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REVIEW

DRD4 and DAT1 in ADHD: Functional neurobiology to pharmacogenetics

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Abstract: Attention deficit/hyperactivity disorder (ADHD) is a common and potentially very impairing neuropsychiatric disorder of childhood. Statistical genetic studies of twins have shown ADHD to be highly heritable, with the combination of genes and gene by environment interactions accounting for around 80% of phenotypic variance. The initial molecular genetic studies where candidates were selected because of the efficacy of dopaminergic compounds in the treatment of ADHD were remarkably successful and provided strong evidence for the role of DRD4 and DAT1 variants in the pathogenesis of ADHD. However, the recent application of non-candidate gene strategies (eg, genome-wide association scans) has failed to identify additional genes with substantial genetic main effects, and the effects for DRD4 and DAT1 have not been replicated. This is the usual pattern observed for most other physical and mental disorders evaluated with current state-of-the-art methods. In this paper we discuss future strategies for genetic studies in ADHD, highlighting both the pitfalls and possible solutions relating to candidate gene studies, genome-wide studies, defining the phenotype, and statistical approaches.

Keywords: dopamine, ADHD, pharmacogenetics, candidate gene

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder of childhood affecting around 5% of the population.[1] It is characterized by an early onset and persistent pattern of inattention, impulsivity, and hyperactivity symptoms. The condition is associated with several comorbid disorders (oppositional defiant disorder, anxiety disorders, etc) and conditions (eg, disrupted peer and family relationships), and adverse outcomes emerging with age (eg, educational failure and antisocial behavior). Despite early onset, it is most frequently diagnosed and treated in middle childhood.[2]

There is an overrepresentation of boys over girls by approximately 3:1.[3] ADHD can persist into adulthood, and increases the risk for antisocial personality disorder,[4] later criminality,[5] as well as drug and alcohol misuse.[6] Pharmacologic, neurobiologic, and genetic studies support the notion that ADHD has a neurodevelopmental basis with strong genetic and nongenetic components,[7] implicating neurotransmission dysregulation within brain circuits underpinning cognition and motivation.[8] Disruption of multiple neurotransmitter systems has been proposed. However, the primary focus has been on the catecholamines, dopamine (DA) and noradrenaline (NA). While other papers have focused on NA,[9,10] our focus here is on evidence that variation and disruption of the DA system contributes to the etiology and response to treatment of ADHD.

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Dopamine dysregulation in ADHD

Dopamine neurotransmission

DA is a key neurotransmitter in the biology of a wide range of brain processes.[11–13] It is central to the control of movement,[14] cognition,[15,16] reward,[17] and emotional and motivational responses,[18–20] including the experience of pleasure and pain in response to positive and negative environmental events.[21–23] DA is synthesized from the amino acid tyrosine, which is first converted to L-dihydroxyphenylalanine, and then to DA by the enzyme dihydroxyphenylalanine decarboxylase. DA neurons are clustered in several mid brain regions that project to substantial parts of the brain via three major pathways, ie, the nigrostriatal, mesocorticolimbic, and tuberoinfundibular pathways. The nigrostriatal pathway extends from the substantia nigra to the caudate nucleus/putamen, and plays an essential role in voluntary movement.[24] The mesocorticolimbic pathway projects from the ventral tegmentum to the mesolimbic and mesocortical regions, and is associated with cognition, reward, and emotion processing.[25–27] The tuberoinfundibular pathway plays a role in neuronal control of the hypothalamic-pituitary endocrine system.[28] DA within these pathways modulates functionally and structurally segregated cortical and basal ganglia loops.[29–33] These circuits are involved in well-defined brain networks involved in the processes of attention as well as motivation, and disruption of either or both contribute to the etiology of ADHD.[17,34] Such parallel organization is now thought to be incomplete,[35,36] with thalamic nuclei allowing the passage of signals across different circuits.[37]

DA is released into the synaptic cleft by action potentials via a calcium-dependent mechanism. Calcium influx triggers fusion of the neurotransmitter vesicles with the presynaptic membrane. DA is then released into the synaptic cleft from where it disperses and binds to postsynaptic receptors. Receptors bind neurotransmitter molecules and open nearby ion channels in the postsynaptic cell membrane. This alters the local transmembrane potential of the cell. DA exerts its effects by binding to DA receptors which are functionally categorized into two families, ie, D_1-like and D_2-like. The D_1-type receptors (D_1/D_5) couple to the Gs class of G proteins and activate adenylyl cyclase. D_2-type receptors (D_2/D_3/D_4) couple to Gi protein which inhibits the production of cAMP.[38]

Presynaptic receptors (autoreceptors) monitor extracellular DA levels and modulate impulse-dependent release and synthesis of DA.[39] Blockade of these receptors leads to increased production and presynaptic release of DA. Stimulation has the opposite effect[40] (see later for discussion of the role of presynaptic receptors in the action of methylphenidate). DA clearance from the synaptic cleft is regulated by the products of three genes, ie, DA transporter (SLC6A3/DAT1), monoamine oxidase-A (MAO-A) and catechol-o-methyl transferase (COMT). DAT1 is responsible for the rapid uptake of DA from the synaptic cleft, while MAO-A and COMT are involved in DA catabolism.[41]

Nongenetic evidence for DA dysregulation

Neurochemical studies support a role for neurotransmitter dysregulation in ADHD pathophysiology.[42] Serotonergic, noradrenergic, and glutamatergic pathways have also been implicated.[43] Initial interest in DA in ADHD came from the longstanding observation that catecholamine agonists were psychostimulant medications and provided an effective treatment for many ADHD patients.[20] Since then, methylphenidate has been shown to inhibit the activity of the DA transporter and increase extrasynaptic levels of DA.[44,45] There is evidence that it has little effect on presynaptic DA release,[46] but this has been questioned and the possibility of impulse dependency of transmitter release has been highlighted.[47] Another psychostimulant, amphetamine, has been shown to increase DA levels by modifying its release.[48] It interacts with DA transporters to promote DA efflux from the presynaptic neuron into the synaptic cleft.[49,50] Other evidence in support of the DA dysregulation hypothesis of ADHD comes from two main sources (other than the genetic evidence described later).

