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Scanning the Genome for Attention Deficit Hyperactivity Disorder

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1. INTRODUCTION

In the past decade, there have been exciting developments in the understanding of the genetic basis of susceptibility to attention deficit hyperactivity disorder (ADHD). This chapter reviews the genetic epidemiology (family, twin, and adoption studies) of ADHD and summarizes the neurobiological evidence (pharmacology, animal models, and neuroimaging studies) that points to particular candidate genes. Relevant findings from genetic studies of dopaminergic, serotonergic, and noradrenergic candidate genes are provided. New directions in the field are discussed briefly, such as the move to characterize endophenotypes, meta-analyses of association studies, and emerging genetic linkage studies.

2. GENETIC EPIDEMIOLOGY OF ADHD

Evidence reviewed in the preceeding chapter suggests that ADHD is a heterogeneous condition that has many causes, and is considered as a final common pathway for a variety of complex brain developmental processes *(1)*. The exact etiology of ADHD is unknown, but a substantial genetic element has been implicated from family, twin, and adoption studies.

2.1. Family Studies in ADHD

Family studies investigate the degree of familial clustering of a disorder. Thapar and Scourfield *(2)* summarize family, twin, and adoption studies in ADHD. Family studies have shown an increased risk of ADHD in the families of children with ADHD (whether defined using the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition (DSM-III) or DSM-III-R diagnostic criteria) with reported relative risks (λ) of between 4 and 5.4 for first-degree relatives *(3,4)*.

2.2. Twin Studies in ADHD

A drawback of family studies is that they cannot disentangle genetic from environmental sources of transmission. Twin and adoption studies assist in doing so. The occurrence of twinning creates a natural experiment in psychiatric genetics *(5)*. If a disorder is strongly influenced by genetic factors then the risk to co-twins of ill probands should be greatest when the twins are monozygotic. The risk to dizygotic twins should exceed the risk to controls but

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should not be greater than the risk to siblings. Twin data are used to estimate heritability (h^2), which measures the degree to which a disorder is influenced by genetic factors. Twin studies *(2)* have consistently shown the importance of genetic influences on ADHD, whether defined as a categorical diagnosis (i.e., as defined by DSM) or as a quantitative measure of symptomatology, with reported h^2 estimates of between 0.39 and 0.91.

2.3. Adoption Studies in ADHD

As with twinning, the occurrence of adoption provides another useful experiment for psychiatric genetics *(5)*. Whereas parents can confer a disease risk to their biological children via both biological and environmental pathways, they can confer risk to adoptive children only via an environmental pathway. Thus by examining both the adoptive and the biological relatives of ill probands, genetic and environmental sources of familial transmission can be disentangled. Thapar and Scourfield *(2)* provide an overview of adoption studies in ADHD. Although published adoption studies of ADHD are much less recent than the twin studies and have some methodological drawbacks, such as small sample size, nonsystematic ascertainment, or the failure to use standardized measures or diagnostic criteria, overall the findings have been consistent in showing the importance of genetic factors. Biological parents of hyperactive children appear to show higher rates of hyperactivity and ADHD *(4,6,7)*, and poorer performance on cognitive measures of attention *(8)* than adoptive relatives. Similarly in a study of separately fostered siblings, in accordance with expectations of a genetic etiology, hyperactive children showed greater concordance with their biological siblings than their half-siblings *(9)*.

2.4. Mode of Genetic Transmission of ADHD

The exact mode of transmission for genes underlying ADHD remains unknown. Segregation analyses *(6,10–12)* have proposed models of inheritance from major gene effects through oligogenic to polygenic and multifactorial models, but the differences in statistical "fit" between multifactorial genetic models and single-gene inheritance is modest. It appears more likely that several interacting genes of modest effect cause ADHD. This multifactorial concept is consistent with ADHD's high population prevalence (2–7%) and high concordance in monozygotic twins (68–81%), but modest recurrence risks to first-degree relatives.

3. NEUROBIOLOGICAL THEORIES OF ADHD

The overall pattern of neuropsychological, neuroimaging, and neurotransmitter-related findings in ADHD is consistent with the hypothesis that ADHD is associated with dysfunction in the frontosubcortical pathways mediated by catecholamine neurotransmission, which control attention and motor behavior. Dopaminergic, serotonergic, and noradrenergic systems have come under close scrutiny and each has contributed candidate genes for genetic analysis.

