditions may aid in our understanding of the pathogenesis of AD in general. For example, among individuals with tuberous sclerosis and AD, the prevalence of temporal lobe tubers is higher than that found in tuberous sclerosis individuals without AD (Smalley 1995; Bolton and Griffiths 1997), suggesting the importance of temporal lobe abnormalities in the development of AD. Recent studies of 15q duplications and AD suggest that maternal imprinting of a gene(s) in this region may contribute to the development of AD (Flejter et al. 1996; Cook et al. 1997). Cook et al. (1997) have reported that a short, maternally inherited duplication of chromosome 15 markers, D15S128-D15S217, resulted in the AD phenotype in two siblings.

Although environmental risk factors are considered negligible in AD, primarily on the basis of the high MZ concordance rate, MZ concordance is less than unity, suggesting a minor role for specific environmental factors. Immunological abnormalities (Warren et al. 1986, 1990), as well as early prenatal insults in development (for review, see Nelson 1991), are evident in some cases of AD. Abnormal T-cell functions, an HLA association, and high rates of minor physical anomalies have led to the hypothesis that AD may in some cases result from an autoimmune response perhaps in response to early exposure to pathogens (Warren et al. 1990).

In contrast to AD, ADHD is the most common childhood-onset behavioral disorder, affecting ~5%–10% of children and adolescents (Wolraich et al. 1996). In this condition, persistent inattention and/or hyperactive-impulsive behavior results in impaired social and/or academic functioning. Behavioral symptoms of ADHD include an inability to sit still, difficulty organizing tasks or activities, distractibility, forgetfulness, fidgeting, blurting out answers, not listening, and risk-taking behavior. Males are more often affected than females, with a population-based sex ratio of 4:1. Ratios among clinic referrals are often much higher. Operational criteria for ADHD have changed with the most recent diagnostic classification system, DSM-IV (American Psychiatric Association 1994). Under DSM-IV, an individual may be diagnosed with ADHD and have few to no signs of hyperactive/impulsive behavior (i.e., inattentive type), only signs of hyperactivity (i.e., impulsive type), or both (i.e., combined type).

ADHD, although a categorical diagnosis, correlates highly with extreme scores on dimensional scales measuring individual variations in attention and impulsivity. Dimensional questionnaires that are used in the diagnosis of ADHD include the Child Behavior Checklist (Achenbach 1993), Conners's (1994) scale, and the SNAP-IV scale (Swanson 1995).

ADHD has its onset in childhood. The condition may

or may not continue into adulthood, unlike AD, which persists throughout the life span. On the basis of a review of nine prospective studies, Hill and Schoener (1996) found that ~10%–60% of ADHD children continue to meet criteria for ADHD as adults. An exponential decline in ADHD diagnosis was observed from adolescence into adulthood. The exact prevalence of ADHD in adults remains unknown, since childhood diagnostic criteria may be inappropriate or inadequate for diagnosis of ADHD in adults.

ADHD is a familial disorder. The frequency of ADHD is approximately five- to sixfold greater among first-degree relatives than in the general population (Beiderman et al. 1992). Estimates of relative risk ratios for more distant relatives have been based on family-history methods of data collection, which are known to have lower sensitivity than direct-interview methods. Hence, a lower-bound estimate of the risk of ADHD among second-degree relatives is probably the 1.7% found among 1,201 second-degree relatives assessed by use of a family-history method (Faraone et al. 1994). A segregation analysis of ADHD, using direct and indirect methods of assessment, suggested that a major autosomal gene may contribute to the genetic liability to ADHD (Faraone et al. 1992).

Twin studies of the clinical diagnosis of ADHD are few, but results are consistent with the hypothesis that genes account for the observed familiarity of ADHD. In three studies of unselected twin samples, using questionnaire assessments (e.g., maternal report) of attentional problems and hyperactive/impulsive behavior, the range of heritability estimates was 80%–88% (Stevenson 1992; Thapar et al. 1995; Gjone et al. 1996). Using direct interview assessments of ADHD, Gillis et al. (1992) found a probandwise concordance rate of 79% in 37 MZ twins and 32% in 37 same-sex DZ twins, in a sample identified through a reading-disabled proband.

