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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 inprovement 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 familiality, 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 chromosomal 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 (Biederman 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 familiality 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 psychiatric 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-IIIR 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 neurobiological 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 (~5% of all families), collaborative studies are underway to identify the number of families that is sufficiently large to allow detection of susceptibilty genes of small effect. Furthermore, findings from affected-sibling-pair studies may not be generalizeable 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 likley 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.

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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.

References

Achenbach TM (1993) Empirically based taxonomy: how to use syndromes and profile types derived from the CBCL from 4 to 18, TRF, and WSR. Department of Psychiatry, University of Vermont, Burlington

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th ed. American Psychiatric Association, Washington DC

Bailey A, Phillips W, Rutter M (1996) Towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. J Child Psychol Psychiatry 37:89–126

Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH (1996) Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. Nat Genet 12:81–84

Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, Sprich-Buckminster S, et al (1992) Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Arch Gen Psychiatry 49:728–738

Biederman J, Faraone SV, Keenan K, Steingard R, Tsuang MT (1991) Familial association between attention deficit disorder and anxiety disorders. Am J Psychiatry 148:251–255

Bolton PF, Griffiths PD (1997) Association of tuberous sclerosis of temporal lobes with autism and atypical autism. Lancet 349:392–395

Bolton P, MacDonald H, Pickles A, Rios P, Goode S, Crowson M, Bailey A, et al (1994) A case-control family history study of autism. J Child Psychol Psychiatry 35:877–900

Campbell M, Schopler E, Cueva JE, Hallin A (1996) Treatment of autistic disorder. J Am Acad Child Adolesc Psychiatry 35:134–143

Cantwell DP (1996) Attention deficit disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 35:978–987

Cardon LR, Smith SD, Fulker DW, Kimberling WJ, Pennington BF, DeFries JC (1994) Quantitative trait locus for reading disability on chromosome 6. Science 266:276–279

Comings DE (1987) A controlled study of Tourette syndrome. VII. Summary: a common genetic disorder causing disinhibition of the limbic system. Am J Hum Genet 41:839–866

——— (1989) Presidential address: the genetics of human behavior—lessons for two societies. Am J Hum Genet 44: 452–460

——— (1995) The role of genetic factors in conduct disorder based on studies of Tourette syndrome and attention-deficit hyperactivity disorder probands and their relatives. Dev Behav Pediatr 16:142–157

Comings DE, Comings BG, Muhleman D, Dietz G, Shahbahrami B, Tast D, Knell E, et al (1991) The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. JAMA 266:1793–1800

Comings DE, Wu SJ, Chiu C, Muhleman D, Sverd J (1996) Studies of the c-Harvey-Ras gene in psychiatric disorders. Psychiatry Res 63:25–32

Conners K (1994) Conners abbreviated symptom questionnaire. Multi Health Systems, North Tonawanda, NY

Cook EH, Courchesne R, Lord C, Cox NJ, Yan S, Lincoln A, Haas R, et al (1997*a*) Evidence of linkage between the serotonin transporter and autistic disorder. Mol Psychiatry 2:247–250

Cook EH, Leventhal BL (1996) The serotonin system in autism. Curr Opin Pediatr 8:348–354

Cook EH Jr, Lindgren V, Leventhal BL, Courchesne R, Lincoln A, Shulman C, Lord C, et al (1997*b*) Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. Am J Hum Genet 60:928–934

Cook EH Jr, Stein MA, Krasowski MD, Cox NJ, Olkon DM, Kieffer JE, Leventhal BL (1995) Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genet 56:993–998

Daniels WW, Warren RP, Odell JD, Maciulis A, Burger RA, Warren WL, Torres AR (1995) Increased frequency of the extended or ancestral haplotype B44-SC30-DR4 in autism. Neuropsychobiology 32:120–123

DeLong GR, Dwyer JT (1988) Psychiatric family history and neurological disease in autistic spectrum disorders. Dev Med Child Neurol 36:441–448

DeMyer MK, Hingtgen JN, Jackson RK (1981) Infantile autism reviewed: a decade of research. Schizophr Bull 7:388–451

Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett ER, et al (1996) Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of novelty seeking. Nat Genet 12:78–80

Faraone SV, Biederman J, Chen WJ, Krischer B, Keenan K, Moore C, Sprich S, et al (1992) Segregation analysis of attention deficit hyperactivity disorder: evidence for single gene transmission. Psychiatr Genet 2:257–275