3.1. Dopaminergic Theories of ADHD

Evidence to support dopaminergic dysfunction in ADHD derives from the neuropharmacology of stimulant medication, the behavior and biochemistry of animal models, and neuroimaging studies.

3.1.1. Neuropharmacological Evidence

The mainstay of treatment for ADHD is methylphenidate and other psychostimulant medications (dextroamphetamine, pemoline), which are known to inhibit the dopamine transporter *(13)*, thus increasing the availability of dopamine in the synaptic cleft. Knowledge of the mechanism of action for methylphenidate and its possible inhibitory cortical effects via dopaminergic and/or noradrenergic pathways *(14)* strongly support a theory of dopaminergic dysfunction in ADHD.

3.1.2. Animal Studies

Animal models also support a dopaminergic hypothesis in ADHD. Mice without a functioning dopamine transporter (DAT1 knockout [KO] mice) have high extracellular striatal dopamine levels, a doubling of the rate of dopamine synthesis *(15)*, decreased dopamine and tyrosine hydroxylase in striatum *(16)*, and a nearly complete loss of functioning of dopamine autoreceptors *(17)*. They display markedly increased locomotor and stereotypic activity compared to normal (wild-type) mice *(15,18)*. The reduced striatal dopamine may be most relevant to a hypodopaminergic theory of ADHD. Also, selective destruction of dopamine neurons by 6-hydroxydopamine results in hyperactivity and learning difficulties in mice *(19)*. The spontaneously hypertensive rat (SHR) has also been used as an animal model of ADHD because of the SHR's locomotor hyperactivity and impaired discriminative performance. Russell *(20)* showed that the altered presynaptic regulation of dopamine in SHR led to the downregulation of the dopamine system. The authors hypothesized that this may have occurred early in development as a compensatory response to abnormally high dopamine concentrations. The coloboma mouse mutant exhibits a behavioral phenotype similar to that of ADHD. It is characterized by spontaneous motor hyperactivity, head-bobbing, and ocular dystrophy. The phenotype of this model has been shown to be the result of a deletion of the Synaptosomal-associated protein 25 (*SNAP-25*) gene (located in mouse chromosome 2) *(21)*. *SNAP-25* is a presynaptic plasma membrane protein that is expressed highly and specifically in the nerve cells. The gene encodes a protein essential for synaptic vesicle fusion and neurotransmitter release. Interestingly, it is possible to treat the hyperactivity of this mouse with D-amphetamine and it can be genetically "rescued" by a transgene-encoding *SNAP-25* inserted within the Cm deletion.

3.1.3. Neuroimaging Studies

Structural brain imaging studies *(22)* have shown abnormalities in the frontal lobe and subcortical structures (globus pallidus, caudate, corpus callosum), regions known to be rich in dopamine neurotransmission and important in the control of attention and response to organization *(23–25)*. The most consistent findings are hypoactivity of frontal cortex and subcortical structures, usually on the right side. Functional imaging has shown that dopamine transporter density is increased in ADHD patients compared with controls *(26–29)*, and that administration of methylphenidate reduces transporter density to near-normal levels in ADHD patients *(27,28)*. These findings lend further support to dopaminergic dysfunction in ADHD.

3.2. Serotonergic Theories of ADHD

As reviewed by Manor et al. *(30)* and Quist et al. *(31)*, evidence from human and animal studies suggests that serotonergic system genes should also be considered as likely candidates genes in ADHD. For example, whole blood, serum, and platelet serotonin concentrations

have been noted as decreased in children with ADHD *(32–34)*. Selective serotonin reuptake inhibitors are moderately efficacious in the treatment of ADHD *(35)*. Animal studies indicate that both frontal cortex dopamine and serotonin play important roles in the modulation of attention and response control *(36,37)*. Disruption of the dopamine transporter in mice (DAT-KO mice) results in a phenotype that resembles human ADHD, a marked hyperactivity apparently resulting from high extracellular dopamine levels in the absence of the dopamine transporter *(18)*. Treatment of these mice with both psychostimulants and serotonergic drugs produced a paradoxical calming effect that was independent of any changes of extracellular levels of dopamine in the striatum. These results suggested that a different mechanism must be involved in DAT-KO mice. The hypothesis was that serotonin neurotransmission mediated motor activity alterations in the mice, whereas extracellular dopamine concentrations remained unchanged *(15)*.