Relative risk ratios for ADHD across various classes of relatives support substantial genetic involvement; however, patterns across MZ twins ($\lambda \cong 12-16$), DZ twins and other first-degree relatives ($\lambda \cong 5-8$), and second degree relatives ($\lambda \cong 2$) are more consistent with an additive, rather than a multiplicative, mechanism of gene action. Support for a strong role of genetic involvement in ADHD also is evident on the basis of animal models (Hunziker et al. 1996). A knockout mouse for the dopamine transporter gene (*DAT1*), showing compromised dopamine transport, exhibits extreme hyperactivity (Giros et al. 1996).

As with AD, the boundaries of the ADHD phenotype are unclear, in part because of the high rates of comorbidity of psychiatric and learning disabilities seen with ADHD (Cantwell 1996). Approximately two-thirds of elementary school-age children with ADHD referred for clinical evaluation have at least one comorbid psychi-

atric disorder, most commonly oppositional and conduct disorders, anxiety, and mood disorders (Cantwell 1996). In addition to high rates of psychiatric disorders, ~30% of children with ADHD have a comorbid learning disability, often a reading disability (Semrud-Clikeman et al. 1992). Because of the high comorbidity of these conditions with ADHD, the traditional behavioral genetic methods (Sherman et al. 1997) have been used to test genetic and environmental sources underlying the comorbidity.

Relatives of ADHD probands have increased rates not only of ADHD but also of conduct and oppositional disorders, antisocial personality disorder, substance abuse, depression, and anxiety, as well as learning disabilities (Biederman et al. 1992). Family studies of anxiety and mood disorders among relatives of ADHD probands suggest that independent familial factors underlie the cooccurrence of anxiety in ADHD (Biederman et al. 1991) but that mood disorders, particularly bipolar disorder, may reflect a specific subtype of ADHD (Wozniak et al. 1995). A family study of ADHD probands with and without learning disabilities lends support to the hypothesis that learning disabilities and ADHD are independently transmitted and that nonrandom mating may account, in part, for the comorbidity of these two conditions (Faraone et al. 1993). The underlying mechanism of the association between tic disorders, Gilles de Tourette syndrome (TS), and ADHD has been a topic of controversy (Comings 1987, 1989; Pauls et al. 1988) and remains unresolved. Comings (1995) has proposed that TS and ADHD, as well as other neuropsychiatric disorders, are manifestations of a common set of susceptibility genes. Other family studies have not supported the familial comorbidity of TS and ADHD, except perhaps in a subgroup of individuals (Pauls et al. 1986, 1993), and clarification of the relationship of these two conditions may require identification of underlying susceptibility genes. Careful study of patterns of comorbidity in families has helped clarify the extent to which ADHD and comorbid conditions are associated in families or whether they assort independently in families. However, such data do not necessarily exclude shared environment as a factor contributing to the comorbidity. Adoption studies provide useful information regarding shared versus nonshared environmental sources of variation. The few adoption studies in ADHD support a genetic basis in ADHD, as well as a role for family environmental stressors (reviewed in Hechtman 1994), but data are too few to clarify the specific role of each in the comorbidity of ADHD with other conditions.

Investigators studying the genetics of ADHD have begun to apply the new approaches in gene detection that have been described by Sherman et al. (1997). As yet, no linkage investigations of ADHD have been reported, although genome scans are under way by several groups,