First, ADHD animal models show dysregulation of DA function.[51–55] The earliest animal model was developed by administration of 6-hydroxydopamine to neonatal rats that resulted in depletion of DA.[56] After treatment with 6-hydroxydopamine, the activity of animals was initially greater than that of controls. This then declined as a result of profound depletion of brain DA. Genetic models also provide evidence. The ADHD-type characteristics of the spontaneously hypertensive rat (SHR)[57–60] are reduced by DA agents,[61,62] while those of the Naples high-excitability/low-excitability strain is associated with larger DA neurons and altered DA functioning in the limbic and cortical areas of the forebrain.[63–66] In the case of the coloboma mouse, these are associated with altered activity within specific surface proteins that mediate the process of docking and fusion of DA synaptic vesicles to the presynaptic plasma membrane.[67] This results from a 2-cM deletion of mouse chromosome 2 containing several genes including SNAP-25. These effects can be reversed by either transgenic insertion or stimulant medication.[68]

Second, brain imaging studies using positron emission tomography and single photon emission computed tomography suggest altered regulation of striatal DA transporter levels.

Studies vary greatly in their methodologic rigor and, perhaps because of this, there are inconsistencies between them.[17,69] On the one hand, upregulation of striatal DA transporter densities has been reported in studies with small samples of mostly methylphenidate-treated cases.[70–73] Other studies with larger sample sizes found no evidence of altered DA transporter activity.[74] A recent study with a large sample of treatment-naïve adults with ADHD but without a history of comorbid substance use disorder[17] reported downregulation of striatal DAT consistent with higher levels of extracellular DA. This has been confirmed in a recent study in drug-naïve ADHD patients[75] that found decreased striatal DA transporter availability in the basal ganglia. It seems likely that initial reports suggesting DAT upregulation were due to methodologic research limitations. The altered levels of DA transporters are difficult to interpret given the reciprocal and adaptive nature of the relationship between DA transporter densities and DA synthesis and release.[17,76]

Background genetics

Research has consistently shown a strong genetic component in the etiology of ADHD. Twin studies suggest heritability between 0.7 and 0.8.[77–79] The effect is similar for boys and girls.[80,81] The nonheritable component appears to be attributable almost exclusively to nonshared environmental influences,[82,83] but consideration has also been given to "contrast" effects in twin studies.[84] Heritability estimates[85] themselves include gene–environment interaction and correlation[86] (see later for discussion in relation to DAT1 and DRD4).

There are two commonly used approaches in molecular genetic studies, ie, candidate gene approaches based on theoretical involvement of neurobiologic pathways leading to specific hypotheses, and nonhypothesis-driven genome-wide approaches that consider all genes as equally plausible candidates. Candidate gene approaches use either case-control or family-based association designs. In case-control studies, the frequency of candidate alleles or genotypes is compared in ADHD cases and controls. Family-based approaches such as the transmission disequilibrium test (TDT) examine patterns of genetic transmission disequilibrium[87] across generations within affected families to examine whether the probability of transmission of an allele from parents to affected offspring differs from the expected Mendelian pattern of inheritance. There are advantages and disadvantages to these approaches. Family-based studies have an advantage over case-control studies because they are designed to be immune to population stratification.[88] By population stratification we mean that in a mixed population, any trait present at a higher frequency in an ethnic group will show a positive association with any allele that also happens to be more common in that group. This can lead to spurious associations and so it is important that the two groups compared are of the same ethnic origin. However, the use of TDT in family-based studies is subject to selection effects due to missing parents and genotyping errors.[89,90] Morton and Collins[91] argue that stratification, which reduces the accuracy and power of the case-control design, is a problem only under rare circumstances, while the impact of genotyping errors in family-based approaches may have been underestimated.[92] Nonhypothesis-based approaches[93] have also used genome-wide association (GWA) studies and linkage design models. In genome-wide linkage studies, related individuals, either siblings or those in extended pedigrees, are studied in an attempt to localize chromosomal regions which may harbor genes influencing a trait by examining the familial cosegregation of the phenotype and genetic markers.[94] GWA studies compare markers across a population rather than within families, either for groups with or without a disorder or across the range of a trait in the population. More than a decade ago, it was predicted that GWA study designs are more powerful in detecting common alleles with small effects than are linkage approaches.[93] GWA studies require very large numbers of markers (ie, perhaps even millions[95,118]) to cover the whole genome.

In both candidate gene and genome-wide approaches, the ADHD phenotype can be characterized as a diagnostic category or a quantitative trait. Fisher[96] developed the theory of quantitative trait loci (QTL) based on the operation of multiple genes of varying effect. Broadly speaking, a continuous trait (rather than a diagnostic category) can be influenced by a few oligogenes with a moderate effect on the phenotype, or by many polygenes each with a very small effect, or by a combination of the two. The polygene example proposed by Fisher[96] (for the trait of human height) has recently been used to identify multiple loci (at this time, up to 54) associated with height,[97] with many more genes predicted to contribute but which remain to be discovered.[98] While most studies have defined the ADHD phenotype in terms of diagnostic categories, impulsivity, attention, and activity can be adequately measured in a quantitative way,[99,100] and researchers have argued for the use of dimensional approaches in the ADHD field.[101,102] Although statistically powerful,[103] and despite the fact that they have been successfully applied both in human and animal behavioral studies,[104] QTL approaches have so far attracted relatively little interest in the ADHD field. This is probably because the quantification of ADHD when measured using common rating scales focuses only on the severity of psychopathology and does not capture the entire range of the underlying dimensions of attention/inattention and reflectivity/impulsivity.[84,102,105]

