

DRD4 and DAT1 in ADHD: Functional neurobiology to pharmacogenetics

Darko Turic¹
James Swanson²
Edmund Sonuga-Barke^{1,3}

¹Institute for Disorders of Impulse and Attention, School of Psychology, University of Southampton, UK;

²Child Development Center, University of California, Irvine, California, US; ³Department of Experimental, Clinical and Health Psychology, Ghent University, Belgium

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.

Correspondence: Edmund Sonuga-Barke
Institute for Disorders of Impulse
and Attention, School of Psychology,
University of Southampton, Southampton,
SO17 1BJ, UK
Email ejb3@soton.ac.uk.

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, D₁-like and D₂-like. The D₁-type receptors (D₁/D₅) couple to the G_s class of G proteins and activate adenylyl cyclase. D₂-type receptors (D₂/D₃/D₄) 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 effect⁴⁰ (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 disorder¹⁷ reported downregulation of striatal DAT consistent with higher levels of extracellular DA. This has been confirmed in a recent study in drug-naïve ADHD patients⁷⁵ 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 estimates⁸⁵ themselves include gene–environment interaction and correlation⁸⁶ (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 disequilibrium⁸⁷ 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 Collins⁹¹ 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 approaches⁹³ 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. Fisher⁹⁶ 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 Fisher⁹⁶ (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 Columbia¹⁰⁷ 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-analysis¹⁰⁹ 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 association⁹⁷ 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 DAT1¹¹⁸ and DRD4.¹⁵⁴ Since then, other candidates within the DA system¹¹⁹ 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 D₄ gene

Distribution and functional polymorphisms

DA receptor D₄ (DRD4) is a member of the D₂ class of receptors. The D₂-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 D₄ 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 ($\sim 48\%$).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 $\sim 300,000$ 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 selection¹³⁶ 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 DRD4¹⁵⁰ 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 large¹⁵³ (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 al¹⁵⁴ first reported the association between DRD4 7R and ADHD. Many studies have followed this lead and the first meta-analysis¹⁵⁵ 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 al¹⁵⁹ first reported

an association between the DRD4 7R allele and ADHD trait scores. Lasky-Su et al¹⁶⁰ 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 al¹⁶¹ and Todd et al¹⁶² 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 processing¹⁷⁴ 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 pregnancy¹⁷⁸) 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 al¹⁸⁰ reported an interaction between maternal smoking during pregnancy and the 7R allele but Langley et al¹⁸¹ 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 studies¹⁹¹ and studies of RNA expression in human tissues¹⁹² have shown that expression is significantly higher for the 10R than for other alleles, suggesting this variant may be functional. However, Miller and Madras¹⁹³ found greater gene expression for vectors containing the 9R sequence, while others¹⁹⁴ demonstrated that neither the 9R or the 10R allele had an effect on transcription. Furthermore, a brain imaging study¹⁹⁵ 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 cocaine¹⁹⁸ 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 al²⁰³ reported a small, positive, but nonsignificant OR of 1.16, while Maher et al¹⁵⁷ 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 al²⁰⁵ 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 al¹⁰⁵

and Mill et al¹⁶¹ evaluated ADHD as a continuous trait and found an association between the DAT1 10R allele and ADHD symptom score measure. Most recently Cornish et al²⁰⁶ 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 al²⁰⁷ 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 aversion²⁰⁹ 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 al²¹¹ 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 al¹⁸⁰ reported an association between DAT1 9R and prenatal smoking, while others have found no effect at all.¹⁸¹ Brookes et al¹⁷⁸ 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 al²¹⁴ reported that DAT1 moderated the effect of parental expressed emotion on the development of conduct problems in ADHD. Stevens et al²¹⁵ 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 study²²⁸ 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 al²²⁹ and Cheon et al²³⁰ 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 al²³⁹ found that patients with the 7R allele required higher doses for symptom improvement, while Cheon et al²⁴⁰ 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 endo-phenotypes 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 samples²⁴⁶ 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 al⁹² 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 Sham²⁴⁹ showed that computation of the TDT in trios when one parent is missing genotype data increases the false-positive error rate. Weinberg⁹⁰ and Gordon et al²⁴⁸ 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 studies¹¹⁷ (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 al⁹² 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 al²⁴⁸ 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 Fisher⁹⁶ 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 al¹¹⁷ 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 biological 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 Fisher⁹⁶ 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 categorical 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 studies¹⁰⁵ and in population-based twin studies.^{84,262,263}