including our own. Several studies have examined candidate-gene associations in ADHD. Candidate genes usually have been suggested by the response of ADHD children and adolescents to psychopharmacological intervention. Approximately 70% of children and adolescents with ADHD respond to stimulant medications that target dopamine transport, release, and reuptake (Spencer et al. 1996). Given the efficacy of these drugs, Cook et al. (1995) studied allelic variants at the dopamine transporter gene (*DAT1*) and ADHD in a sample of 57 probands diagnosed by use of DSM-III-R criteria for ADHD ($n = 49$) or undifferentiated ADD ($n = 8$), using family-based case controls. They found a significant association between a 480-bp repeat polymorphism and ADHD. Replication of this finding has not been presented formally, but an abstract describing a replication study supports this association (Waldman et al. 1996). Other candidate-gene studies of dopamine-related genes have yielded positive findings in population-based studies but have not been studied by investigators using family-based controls. An association of an allele at the dopamine D4 receptor gene, a gene involved in novelty-seeking and risk-taking behavior (Ebstein et al. 1996; Benjamin et al. 1996), and ADHD, a disorder in which risk-taking behavior is a common feature, has been reported by LaHoste et al. (1996) but has yet to be replicated in a family-based case-control study. Positive associations between ADHD and the dopamine D2 receptor also have been suggested by population-based studies (Comings et al. 1991). Again, no family-based control studies have been reported. In addition to dopamine-related genes, Warren et al. (1996) reported an association between ADHD and a null allele of the C4B complement locus in the MHC-gene region of chromosome 6, a locus also associated with reading disability (Cardon et al. 1994; Grigorenko et al. 1997). These findings suggest that a possible genetic mechanism (i.e., linkage disequilibrium or a common susceptibility gene) may underlie the observed phenotypic association between ADHD and reading disability. Other candidate-gene locations are suggested by the comorbidity of ADHD with rare genetic syndromes, including fragile X and generalized resistance to thyroid hormone, an autosomal dominant condition afflicting $<1/2,500$ ADHD individuals (Stein et al. 1995). However, the association between ADHD with these genetic disorders may be due to disruption in a common neurobiological pathway rather than to a genetic mechanism. As with AD, gene-brain-behavior pathways in rare associated conditions may shed some light on the pathophysiology of ADHD in general.

The identification of susceptibility genes in AD or ADHD likely will be accomplished through the efforts of many groups, using multifaceted approaches, including affected sibling pairs, candidate genes, and neurobiolog-

ical investigations. Subgrouping based on comorbid conditions or neurobiological subtypes (i.e., from neuroimaging, neurofunctional studies, neuropsychological test performance, or neuropharmacological response) may be needed in order to increase the power to detect underlying susceptibility genes. For AD, for which multiplex families are rare ($\sim 5\%$ of all families), collaborative studies are underway to identify the number of families that is sufficiently large to allow detection of susceptibility genes of small effect. Furthermore, findings from affected-sibling-pair studies may not be generalizable to sporadic cases. A comprehensive search will include all types of families, as well as collaboration among investigators from very different disciplines. Not only will the outcome of this research lead to earlier and clearer diagnoses and to better interventions, but the detection of susceptibility genes in AD and ADHD also may shed light on the genetic bases of communication, social behavior, attention, learning, mood, and anxiety.

AD and ADHD reflect the diverse types of psychiatric conditions faced by behavioral geneticists who study early-onset conditions. The early age at onset makes identification of affected status easier and allows the investigator to avoid some of the difficulties faced by researchers in studying late-onset disorders (e.g., death of the subject before completion of the risk period). However, high rates of comorbidity with either other neurodevelopmental disorders (e.g., mental retardation and learning disabilities) or psychiatric disorders (e.g., anxiety) makes delineation of the phenotype difficult. Furthermore, familial clustering of psychiatric and learning disorders suggests that phenotypes may be quite variable in their nature and severity. Clinical heterogeneity is evident and etiological heterogeneity is likely. Multigenic inheritance is indicated for AD and ADHD, although multiplicative gene action is likely in autism and additive gene action is likely in ADHD. There is a pronounced sex difference in the prevalence of both conditions, for which the mechanism remains unknown. Immunological abnormalities and minor physical anomalies are common in both AD and ADHD, suggesting that there may be a common role for prenatal environmental exposure or delays in development that disrupt the developing nervous system in these conditions. The task of future investigations will be to identify common susceptibility factors, unique susceptibility genes, their elaborate interactions in the developing brain, and the ultimate outcome as a behavioral disorder.

Acknowledgments

In the course of my writing this review, Dennis Cantwell, M.D. passed away. He was a world-renowned figure in the field of childhood psychiatry, particularly for his seminal work

in ADHD. He was a mentor and friend; this article is dedicated to his memory.

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