Faraone SV, Biederman J, Lehman BK, Keenan K, Norman D, Seidman LJ, Kolodny R, et al (1993) Evidence for the independent familial transmission of attention deficit hyperactivity disorder and learning disabilities: results from a family genetic study. Am J Psychiatry 150:891–895

Faraone SV, Biederman J, Milberger S (1994) An exploratory study of ADHD among second-degree relatives of ADHD children. Biol Psychiatry 35:398–402

Flejter WL, Bennett-Baker PE, Ghaziuddin M, McDonald M, Sheldon S, Gorski JL (1996) Cytogenetic and molecular analysis of inv dup (15) chromosomes observed in two patients with autistic disorder and mental retardation. Am J Med Genet 61:182–187

Folstein S, Rutter M (1977) Infantile autism: a genetic study of 21 twin pairs. J Child Psychol Psychiatry 18:297–321

Gillberg C, Coleman M (1996) Autism and medical disorders: a review of the literature. Dev Med Child Neurol 38:191–202

Gillis JJ, Gilger JW, Pennington BF, DeFries JC (1992) Attention deficit disorder in reading-disabled twins: evidence for a genetic etiology. J Abnorm Child Psychol 20:303–315

Giros B, Jaber M, Jones SR, Wightman RM, Caron MG (1996) Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. Nature 379:606–612

Gjone H, Stevenon J, Sundet JM (1996) Genetic influence on

parent-reported attention-related problems in a Norwegian general population twin sample. J Am Acad Child Adolesc Psychiatry 35:588–596

Gordon CT, State RC, Nelson JE, Hamburger SD, Rapoport JL (1993) A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of austistic disorder. Arch Gen Psychiatry 50:441–447

Grigorenko EL, Wood FB, Meyer MS, Hart LA, Speed WC, Shuster A, Pauls DL (1997) Susceptibility loci for distinct components of developmental dyslexia on chromosomes 6 and 15. Am J Hum Genet 60:27–39

Hallmayer J, Hebert JM, Spiker D, Lotspeich L, McMahon WM, Petersen PB, Nicholas P, et al (1996) Autism and the X chromosome: multipoint sib-pair analysis. Arch Gen Psychiatry 53:985–989

Hechtman L (1994) Genetic and neurobiological aspects of attention deficit hyperactive disorder: a review. J Psychiatry Neurosci 19:193–201

Herault J, Martineau J, Petit E, Perrot A, Sauvage D, Barthelemy C, Mallet J, et al (1994) Genetic markers in autism: association study on short arm of chromosome 11. J Autism Dev Disord 24:233–236

Herault J, Perrot A, Barthelemy C, Buchler M, Cherpi C, Leboyer M, Sauvage D, et al (1993) Possible association of c-Harvey-Ras-1 (HRAS) marker with autism. Psychiatry Res 46:261–267

Hill JC, Schoener EP (1996) Age-dependent decline of attention deficit hyperactivity disorder. Am J Psychiatry 153: 1143–1146

Hunziker MHL, Saldana RL, Neuringer A (1996) Behavioral variability in SHR and WKY rats as a function of rearing environment and reinforcement contingency. J Exp Anal Behav 65:129–144

Jorde LB, Hasstedt SJ, Ritvo ER, Mason-Brothers A, Freeman BJ, Pingree C, McMahon WM, et al (1991) Complex segragation analysis of autism. Am J Hum Genet 49:932–938

Kanner L (1943) Autistic disturbances of affective contact. J Nerv Child 2:217–250

LaHoste GJ, Swanson JM, Wigal SB, Glabe C, Wigal T, King N, Kennedy JL (1996) Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol Psychiatry 1:121–124

Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, et al (1996) Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274:1527–1531

McDougle CJ, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH (1996) A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry 53:1001–1008

Nelson KB (1991) Prenatal and perinatal factors in the etiology of autism. Pediatrics 87:761–766

Pauls DL, Cohen DJ, Kidd KK, Leckman JF (1988) Tourette syndrome and neuropsychiatric disorders: is there a genetic relationship? Am J Hum Genet 43:206–209

Pauls DL, Hurst CR, Kruger SD, Leckman JF, Kidd K, Cohen DJ (1986) Gilles de al Tourette's syndrome and attention deficit disorder with hyperactivity: evidence against a genetic relationship. Arch Gen Psychiatry 43:1177–1179

Pauls DL, Leckman JF, Cohen DJ (1993) Familial relationships between gilles de la Tourette's syndrome, attention deficit disorder, learning disabilities, speech disorders, and stuttering. J Am Acad Child Adolesc Psychiatry 32:1044–1050