The first ADHD genome scan based on 126 affected sib-pairs identified four regions (5p13, 10q26, 12q23, and 16p13) showing some evidence of linkage with logarithm (base 10) of odds scores >1.5.[106] Later genome-wide linkage scans were based on large families in population isolates in Columbia[107] and the Netherlands,[108] which provided a design with much greater statistical power for linkage analysis than the affected-sib pair design. A recent meta-analysis[109] of seven ADHD linkage scans[107,110–115] identified the genomic region on chromosome 16, between 16q21 and 16q24, as the most consistent linkage evidence across the studies. Ten other regions on chromosomes 5, 6, 7, 8, 9, 15, 16, and 17 had nominal significance levels for linkage.[109] Two genome-wide linkage studies in humans employing QTL methods have identified linkage to chromosomes 1p36 and 3q13 for ADHD traits.[109,116] Interestingly, the chromosomal region 1p36 overlaps with a dyslexia QTL, raising the possibility that pleiotropy (ie, where a single gene may impact on several phenotypes) might play a role in the genetic origins of ADHD and dyslexia.[109]

Initial GWA studies with hundreds of thousands of markers and thousands of patients have so far failed to identify a significant genome-wide association between ADHD and these markers.[2,117] Based on the literature on height, this is not unexpected, because the initial GWA studies of 2000–3000 participants also failed to reveal any associations that reached genome-wide levels of significance, but the strategy of combining samples to achieve increased power did identify loci on chromosome 12 and 20 with strong evidence of association[97] that led to the documentation of an association with genes in these regions (HMAG2 and GDF5). The same approach may be productive for studies of ADHD.

In contrast, candidate gene approaches have been more successful. The first two relevant studies evaluated functional variants of DA genes, and showed an association of ADHD with DAT1[118] and DRD4.[154] Since then, other candidates within the DA system[119] and other neurotransmitter systems[120,121] have been proposed, but few of these have produced robust and replicable effects. Several meta-analyses for single and multiple loci have been published that review these data.[122–124]

ADHD and the dopamine receptor D_4 gene

Distribution and functional polymorphisms

DA receptor D_4 (DRD4) is a member of the D_2 class of receptors. The D_2-like receptors regulate several signaling events, including inhibition of adenylate cyclase, stimulation of arachidonic acid release, and modulation of potassium channels.[125–128] The human D_4 receptor gene maps to chromosome 11p15.5. It consists of four exons and encodes a putative 387-amino acid protein with seven transmembrane domains.[129] DRD4 is highly expressed in pyramidal neurons and interneurons in the prefrontal cortex and in the retina. There are lower concentrations in the basal ganglia, hippocampus, and thalamus.[128,130–133] Genetic variations in the DRD4 sequence have been examined in relation to various neuropsychiatric disorders. These have focused on a variable number of the tandem repeat (VNTR) polymorphism in exon 3, consisting of a 48-base-pair repeat unit. This unit codes for an amino acid sequence located in the third cytoplasmic loop of the receptor, thought to be involved in G-protein coupling.[134] In the human population, this VNTR displays a high degree of variability, with multiple nucleotide variation within each repeat.[135–137] The most common repeat variants are the 4R, 7R, and 2R alleles, respectively. The frequency of these alleles varies widely among different ethnic groupings.[136] The 7R allele, for example, has an extremely low prevalence in Asian populations (<2%) but a high frequency in native American populations (~48%).[135] As yet, there is no commonly accepted explanation for this variability at the DRD4 locus. The common and probably ancestral allele has four repeats (4R) originating ~300,000 years ago, whereas the 7R allele, often associated with psychiatric disorders, is up to 10 times "younger".[138,139] The 7R allele may have arisen as a rare mutational event and then become a high frequency allele by positive selection[136] at a time of the major expansion of human population (the upper Paleolithic).[140] In this way, individuals with novelty-seeking personality traits may have driven the expansion of the 7R variant,[136] or it may have conferred a reproductive advantage in male-competitive societies.[141] In the Americas, an increase in the 7R allele may have been due to a successive founder effect,[140] and in China a decrease in the 7R may have been due to selective reproduction of males without the 7R allele.[141] At the same time there appears to be selective forces working to balance the alleles in modern societies (balancing selection), and the prevalence of the 7R allele may now be at a stable level or near a fixation point.[136]

The neurofunctional significance of the DRD4 7R allele is not fully understood. *In vitro* studies indicate that the sensitivity of the 7R allele to DA is half that of the 2R and 4R variants.[134,142] Moreover, DRD4 mRNA is distributed in the prefrontal cortex[133,143,144] but also to a lesser extent in the parietal and temporal lobes, cingulate cortex, and cerebellum.[132,144] It is found in the basal ganglia, although

its density relative to DRD2 is low.[143] This suggests it plays a role in cognitive and motivational processes.[145,146] DRD4 and DAT1 seem not to be colocalized within brain regions (unlike DRD2 and DAT1), suggesting a different role for these two DA receptors.[143] Synthesis and clearance of DA are elevated in mice lacking the DRD4 gene.[147] Also, mice lacking a functional DRD4 receptor display cortical hyperexcitability[148,149] and hypersensitivity to single administrations of alcohol, methamphetamine, and cocaine.[147]

Categorical diagnoses and quantitative traits

The developing understanding of the neurofunctional significance of DRD4 7R has led to investigation of its association with disorders with a putative DA basis. In relation to ADHD, most studies have focused on the 7R polymorphism. An additional 120-base-pair duplication polymorphism located in the 5′ flanking region of DRD4[150] has also been studied recently,[151] as well as a single nucleotide polymorphism (−521 C/T; rs1800955) in the same region.[152] The association between the 7R allele DRD4 polymorphism and ADHD is well replicated. However, the findings are not completely consistent, and the absolute size of the effects is small, although relative to the maximum size possible if all cases had the allele (which is limited by the allele proportion in the population), in some ethnic groups it may be considered large[153] (ie, if the allele probability is .20 in the population, then the maximum is 1/.2 = 5, and 1.9/5 is about 40%). In a ground-breaking study, LaHoste et al[154] first reported the association between DRD4 7R and ADHD. Many studies have followed this lead and the first meta-analysis[155] of this association was published in 2001 including both family-based (14 studies, 1665 probands) and case-control studies (eight studies, 1266 children with ADHD and 3068 controls). This gave an odds ratio (OR) of 1.9 for case-control studies (95% confidence interval [CI]: 1.5–2.2, $P < 0.001$) and 1.4 for family-based studies (95% CI: 1.1–1.6, $P = 0.02$). Five more meta-/pooled analyses of the 7R allele and ADHD have been published.[43,122,156–158] All of them have demonstrated a significant association, although the effect has reduced in size as more studies have been conducted and the total sample size has increased.[43,122,156–158] The most recent meta-analysis showed a fixed effects significance of $P < 0.00001$ with evidence of significant heterogeneity between studies.[43] In contrast with the 7R allele, the 4R allele may confer a protective effect (OR = 0.9, 95% CI: 0.84–0.97).[156]