3.3. Noradrenergic Theories of ADHD

Recent work in human and animal studies also suggests the involvement of the adrenergic system in ADHD. In rodents, norepinephrine (NE) depletion results in increased distractibility and motor hyperactivity *(38)*, and in nonhuman primates, stimulation of the noradrenergic system has been shown to improve cognitive function and distractibility *(39)*. Noradrenergic projections are particularly dense in the frontal cortex and cingulate gyrus. These regions are involved in mood stabilization and sleep regulation, as well as attention and alertness *(40,41)*. Animals and humans with lesions in the prefrontal cortex show poor attention regulation and disorganized, impulsive, and hyperactive behaviors, similar to those observed in ADHD. Pharmacological studies have demonstrated the clinical usefulness of NE inhibitors (such as desipramine, nortriptyline, and atomoxetine) in the treatment of ADHD *(42,43)*. The mode of action of these antidepressants is to block the reuptake of dopamine and norepinephrine and consequently increase the release of the monoamines into the extraneuronal space. The improvement in ADHD symptoms with tricyclic antidepressants has been attributed to the actions of these drugs in the reuptake of NE *(44)*.

4. FINDINGS FROM GENETIC STUDIES IN ADHD

Having reviewed the evidence for involvement of catecholamine dysregulation in ADHD, molecular genetic studies of candidate genes from these systems are summarized. To date, most reported findings relate to dopaminergic system genes, but emerging evidence also implicates serotonergic and noradrenergic system genes.

4.1. Dopaminergic System Genes

Molecular genetic studies have produced strong evidence for dopaminergic involvement in ADHD. The gene encoding the dopamine transporter, *DAT1*, was the initial candidate gene studied. This gene is of particular interest as the transporter is the principal target for methylphenidate and other psychostimulant medication used to treat patients with ADHD *(45,46)*. The polymorphism of interest is a 40-bp sequence of a variable number tandem repeat (VNTR) located in the 3′ untranslated region of the *DAT1* gene, which maps to chromosome 5p15.3 *(47,48)*. Ten different alleles can be found, according to the presence of 3 to 13 copies of this 40-bp repeat, the most prevalent allele being the 10-repeat (or 480-bp) allele *(49)*. Cook et al. *(50)* first reported association between the 480-bp *DAT1* allele and ADHD. Since then, this finding has been replicated by some groups *(51–56)*, but not by others *(57–64)*.

The reported odds ratios for the *DAT1* 480-bp allele from the above studies range from 1.38 to 2.67 and suggest that *DAT1* is a gene of small effect in ADHD. Conflicting results may be owing to many factors, such as the lack of statistical power, in individual samples, to find genes of small effect, differences in the diagnostic definition of ADHD, hidden population stratification, genetic heterogeneity, and a variation between samples of linkage disequilibrium with a nearby "causal" variant. A meta-analysis by Maher et al. *(65)*, in which eleven studies were included, yielded a marginally nonsignificant pooled odds ratio estimate of 1.27 (95% CI 0.99–1.63, $p = 0.06$).

DRD4, the gene encoding the dopamine D4 receptor, has also attracted interest as a candidate gene. The dopamine D4 receptor mediates the postsynaptic action of dopamine. There have been several studies examining for association between the 7 repeat (148-bp) allele of the 40-bp VNTR in exon 3 of the *DRD4* gene and ADHD with positive results in many *(66–76)* but not all *(77–82)* studies. A recent meta-analysis of *DRD4* by Faraone et al. *(83)* supported an overall association with a small odds ratio between *DRD4* and ADHD. Case-control studies were more strongly significant (OR = 1.9, $p = 0.00000008$) than family-based studies (OR = 1.4, $p = 0.02$).

Other dopamine receptor genes have also been investigated as candidate genes in ADHD. There have been published reports of association between the 148-bp *DRD5* allele and ADHD *(52,53,75,84,85)*. Moreover, a recent joint and meta-analysis by Lowe et al. *(86)* confirms that *DRD5* is a susceptibility gene (of minor effect) for ADHD (OR = 1.25, $p = 0.00005$). Further analysis of the data suggested that *DRD5* contributes risk for the inattentive but not the hyperactive symptoms.

Other studies have focused on genes involved in regulation of dopamine synthesis and metabolism. Eisenberg et al. *(87)* reported association between a high-activity related catechol-*O*-methyltransferase (*COMT*) allele and ADHD. Other groups refuted this finding *(53,88–91)*. A number of groups *(52,53,92,93)* have reported association at the A2 allele of the TaqI polymorphism of the gene (*DBH*) encoding the enzyme dopamine β-hydroxylase.