Pickles A, Bolton P, MacDonald H, Bailey A, Le Couteur A, Sim C-H, Rutter M (1995) Latent-class analysis of recurrence risks for complex phenotypes with selection and measurement error: a twin and family history study of autism. Am J Hum Genet 57:717–726

Piven J, Chase GA, Landa R, Wzorek M, Gayle J, Cloud D, Folstein S (1991) Psychiatric disorders in the parents of autistic individuals. J Am Acad Child Adolesc Psychiatry 30: 471–478

Piven J, Gayle J, Chase GA, Fink B, Landa R, Wzorek MM, Folstein SE (1990) A family history study of neuropsychiatric disorders in the adult siblings of autistic individuals. J Am Acad Child Adolesc Psychiatry 29:177–183

Rossi PG, Parmeggiani A, Bach V, Santucci M, Visconti P (1995) EEG features and epilepsy in patients with autism. Brain Dev 17:169–174

Rutter M, Bailey A, Bolton P, Le Couteur A (1994) Autism and known medical conditions: myth and substance. J Child Psychol Psychiatry 35:311–322

Rutter M, Schopler E (1988) Autism and pervasive developmental disorders. In: Rutter M, Tuma AH, Lann IS (eds) Assessment and diagnosis in child psychopathology. Guilford, New York, pp 408–434

Semrud-Clikeman M, Biederman J, Sprich-Buckminster S, Lehman BK, Faraone SV, Norman D (1992) Comorbidity between ADHD and learning disability: a review and report in a clinically referred sample. J Am Acad Child Adolesc Psychiatry 31:439–448

Sherman SL, DeFries JC, Gottesman II, Loehlin JC, Meyer JM, Pelias MZ, Rice J, et al (1997) Recent developments in human behavioral genetics: past accomplishments and future directions. Am J Hum Genet 60:1265–1275 (in this issue)

Smalley SL (1995) Autism and tuberous sclerosis. Psychiatr Genet 5 Suppl 1:S88

Smalley SL, Asarnow RF, Spence MA (1988) Autism and genetics: a decade of research. Arch Gen Psychiatry 45:953–961

Smalley SL, Levitt JL, Bauman M. Autism: diagnosis, etiology, and treatment. In: Coffey CE, Brumback RA (eds) Textbook of pediatric neuropsychiatry. American Psychiatric, Washington, DC (in press)

Smalley SL, McCracken J, Tanguay P (1995) Autism, affective disorders, and social phobia. Am J Med Genet 60:19–26

Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S (1996) Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. J Am Acad Child Adolesc Psychiatry 35:409–432

Stein MA, Weiss RE, Refetoff S (1995) Neurocognitive characteristics of individuals with resistance to thyroid hormone: comparisons with individuals with attention-deficit hyperactivity disorder. Dev Behav Pediatr 16:406–411

Stevenson J (1992) Evidence for a genetic etiology in hyperactivity in children. Behav Genet 22:337–344

Swanson JM (1995) SNAP-IV scale. University of California Child Development Center, Irvine

Thapar A, Hervas A, McGuffin P (1995) Childhood hyperac-

tivity scores are highly heritable and show sibling competition effects: twin study evidence. Behav Genet 25:537–544

Waldman ID, Rowe DC, Abramowitz A, Kozel S, Mohr J, Sherman SL, Cleveland HH, et al (1996) Association of the dopamine transporter gene (DAT1) and attention deficit hyperactivity disorder in children. Am J Hum Genet Suppl 59:A25

Warren RP, Nadine CM, Pace NC, Foster A (1986) Immune abnormalities in patients with autism. J Autism Dev Disord 16:189–197

Warren RP, Singh VK, Averett RE, Odell JD, Maciulis A, Burger RA, Daniels WW, et al (1996) Immunogenetic studies in autism and related disorders. Mol Chem Neuropathol 28:77–81

Warren RP, Yonk LJ, Burger RW, Odell D, Warren WL, White E, Singh VK (1990) Deficiency of suppressor-inducer (CD4+ CD45RA+) T cells in autism. Immunol Invest 19:245–251

Wolraich ML, Hannah JN, Pinnock TY, Baumgaertel A, Brown J (1996) Comparison of diagnostic criteria for attention-deficit hyperactivity disorder in a county-wide sample. J Am Acad Child Adolesc Psychiatry 35:319–324

Wozniak J, Biederman J, Mundy E, Mennin D, Faraone SV (1995) A pilot family study of childhood onset mania. J Am Acad Child Adolesc Psychiatry 34:1577–1583