Several studies have examined DRD4 in relation to ADHD as a quantitative trait. Curran et al[159] first reported an association between the DRD4 7R allele and ADHD trait scores. Lasky-Su et al[160] found evidence for an association between two single nucleotide polymorphisms in the promoter region of DRD4 and the quantitative phenotype (mainly inattentive symptoms) generated from the ADHD symptoms. In contrast Mill et al[161] and Todd et al[62] failed to find evidence for an association between DRD4 and ADHD trait symptoms in the general population. None of these studies used a measure of the full range of attentional abilities in the population, and this could account for these negative results.[102]

DRD4 and putative ADHD endophenotypes

Endophenotypes are conceptualized as "sitting between" genes and the clinical expression of the disorder.[163] To be of value in genetic studies, they should be heritable, cosegregate with a psychiatric illness, be present even when the disease is not (ie, state-independent), and be found in nonaffected family members at a higher rate than in the population.[163] Endophenotypes are postulated to be influenced by fewer genes than the clinical phenotype, and consequently the size of the effects of genetic loci contributing to endophenotypes is postulated to be larger than that to disease susceptibility. The fewer the genes that give rise to an endophenotype, the better the chances of revealing their genetic mode of action.[163] This concept has been controversial, with the suggestion that genetic effects are no greater in those studies employing endophenotypes than those using standard clinical phenotypes.[164] A range of candidate endophenotypes in ADHD has been proposed.[165] The best evidence has been found in relation to response inhibition,[166,167] temporal processing,[168] verbal and visuospatial working memory,[166] and delay aversion.[169] A number of recent studies have found associations between DRD4 7R and performance on putative endophenotypes of ADHD, although the effects are inconsistent.[170] The first study of this sort in ADHD demonstrated the then seemingly paradoxical effect that in a small ADHD sample cases with the 7R-present genotype showed better neuropsychologic performance (faster and less variable reaction time on three tasks) than those with the 7R-absent genotype.[171] This direction of findings has been replicated,[172,173] although some studies have also shown DRD4 7R is related to worse performance.[174] The association between DRD4 7R and neuropsychologic performance is not task-specific. but the strongest and most consistent effects seem to be in relation to high reaction time variability and the absence of 7R.[170] There is some evidence for altered speed of processing[174] and cognitive impulsiveness

on nonreaction tasks in 7R carriers.[172] However, there is no effect of genotype on response inhibition.[172]

DRD4 and gene–environment interactions

Results of behavioral genetic studies are consistent, with a role for environmental factors in ADHD and in personality characteristics in general.[175] Gene–environment interaction (GxE) has been an increasing focus of study. Here specific gene variants are shown to exert only a risk effect for a disorder if they are accompanied by exposure to a particular environmental risk factor.[176,177] In relation to ADHD, these studies can be divided up into two types, ie, those focusing on the role for pre- and perinatal physical environmental risk factors (eg, maternal smoking and alcohol consumption during pregnancy[178]) and those focusing on the postnatal social environment (eg, expressed emotion and social deprivation).[179] There have been a small number of replicated effects for GxE with DRD4 specifically and the results are currently unconvincing, but this may be due to inadequate statistical power in studies. Neuman et al[180] reported an interaction between maternal smoking during pregnancy and the 7R allele but Langley et al[181] failed to replicate this. Other DRD4 7R GxE findings include effects of season of birth.[182] DRD 7R has also been shown to moderate the effects of parenting on externalizing behavior including ADHD.[175,183]

ADHD and the SLC6A3/DAT1 gene

Distribution and functional polymorphisms

The DA transporter is a plasma membrane protein that belongs to the large family of NaCl-dependent transporters. It is responsible for terminating neurotransmission by rapid reuptake of DA into presynaptic terminals.[184] It has been shown to control the intensity and duration of DA neurotransmission by resetting the DA concentration in the extracellular space.[185,186] *In situ* hybridization and immunochemistry studies have shown that DAT1 mRNA is primarily present in DA-synthesizing neurons of the substantia nigra and ventral tegmentum, and that the corresponding protein coincides with dopaminergic innervation of regions including the ventral mesencephalon, medial forebrain bundle, and dorsal and ventral striatum.[187,188] The human DAT1 gene maps to chromosome 5p15.3. Sequence analysis of the 3′UTR of this gene revealed a variable number of tandem repeat (VNTR) polymorphisms with a 40-base-pair unit repeat length, ranging from three to 11 repeats.[189] In humans, the 9R and 10R are most common.[190] Reporter gene studies[191] and studies of RNA expression in human tissues[192] have shown that expression is significantly higher for the 10R than for other alleles, suggesting this variant may be functional. However, Miller and Madras[193] found greater gene expression for vectors containing the 9R sequence, while others[194] demonstrated that neither the 9R or the 10R allele had an effect on transcription. Furthermore, a brain imaging study[195] showed higher density of striatal DAT1 in 10R homozygotes compared with the 9/10 genotype, but another *in vivo* experiment yielded conflicting results showing that the 9R carriers (9/9 homozygotes and 9/10 heterozygotes) had significantly higher striatal DAT1 availability.[196] However, the density of DAT is not fixed. Turnover of DA transporter protein takes about two days,[197] and plasticity has been documented, eg, the effects of drugs on DA transporter density have been established in studies of cocaine[198] and methylphenidate.[17] In as much as the brain "strives" for biochemical equilibrium, the impact of exposure to high levels of synaptic DA is thought to result in a compensatory increase in DAT to keep DA levels in a narrow range. Thus, exposure to stimulants that block DA transporters and increase synaptic DA is thought to increase the density of DA transporters. However, this must be measured when the drugs are not present in the brain, because occupancy of DA transporters would interfere with estimates of DA transporter density and suggest the opposite.[72]