The approach developed by Fisher⁹⁶ 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 al²⁵³ 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 Fisher⁹⁶ 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 ADHD¹¹¹ did not identify any loci associated with ADHD, and the most rigorous GWA study of ADHD¹¹⁷ 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 categorical 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 categorical 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 effects²⁶⁵ 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 adaptations²⁶⁶ which has been proposed as an important etiology of ADHD, based on children born under conditions of stress during pregnancy²⁶⁷ 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 pathways⁹⁷ 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.

References

- Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: A systematic review and meta-regression analysis. *Am J Psychiatry*. 2007;164(6):942-948.
- Lasky-Su J, Anney RJ, Neale BM, et al. Genome-wide association scan of the time to onset of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(8):1355-1358.
- Reiff MI, Stein MT. Attention-deficit/hyperactivity disorder evaluation and diagnosis: A practical approach in office practice. *Pediatr Clin North Am*. 2003;50(5):1019-1048.
- Mannuzza S, Klein RG, Konig PH, Giampino TL. Hyperactive boys almost grown up. IV. Criminality and its relationship to psychiatric status. *Arch Gen Psychiatry*. 1989;46(12):1073-1079.
- Satterfield JH, Faller KJ, Crinella FM, Schell AM, Swanson JM, Homer LD. A 30-year prospective follow-up study of hyperactive boys with conduct problems: Adult criminality. *J Am Acad Child Adolesc Psychiatry*. 2007;46(5):601-610.
- Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult follow-up of hyperactive children: Antisocial activities and drug use. *J Child Psychol Psychiatry*. 2004;45(2):195-211.
- Swanson JM, Kinsbourne M, Nigg J, et al. Etiologic subtypes of attention-deficit/hyperactivity disorder: Brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. *Neuropsychol Rev*. 2007;17(1):39-59.
- Sonuga-Barke EJ, Elgie S, Hall M. More to ADHD than meets the eye: Observable abnormalities in search behaviour do not account for performance deficits on a discrimination task. *Behav Brain Funct*. 2005;1(1):10.
- Arnsten AF, Li BM. Neurobiology of executive functions: Catecholamine influences on prefrontal cortical functions. *Biol Psychiatry*. 2005;57(11):1377-1384.
- Pliszka SR, McCracken JT, Maas JW. Catecholamines in attention-deficit hyperactivity disorder: Current perspectives. *J Am Acad Child Adolesc Psychiatry*. 1996;35(3):264-272.
- Schultz W. Getting formal with dopamine and reward. *Neuron*. 2002;36(2):241-263.
- Schultz W. Multiple dopamine functions at different time courses. *Annu Rev Neurosci*. 2007;30:259-288.
- Seeman P, Madras BK. Anti-hyperactivity medication: Methylphenidate and amphetamine. *Mol Psychiatry*. 1998;3(5):386-396.
- Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet*. 2009;373(9680):2055-2066.
- Aultman JM, Moghaddam B. Distinct contributions of glutamate and dopamine receptors to temporal aspects of rodent working memory using a clinically relevant task. *Psychopharmacology (Berl)*. 2001;153(3):353-364.
- Floresco SB, Phillips AG. Delay-dependent modulation of memory retrieval by infusion of a dopamine D1 agonist into the rat medial prefrontal cortex. *Behav Neurosci*. 2001;115(4):934-939.
- Volkow ND, Wang GJ, Kollins SH, et al. Evaluating dopamine reward pathway in ADHD: Clinical implications. *JAMA*. 2009;302(10):1084-1091.
- Hranilovic D, Bucan M, Wang Y. Emotional response in dopamine D2L receptor-deficient mice. *Behav Brain Res*. 2008;195(2):246-250.
- Pezze MA, Feldon J. Mesolimbic dopaminergic pathways in fear conditioning. *Prog Neurobiol*. 2004;74(5):301-320.
- Wender PH. A possible monoaminergic basis for minimal brain dysfunction. *Psychopharmacol Bull*. 1975;11(3):36-37.