Another candidate gene potentially related to dopamine transmission is the gene for the synaptic vesicle docking fusion protein, *SNAP-25*. As described previously, this gene has also been implicated in the etiology of ADHD based on the mouse mutant strain coloboma *(94)*. Recent studies by Barr et al. *(95)*, Brophy et al. *(96)*, and Kustanovich et al. *(97)* reported evidence for association with polymorphisms in the 3′ untranslated region of this gene. However, another study by Mill et al. *(98)* found association with variants at the opposite end of the *SNAP-25* gene (near the 5′-untranslated region).

4.2. Serotonergic System Genes

The efficiency of serotonergic signaling is controlled by the serotonin transporter 5-hydroxytryptamine transporter (*5-HTT*), which removes serotonin from the synaptic cleft. A polymorphism (44-bp insertion/deletion) located upstream of the transcriptional site of the transporter was found to influence the expression of the gene, consequently altering the levels of reuptake of dopamine. The homozygous insertion (*L/L*) yields a higher level of *5-HTT* expression than the heterozygous (L/S) or the homozygous deletion (*S/S*). An association between the *L/L 5-HTTLPR* (5-HTT promoter region) genotype and ADHD has been reported *(99–101)*. Zoroglu et al. *(102)* observed that the *5-HTTLPR S/S* genotype was significantly lower in ADHD patients than in the controls. Pharmacological studies using the 5-hydroxytryptamine 1B receptor (*5-HT1B*) agonist RU24969 suggest that the activation of the 5-HT1B receptor in mice leads to increased anxiety and locomotion in these animals. In addition,

5-HT1B knockout mice display an increased locomotor response to cocaine acquisition and alcohol intake, along with hyperactivity and aggressive behavior *(103)*. The hyperlocomotion effect of this agonist is absent in the mouse lacking 5-HT1B, indicating that the agonist effect is mediated by this receptor. Hawi et al. *(104)* and Quist et al. *(105)* reported association between a 5-HT1B polymorphism (861G-C) and ADHD. The serotonin HTR2A is a G protein-coupled receptor functioning in signal transduction. Antagonism of 5HT2A has been shown to reduce dopamine-induced hyperactivity in mice *(106,107)*. Hyperlocomotion induced by the noncompetitive *N*-methyl-D-aspartate antagonist (MK-801) in mice is attenuated by the nonselective 5-HT2A antagonist ritanserine and by the 5-HT2A selective antagonist MDL100907 *(107)*. Several recent studies have investigated 5-HT2A markers for possible association with ADHD, with association reported by Quist et al. *(106)* and Levitan et al. *(108)* but not by Hawi et al. *(104)* and Zoroglu et al. *(109)*.

4.3. Noradrenergic System Genes

Molecular genetic analysis of ADHD and noradrenergic system genes is an emerging area but there have been few findings of association to date. Barr et al. *(110)* and McEvoy et al. *(111)* found no association between polymorphisms at the norepinephrine transporter protein and ADHD. Similarly, negative findings of association have reported for the adrenergic α2A ($ADRA_{2A}$) *(112)* and α2C ($ADRA_{1C}$ and $ADRA_{2C}$) receptors *(113)*.

5. CONFLICTING FINDINGS IN GENETIC STUDIES OF ADHD

Despite compelling evidence for a genetic basis to ADHD and findings of association replicated across several studies, the findings in ADHD are, to date, not definitive. If, as hypothesized, ADHD is a complex genetic disorder, with many susceptibility genes each of small effect *(114–116)*, the pattern of results seen to date is to be expected. Other factors that might account for conflicting results include power limitations secondary to small sample size, differences between the populations of origin of the samples, differences in measuring and defining the phenotype, and clinical heterogeneity with different distributions of the subtypes between samples.