Categorical diagnoses and quantitative traits of DAT1

The DAT1 gene was the first DA gene examined in candidate gene association studies.[118] Using a family-based association design, the authors reported an association between the 10R allele and ADHD. Since the first publication, a number of studies have also reported an association between the DAT1 10R and ADHD.[199,200] However, this association has not always been replicated.[201,202] Overall, the evidence from meta-analyses is less supportive for DAT1 than for DRD4. For instance, Curran et al[203] reported a small, positive, but nonsignificant OR of 1.16, while Maher et al[157] also reported a nonsignificant OR. The most recent study found a significant association (OR = 1.12; $P = 0.028$), but also significant heterogeneity between studies.[43] It has been suggested that specific haplotypes rather than single markers are associated with ADHD.[204] Muglia et al[205] tested for an association between DAT1 and ADHD, considering the disorder as a category as well as a QTL, finding no association for either measure. Unlike Muglia et al,[205] Cornish et al[105]

and Mill et al[161] evaluated ADHD as a continuous trait and found an association between the DAT1 10R allele and ADHD symptom score measure. Most recently Cornish et al[206] used a QTL approach to assess the association between the DAT1 high-risk genotype, visual search and vigilance, and ADHD symptoms in a community sample of boys aged 6–11 years. DAT1 genotypes were only related to ADHD symptoms. In contrast, Todd et al[207] found that the lower frequency allele (9R), along with the DRD4 7R allele, was overtransmitted in ADHD families.

DAT1 and putative ADHD endophenotypes

The data linking DAT1 to putative endophenotypes of ADHD is less compelling than for DRD4, given the dynamic properties of DA transporter densities. However, once again, high reaction time variability seems to be the most replicated cognitive marker associated with 10R homozygosity.[208] It is far from clear what causes such inconsistent results, but it has been suggested that endophenotypes such as delay aversion[209] may be better suited when studying DAT1 and ventral striatum-related functions. It is also possible that any association between DAT1 and neuropsychologic performance may be age-specific.[210]

DAT1 and gene–environment interactions

DAT1 has been implicated in a broader range of GxE effects than has DRD4. In the first study of its kind in ADHD, Kahn et al[211] reported that hyperactivity/impulsivity symptom scores in young children were associated with a 10/10 genotype, but only in children exposed to prenatal smoking. It should be noted that the number of cases of children affected by both genetic and environmental risks was small. This was recently replicated in males.[212] In contrast, Neuman et al[180] reported an association between DAT1 9R and prenatal smoking, while others have found no effect at all.[181] Brookes et al[178] examined alcohol consumption during pregnancy and found an interaction with a DAT1 haplotype. In terms of psychosocial factors, it has been reported that family adversity moderates the impact of the DAT1 genotype on the expression of ADHD symptoms.[213] Sonuga-Barke et al[214] reported that DAT1 moderated the effect of parental expressed emotion on the development of conduct problems in ADHD. Stevens et al[215] showed that the risk of ADHD was increased only in those children who had experienced severe early institutional deprivation and were either homozygous for the 10R allele or carried a DAT1 haplotype combining a 40-base-pair VNTR in 3'UTR and a 30-base-pair VNTR in intron 8.

Overall the molecular-genetic evidence for DAT1 involvement in the etiology of ADHD is not as strong as for DRD4. The inconsistencies and small ORs may be explained by gene heterogeneity (different mutations at the same locus/gene resulting in an identical phenotype) as suggested in several studies.[158] One possibility to overcome this problem might be to examine haplotypes, as has been successfully done in the study by Asherson et al.[205]

Clinical implications

Pharmacogenetics of DRD4 and DAT1

Individual differences in drug response are well documented in medicine, including psychiatry. A specific drug can be highly beneficial for some patients but can produce little or no effect in others and, for others, the same drug can have serious side effects.

The therapeutic value of medication (stimulants) in ADHD patients was first reported more than 70 years ago.[216] Since then, multiple randomized controlled trials have been published confirming without doubt the therapeutic effects of stimulants (eg, methylphenidate and amphetamines).[217–220] More recently, nonstimulants (eg, atomoxetine) have also been licensed.[221] While these treatments are, at least in the short term, very efficacious (eg, response rates of 85% to 90% when titration includes a range of doses for each stimulant and multiple stimulants), and generally well tolerated, there is still a range in the degree of responses.[222] The reduction of levels in ADHD to the levels found in healthy controls is relatively uncommon in clinical trials or in normal clinical practice.[223] Furthermore, there is likely to be much greater variability in the long-term effect of stimulants, and the optimal clinical dose appears to vary sixfold or more across individuals. These two dimensions of treatment response will be important sources of variance that may be interesting targets for future pharmacogenetic studies (especially given the high "response rates").

There have been a number of attempts to identify predictors of response with the aim of improved tailoring of treatments to patient characteristics and needs. Factors such as age, gender, comorbidity and clinical have been considered, although evidence of significant effects of these is limited.[224,225] In general, pharmacogenetic research in psychiatry studies of gene-drug interactions can help in the validation of therapeutic targets, the detection of factors determining response, and the identification of genetically induced side effects. The long-term goal is to develop more effectively tailored treatment and integrated personalized therapeutics. The therapeutic effects of stimulants at the

neuronal level will depend on their ability to alter the release, uptake, and/or enzymatic inactivation of neurotransmitters (see discussion of the effects of methylphenidate and amphetamine earlier.[13,52]) As we have reviewed, these effects appear to vary as a function of DRD4 and DAT1 variants, and polymorphisms in these genes are important candidates for pharmacogenetic investigation. The working hypothesis is that such polymorphisms alter the impact of stimulant medication on brain systems as well as treatment efficacy.[226] Given that methylphenidate is only an "indirect agonist" of DA, via DA transporter blockade, this hypothesis may hold for DAT1 but not DRD4.

A number of pharmacogenetic studies have examined the relationship between methylphenidate response and DA gene polymorphisms in ADHD. The majority of studies have focused on DAT1. The results, so far, are inconclusive for both genes.[226,227] The first relevant study[228] reported a better therapeutic response to methylphenidate in ADHD children with the 9/10 genotype compared with children having the 10/10 genotype. While Roman et al[229] and Cheon et al[230] replicated this finding, others[231,232] found a better treatment response in patients homozygous for 10R. A further two studies demonstrated that the 9/9 genotype was associated with a decreased response to methylphenidate.[232,233] In addition, several studies found no effect of DAT1 in terms of medication response.[234–238] For DRD4, Hamarman et al[239] found that patients with the 7R allele required higher doses for symptom improvement, while Cheon et al[240] reported that children homozygous for the 4R allele had a better response to methylphenidate. Other studies did not report a significant association between the DRD4 7R.[236–238] When trying to understand this conflicting and inconsistent set of results it must be acknowledged that studies to date have been in very small samples and therefore papers may be reporting chance findings.

Summary of key findings

- ADHD is highly heritable (among the highest of all psychiatric disorders and nearly as high as the physical traits such as height) and at the advent of molecular genetic studies of ADHD it was assumed that the discovery of specific genes would be relatively easy.
- The initial discoveries of associations with candidate genes was remarkably successful (in the context of general psychiatric genetics), with a significant association with first DAT1 and then DRD4 genetic variants that were chosen as candidate genes because of their pattern of distribution and neurofunctionality with regard to DA activity and a presumed role in the response to common pharmacologic treatment of ADHD with stimulant drugs.
- The subsequent GWA approaches have not discovered additional genes and have not detected the replicated associations with ADHD from the candidate gene studies of DAT and DRD4.[117]
- Association studies provide stronger evidence for DRD4 (ie, the 7R allele) than DAT1 (ie, 10/10 genotype) in the pathogenesis of ADHD, probably because of greater between-study heterogeneity in DAT1 findings, with absolute effect sizes quantified as the relative risk for either gene individually have a restricted range. However, due to high allele proportions in the population, these effects may appear to be much larger when this is taken into account and the relative risk is compared with the maximum possible.
- Evidence relating DRD4 and DAT genotypes to endophenotypes of ADHD is so far weak and inconsistent, but somewhat stronger for DRD4, especially with regard to response time variability.
- There are also inconsistencies in the evidence implicating these genes in gene–environment interactions, with the strongest findings for DAT1, especially with regard to the impact of maternal smoking during pregnancy, although the role of gene–environment correlations cannot be ruled out.
- DRD4 and DAT1 polymorphisms are interesting candidates for pharmacogenetic studies. DAT1 has the best evidence but the specific genotype associated with greater efficacy is yet to be determined definitively. This finding has to be treated cautiously given the inconsistency of findings and the small study samples. Recommendations for future pharmacogenetic studies are presented in a recent review.[241]

Pitfalls and future directions in the ADHD gene search

Despite intense research efforts, progress in understanding the molecular genetic basis of ADHD may seem limited. Over a decade ago, a few candidate genes were found to be associated with ADHD, but their estimated effects were very small. Genome-wide scans have not identified additional loci to be reliably associated with ADHD. So, at the present time, despite high expectations based on heritability of about 0.8, the percentage of variance of the ADHD phenotype that can be explained by specific genetic factors is small. Importantly, this state of affairs is not unique to the ADHD

area, and is a generic problem in research on specific genetic polymorphisms associated with other common disorders and traits.[242,243] It is generally acknowledged that most of the inherited component of susceptibility to common diseases (including ADHD) remains to be explained.[242,243] For ADHD, as for height (which also has high heritability but so far a low amount explained by identified genes), the variance not explained might be best described as "missing" or "dark" heritability.[244]

What are the next steps? There are a number of options. Should we evaluate further the candidate genes with good documented association using functional genomics? Or should we assume that there are many noncandidate genes with small independent effects that remain to be discovered, and use genome-wide (noncandidate) approaches to continue the search to identify an ever larger set of genes with small effects that may eventually account for the large percentage of phenotypic variance predicted by the high heritability of ADHD? Contrasting candidate gene and genome-wide approaches for the investigation of ADHD, as for other common disorders, raise fundamental questions about what is the best strategy for unraveling the mysteries of the disorder. For example, the reviews and meta-analyses of candidate gene findings suggest evidence of an association for a few genes.[43,156] GWA approaches with large samples do not document an association for these replicate candidate genes.[117,245] How do we use these findings to suggest directions for future research? If we rely on the findings from the candidate gene approach, do we run the risk of being misdirected by false positives (as has often been suggested) or, if we rely on findings from the GWA approach, do we run the risk of being misdirected by false negatives? Here we address some of the pitfalls of these two general approaches.

Pitfalls and solutions in candidate gene studies

The pitfalls are different for population-based case-control from family-based approaches. For instance, the question of false-positive effects from the candidate gene approach may be related to methodologic flaws regarding the quality of genotyping and the completeness of samples (especially in family-based studies) and the problems of unbalanced samples in case-control studies. Population-based studies (eg, using case-control approaches) are sometimes easier to do without the need to ascertain parents. However, the methodologic issues associated with unbalanced groups of cases and controls have been a significant stumbling block. The primary "unbalancing" is by ethnicity, and this is particularly relevant for the ADHD area because the 7R allele prevalence of the most replicated candidate gene (DRD4) is known to differ dramatically across ethnicities,[137] with extremes from near 0 in Asian ADHD samples[246] to over 30% in some Latin American ADHD samples.[247]

Family-based studies (eg, the TDT approach with the untransmitted alleles from parents providing a perfectly matched control) can avoid ethnic stratification of cases and controls but have other potential pitfalls. Undetected genotyping errors and missing parents may have a significant impact in TDT analyses.[248] Mitchell et al[92] addressed genotyping error in a review of the literature on candidate gene studies. They noted an interesting difference in family-based studies and population-based studies; in the family-based studies utilizing TDT, most (87%) indicated that the most common allele was overtransmitted to affected offspring (suggesting a risk factor), but in the population-based studies, the most common allele was enriched in only 32% of cases and 68% of controls (suggesting a protective factor). They pointed out that even if undetected genotyping errors are random, their effect may not be nonrandom and, even if low, they can produce apparent transmission distortion at markers with alleles of unequal frequencies. For associations from TDT analyses between a common allele and risk, or a rare allele and protection, the authors recommend caution because this is in the direction of bias introduced by undetected genotyping error. Curtis and Sham[249] showed that computation of the TDT in trios when one parent is missing genotype data increases the false-positive error rate. Weinberg[90] and Gordon et al[248] proposed methods that allow for missing parents in TDT analyses.