6. FUTURE DIRECTIONS IN GENETIC STUDIES OF ADHD

6.1. Endophenotypes for ADHD

Evidence is emerging in support of endophenotypes or ADHD subtypes in which genes may exert a larger effect than in the categorical diagnosis. Recent studies have examined whether specific genetic risk factors for ADHD correlate with measures of hyperactivity in population samples. Their hypothesis is that if ADHD were a continuous trait, investigation of association between genes (quantitative trait loci [QTL]) and continuous measures of the phenotype would be a more appropriate strategy in the identification of susceptibility variants. To date, there have been few QTL association studies in ADHD and findings have been mixed. In an epidemiological sample, Curran et al. *(117)* selected children on the basis of high and low scores on the five ADHD items of the Strengths and Difficulties Questionnaire and found a significant relationship between the *DRD4* 7-repeat allele and high-scoring children. However, Mill et al. *(118)* did not replicate this finding. Similarly, Todd et al. *(119)* failed to demonstrate any significant association between the *DRD4* 7-repeat allele and DSM-IV ADHD subtypes or ADHD subtypes derived by latent class analysis in an epidemiological twin sample.

Several family studies have investigated the effect of comorbid disorders on the familiality of ADHD. These studies *(4,120–130)* suggest that relatives of probands with ADHD and comorbid conduct disorder (CD) are at greater risk for ADHD than relatives of probands with ADHD alone and that ADHD and comorbid CD may represent a separate familial subtype. Data from Faraone *(129)* calculated the risk ratios (λs) of ADHD in relatives when different subtypes of ADHD are used to select families. Relative risk ratios varied from 4 to 5.4 among relatives of probands with ADHD alone but rose from 5 to 8.9 in relatives of probands with ADHD and CD or bipolar disorder. Twin studies also suggest that the genes that influence conduct disorder symptoms are the same as those that contribute to trait measures of ADHD *(125,131,132)*. Overall the evidence reviewed suggests that ADHD and certain comorbid disorders represent groups in which genes exert a greater effect and may prove useful for the identification of genetic risk factors. To date, there have been a limited number of studies investigating genetic association with clinical measures of the ADHD phenotype. Holmes et al. *(133)* reported significant association between the *DRD4* 7-repeat allele and children with ADHD and comorbid "conduct problems" in a clinical sample. Rowe et al. *(134)* examined retrospectively reported conduct disorder symptoms in parents of ADHD children and found that parents with the *DRD4* 7-repeat allele had more conduct disorder symptoms than parents possessing other genotypes. However, Tahir et al. *(75)* reported significant nontransmission of this allele to children with comorbid oppositional/defiant disorder or CD.

There has been increasing interest in investigating genes associated with neuropsychological endophenotypes of ADHD. Given the difficulty in defining the diagnostic phenotype, more objective measures of behavior are attractive. Owing to the extensive literature on neuropsychological abnormalities in ADHD, such markers may prove useful for further genetic study. This is an emerging research area, and to date, there are few consistent findings. A twin study by Goodman and Stevenson *(135)* found that measures of inattentiveness (freedom from distractibility and "E" scan attentiveness) were moderately influenced by genetic factors (32–42%). More recent twin studies found a significant genetic contribution to hyperactivity and variability of reaction times on the "stop" task *(131)* and genetic influences on Matching Familiar Figures Test-derived measures of impulsiveness *(133)*. To date, there have been few findings of association between specific candidate genes and neuropsychological measures of ADHD. Langley et al. *(136)* found that possession of the DRD4 7 repeat allele was associated with an inaccurate, impulsive response style on neuropsychological tasks that was not explained by ADHD symptom severity.

6.2. Alternative Strategies to Association Mapping and Meta-Analysis

The candidate gene approach has been reasonably successful because of the presence of *a priori* hypotheses based on animal and pharmacological studies. However, because of the increased availability of markers for study and advances in gene mapping technology, systematic genome scans will be required for the identification of further risk alleles for ADHD. Such studies are under way *(137,138)*. These might identify new genes and new neurobiological hypotheses. Future directions for studies in ADHD genetics include the use of collaboration to increase sample size and consequently power to detect association with genes of small effect. Meta-analysis of individual studies is becoming more common and will assist confirmation of candidate genes. This approach has been successful in the cases of the *DRD4 (83)* and *DRD5* genes *(86)*. Functional analysis of associated gene variants will be necessary to

assist evaluation of neurobiology. For example, recent studies *(139,140)* have shown that the 10-repeat allele of the *DAT1* VNTR polymorphism increases dopamine transporter expression and work by Miller and Madras *(141)* suggests that single nucleotide polymorphisms within the *DAT1* 480-bp VNTR differentially affect dopamine transporter expression.

Finally, the importance of environmental etiological factors in ADHD should not be overlooked. Future work in ADHD would benefit from incorporating environmental measures into the study design to examine gene–environment interactions.

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