Consideration of genotyping error rate and missing parent genotypes may be particularly relevant to the ADHD area for several reasons. First, the candidate gene approaches (DAT1 and DRD4) have proposed risk alleles with very different population allele frequencies, (ie, the DAT1 10R allele is the most common allele for the 40-base-pair VNTR, with a very high population prevalence that averages about 0.75, while the DRD4 4R allele with a prevalence in most populations of about 0.60 is usually the most common allele for the 48-base-pair VNTR, while the 7R allele has a lower population prevalence that averages about 0.12 in Caucasian populations). Second, the genotyping error rates in ADHD studies have been high for both population-based case-control studies (eg, up to 50% for some genes)[250] and family-based GWA studies[117] (eg, 26% of the 500,000 SNPs failed the rigorous quality control implemented). Third, in family-based studies, the fathers are often missing,[79] and the use of complete trios may bias the sample.[251]

What impact might these methodologic problems have on findings in the ADHD literature? For example, consider the observations and cautions outlined by Mitchell et al[92] for undetected genotyping errors. If undetected genotyping error rate is assumed and included in the TDT analyses of family-based studies, adjustments would reduce the observed effect for DAT1 and increase the observed effect for DRD4. The proposed allele frequency genotyping error rate effect may account for an observation highlighted in meta-analyses of the DRD4 findings, since the effect size for family-based studies using the TDT have been systematically lower (1.3) than the effect sizes for the population-based studies (1.9), which are not subject to this nonrandom effect. Given these problems, an obvious next step in the ADHD area is to increase rigor in checking for artifacts due to genotyping error and systemically biased samples due to self-selection of cases. Statistical methods have been developed to address these two important methodologic issues. For example, Gordon et al[248] developed a variant of the TDT that "allows for error" (ae), and their TDTae is robust to the presence of random genotyping errors and any number of untyped parents.

Pitfalls and solutions in genome-wide studies

In general the GWA approach has been successful in finding genes that were not predicted to be associated with disorders and traits.[252] An example of this success is the finding of genes and loci associated with the classic quantitative trait (ie, human height). After almost a century, the predictions provided by Fisher[96] were finally tested after the 2005 HapMap project provided large sets of SNPs, and GWA methods were developed.[97] Initial GWA studies of 2000 to 3000 participants did not identify any loci that reached genome-wide significance levels for association with height, but the combination of samples increased statistical power and identified two genes (HMG2 and GDF5) associated with height. Further use of this strategy identified larger (20 replicated loci)[253] and even larger number of SNPs (54 associated loci).[254]

However, the limitations as well as successes of the GWA approach were highlighted by the studies of height.[244] The size of the effects of the genes discovered so far has been very small and account for only 5% of population variance, which contrasted with the prediction by the high estimate of heritability,[254] indicating that many other genes will be found. The next step proposed is to conduct GWA studies with even larger sample sizes to identify the many (perhaps hundreds or thousands) genes with small effects that are presumed to contribute to the high heritability of height which have not yet been detected. This approach has been recommended for ADHD research. For example, Neale et al[117] did not detect any associated loci with a sample of about 1000 and a set of 500,000 SNPs, which is reminiscent of the initial GWA studies of height. They recommended the use of a larger sample that could be achieved by combining samples, which was a success strategy for identifying loci and genes associated with height.

However, critics of this approach have pointed out potential pitfalls for studies of height that may also be relevant for ADHD. For example, the loci with the largest effects have probably been identified in the initial GWA studies of height, and these account for only 5% of population variance. The contribution of additional SNPs to be identified in the next step with larger samples is expected to be smaller and smaller, so that one estimate of the number of loci required to reach 80% is extraordinarily high (93,000).[98] In contrast, other have emphasized that the primary purpose of the GWA approach is not to account completely for the percentage of variance predicted by heritability estimates or to predict the trait itself. Instead, the primary purpose is to identify unexpected biologic pathways involved in a disorder or a trait.[97]

The current state of affairs has led to a reassessment of the common disease-common variant (CDCV) hypothesis upon which logic the GWA approach is based. The selection of SNP for GWA studies is based on the assumption derived from linkage disequilibrium that common variants within a haplotype block can stand as markers for the common variants, usually defined as having a minor allele frequency of 0.05 or greater. However, the common disease-rare variant (CDRV) hypothesis may be more appropriate.[255–258] To test the CDRV hypothesis we need a different approach to genotyping (ie, high-depth sequencing) to identify the rare variants, which in absolute numbers (as a set) are expected to be much more frequent than the set of common variants. A next step is to increase the density of SNPs (and eventually to obtain the complete genome sequence of each individual) and this has been proposed to ensure that rare as well as common causal variants could be detected. Several technology developments are currently trying to increase efficiency to a degree that the acquisition of the complete genome sequence for each individual would be feasible. This may be very relevant to the ADHD area. For example, rare variants have been documented for the DRD4 VNTR,[153] and these will be detected by complete sequencing.

Pitfalls and solutions for defining the ADHD phenotype

In the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) the ADHD phenotype is based on categoric

diagnostic criteria. A different approach would involve reconceptualizing the ADHD phenotype as a trait similar to height. For the application of the Fisher[96] model of a quantitative trait, the assumption is that it would be normally distributed in the population. More up-to-date approaches employing multiple regression methods of extreme scores on a continuous trait have also been applied.[259] However, most dimensional measures of ADHD (eg, derived from the Child Behavior Checklist, Strengths and Difficulties Questionnaire, Score for Neonatal Acute Physiology, Conners, Vanderbilt, DuPaul, or other rating scales) are based on severity of symptoms, so they are fundamentally categoric and produce a highly skewed distribution in the population (ie, for a representative sample that would include ADHD cases and noncases).[260]

While the use of symptom-severity ratings as a dimension leaves considerable variance unmeasured in the noncases, adaptations at the item level to measure variation across the entire range of behavior in the population can provide trait measures of ADHD that captures this variance.[84] The strengths and weaknesses of ADHD symptoms and normal behavior (SWAN) method has not been widely used,[261] but it has been used infrequently for the definition of extreme groups for comparison in molecular genetic studies[105] and in population-based twin studies.[84,262,263]

The approach developed by Fisher[96] provided the rationale for the evaluation of a quantitative trait considered to be the product of many independent small genetic effects that are additive and produce a normal distribution of the trait in the population. If a trait measure of ADHD that is normally distributed in the population is adopted, then the literature on the molecular genetics of other traits with high heritability may provide clear direction for a next step in the ADHD area that could follow the successes in the studies of the genetic bases of height. As mentioned above, ADHD, like height, has a very high (about 0.8) estimate of heritability. If a normally distributed trait measure of ADHD is used, then the next step in research could follow a general two-stage approach used to identify many genes associated with height.[253] In Stage 1, stringent GWA statistical safeguards are applied to protect against false-positive findings in the multiple testing of an extremely large set of SNP markers, and then in Stage 2 the significant set of markers (some assumed to be false positives) are evaluated in an even larger sample at a much reduced genotyping cost. Weedon et al[253] described the Stage 1 use of six GWA studies of 13,665 individuals to identify 39 SNPs that exceeded a statistical cut-off to avoid false positives ($P < 10 \times 10^{-4}$), which were investigated for replication in Stage 2 in 16,482 individuals, with replication of association for 20 of the 39 SNPs. This approach has been extended by additional GWA studies of height, which have (so far) identified 54 loci associated with height in a sample of over 63,000 individuals.[254,264]

A similar approach could be taken for evaluation of normally distributed traits related to ADHD. Associations of SNPs with small but reliable effects might be identified in a similar two-stage approach, with 15,000 to 20,000 individuals included in a Stage 1 GWA scan to identify a set of SNPs with alleles associated with risk (high level of the ADHD trait) and protection (low level of the ADHD trait). Then, in Stage 2 the set of SNPs could be genotyped in an additional set of 15,000 to 20,000 individuals, and for those with a replicated association, the distribution of high-ADHD alleles could be specified. The prediction from the Fisher[96] quantitative trait model would be a normal distribution of the number of high-ADHD alleles, and a linear relationship between the number of high-ADHD alleles and rating of the ADHD trait. The most rigorous genome-wide linkage study of ADHD[111] did not identify any loci associated with ADHD, and the most rigorous GWA study of ADHD[117] did not identify any SNP that met the Stage 1 cut-off to carry forward into Stage 2, but this may have been due to the use of a categoric diagnosis of ADHD rather than a normally distributed trait.

Pitfalls and solutions in statistical analyses

The estimate of high heritability (0.80) for ADHD from twin studies includes main effects of genetic factors, as well as interactions of the genetic main effects with environmental effect that have not been measured and included in the model use to generate the estimates of heritability.[85] In the next steps of research on ADHD, it may be important to address the violations of assumptions of additivity of main effects, and to measure environmental exposures that affect phenotype so that in statistical analyses, provisions can be made to separate genetic main effects and gene–environment interaction effects. Several approaches for the measurement of environmental exposures that may be involved in gene–environment interactions have been described in a 2008 special issue of the *Journal of Child Psychology and Psychiatry*.

The strategies to investigate gene–environment interactions will require access to large sample sizes, new technologies, and new analytic methods. Several large samples may be required to take into account differences in the genetic architecture of rare and common alleles that are known to contribute to common disorders and to traits.[255] One future sample

will be provided by the National Children's Study which was initiated in 2009 and plans to acquire a representative birth cohort of 100,000 children by 2015, with broad measures of environmental exposures and phenotypic outcomes starting before birth and continuing at birth, in infancy, during childhood and adolescence, and into adulthood. Eventually, the National Children's Study should have about 5000 cases that would meet the categoric diagnostic criteria for ADHD. Traditionally, these cases would be matched to well-evaluated controls, and a nested case-control study of the disorder. Based on the expected sample of 5000 cases, standard calculations of the statistical power needed to detect association of genetic main effects and gene–environment interaction effects[265] indicated that small association effects should be detectable, and tests of hypotheses of gene–environment interaction would also have adequate power. This would allow for tests of gene–environment interactions that have been proposed based on small samples, such as the interaction of DAT1 genotype and maternal smoking during pregnancy.[211] The prospective birth cohort design will allow for evaluation of epigenetic variation related to fetal adaptations[266] which has been proposed as an important etiology of ADHD, based on children born under conditions of stress during pregnancy[267] and has been revived by imaging studies during follow-up of that cohort.[268]

However, if the example of height is used to direct the next steps in research on the genetic basis of ADHD, then a normally distributed trait related to ADHD should be used instead of categorical diagnosis of a disorder. Then the entire sample of 100,000 could be utilized, which would provide a more powerful statistical approach to identify genes associated with ADHD and as yet unknown biologic pathways[97] that contribute to the etiology, and could be used to develop potential new treatments for this condition.

Disclosures

Dr Sonuga-Barke has been a recent speaker and has done past and present consultancy for Shire and UCB Pharma. He has received past and present research support from Janssen Cilag, Shire, Qbtech, and Flynn Pharma, and is on the advisory boards for Shire, Flynn Pharma, UCB Pharma, and Astra Zeneca, and has had conference support from Shire Dr Swanson has received research support from Alza, Richwood, Shire, Celgene, Novartis, Celltech, Gliatech, Cephalon, Watson, CIBA, Janssen, and McNeil, and has been on the advisory boards of Alza, Richwood, Shire, Celgene, Novartis, Celltech, UCB, Gliatech, Cephalon, McNeil, and Eli Lilly, and has been on the speakers' bureaus of Alza, Shire, Novartis, Celltech, UCB, Cephalon, CIBA, Janssen, and McNeil. He has also consulted to Alza, Richwood, Shire, Celgene, Novartis, Celltech, UCB, Gliatech, Cephalon, Watson, CIBA, Janssen, McNeil, and Eli Lilly. The authors report no conflict of interest in this research.

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