21. Giuliano F, Allard J. Dopamine and sexual function. *Int J Impot Res*. 2001;13 Suppl 3:S18–S28.
22. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: The role of reward-related learning and memory. *Annu Rev Neurosci*. 2006;29:565–598.
23. Pecina S, Berridge KC. Hedonic hot spot in nucleus accumbens shell: Where do mu-opioids cause increased hedonic impact of sweetness? *J Neurosci*. 2005;25(50):11777–11786.
24. Barbeau A. High-level levodopa therapy in Parkinson's disease: Five years later. *Trans Am Neurol Assoc*. 1974;99:160–163.
25. Mogenson GJ, Jones DL, Yim CY. From motivation to action: Functional interface between the limbic system and the motor system. *Prog Neurobiol*. 1980;14(2–3):69–97.
26. Wise RA. Dopamine, learning and motivation. *Nat Rev Neurosci*. 2004;5(6):483–494.
27. Wise RA. Dopamine and food reward: Back to the elements. *Am J Physiol Regul Integr Comp Physiol*. 2004;286(1):R13.
28. Ben-Jonathan N, Hnasko R. Dopamine as a prolactin (PRL) inhibitor. *Endocr Rev*. 2001;22(6):724–763.
29. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. *Trends Neurosci*. 1990;13(7):266–271.
30. Bar-Gad I, Bergman H. Stepping out of the box: Information processing in the neural networks of the basal ganglia. *Curr Opin Neurobiol*. 2001;11(6):689–695.
31. Haber SN. The primate basal ganglia: Parallel and integrative networks. *J Chem Neuroanat*. 2003;26(4):317–330.
32. Middleton FA, Strick PL. Basal-ganglia 'projections' to the prefrontal cortex of the primate. *Cereb Cortex*. 2002;12(9):926–935.
33. Takada M, Tokuno H, Nambu A, Inase M. Corticostriatal projections from the somatic motor areas of the frontal cortex in the macaque monkey: Segregation versus overlap of input zones from the primary motor cortex, the supplementary motor area, and the premotor cortex. *Exp Brain Res*. 1998;120(1):114–128.
34. Sonuga-Barke EJ, Dalen L, Daley D, Remington B. Are planning, working memory, and inhibition associated with individual differences in preschool ADHD symptoms? *Dev Neuropsychol*. 2002;21(3):255–272.
35. Kolomiets BP, Deniau JM, Mailly P, Menetrey A, Glowinski J, Thierry AM. Segregation and convergence of information flow through the cortico-subthalamic pathways. *J Neurosci*. 2001;21(15):5764–5772.
36. McFarland NR, Haber SN. Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. *J Neurosci*. 2002;22(18):8117–8132.
37. Haber SN, Calzavara R. The cortico-basal ganglia integrative network: The role of the thalamus. *Brain Res Bull*. 2009;78(2–3):69–74.
38. Callier S, Snapyan M, Le Crom S, Prou D, Vincent JD, Vernier P. Evolution and cell biology of dopamine receptors in vertebrates. *Biol Cell*. 2003;95(7):489–502.
39. Altar CA, Boyar WC, Oei E, Wood PL. Dopamine autoreceptors modulate the in vivo release of dopamine in the frontal, cingulate and entorhinal cortices. *J Pharmacol Exp Ther*. 1987;242(1):115–120.
40. Marinelli M, Rudick CN, Hu XT, White FJ. Excitability of dopamine neurons: modulation and physiological consequences. *CNS Neurol Disord Drug Targets*. 2006;5(1):79–97.
41. Huotari M, Santha M, Lucas LR, Karayiorgou M, Gogos JA, Mannisto PT. Effect of dopamine uptake inhibition on brain catecholamine levels and locomotion in catechol-O-methyltransferase-disrupted mice. *J Pharmacol Exp Ther*. 2002;303(3):1309–1316.
42. Zametkin AJ, Liotta W. The neurobiology of attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 1998;59 Suppl 7:17–23.
43. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: A meta-analytic review. *Hum Genet*. 2009;126(1):51–90.
44. Volkow ND, Wang GJ, Fowler JS, Ding YS. Imaging the effects of methylphenidate on brain dopamine: New model on its therapeutic actions for attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2005;57(11):1410–1415.
45. Volkow ND, Wang GJ, Fowler JS, et al. Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. *Am J Psychiatry*. 2004;161(7):1173–1180.
46. Patrick KS, Caldwell RW, Ferris RM, Breese GR. Pharmacology of the enantiomers of three-methylphenidate. *J Pharmacol Exp Ther*. 1987;241(1):152–158.
47. Seeman P, Madras B. Methylphenidate elevates resting dopamine which lowers the impulse-triggered release of dopamine: A hypothesis. *Behav Brain Res*. 2002;130(1–2):79–83.
48. Fan X, Xu M, Hess EJ. D2 dopamine receptor subtype-mediated hyperactivity and amphetamine responses in a model of ADHD. *Neurobiol Dis*. 2010;37:228–236.
49. Kuczenski R, Segal DS. Differential effects of D- and L-amphetamine and methylphenidate on rat striatal dopamine biosynthesis. *Eur J Pharmacol*. 1975;30(2):244–251.
50. Kuczenski R, Segal DS. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. *J Neurochem*. 1997;68(5):2032–2037.
51. Accili D, Fishburn CS, Drago J, et al. A targeted mutation of the D3 dopamine receptor gene is associated with hyperactivity in mice. *Proc Natl Acad Sci U S A*. 1996;93(5):1945–1949.
52. Giros B, Jaber M, Jones SR, Wightman RM, Caron MG. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature*. 1996;379(6566):606–612.
53. Granon S, Passeti F, Thomas KL, Dalley JW, Everitt BJ, Robbins TW. Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into rat prefrontal cortex. *J Neurosci*. 2000;20(3):1208–1215.
54. Leo D, Sorrentino E, Volpicelli F, et al. Altered midbrain dopaminergic neurotransmission during development in an animal model of ADHD. *Neurosci Biobehav Rev*. 2003;27(7):661–669.
55. Xu M, Moratalla R, Gold LH, et al. Dopamine D1 receptor mutant mice are deficient in striatal expression of dynorphin and in dopamine-mediated behavioral responses. *Cell*. 1994;79(4):729–742.
56. Shaywitz BA, Yager RD, Klopfer JH. Selective brain dopamine depletion in developing rats: An experimental model of minimal brain dysfunction. *Science*. 1976;191(4224):305–308.
57. Mook DM, Jeffrey J, Neuringer A. Spontaneously hypertensive rats (SHR) readily learn to vary but not repeat instrumental responses. *Behav Neural Biol*. 1993;59(2):126–135.
58. Sagvolden T. Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD). *Neurosci Biobehav Rev*. 2000;24(1):31–39.
59. Wong AH, Buckle CE, Van Tol HH. Polymorphisms in dopamine receptors: What do they tell us? *Eur J Pharmacol*. 2000;410(2–3):183–203.
60. Wyss JM, Fisk G, van Groen T. Impaired learning and memory in mature spontaneously hypertensive rats. *Brain Res*. 1992;592(1–2):135–140.
61. Boix F, Qiao SW, Kolpus T, Sagvolden T. Chronic L-deprenyl treatment alters brain monoamine levels and reduces impulsiveness in an animal model of attention-deficit/hyperactivity disorder. *Behav Brain Res*. 1998;94(1):153–162.
62. Myers MM, Musty RE, Hendley ED. Attenuation of hyperactivity in the spontaneously hypertensive rat by amphetamine. *Behav Neural Biol*. 1982;34(1):42–54.
63. Gonzalez-Lima F, Sadile AG. Network operations revealed by brain metabolic mapping in a genetic model of hyperactivity and attention deficit: The Naples high- and low-excitability rats. *Neurosci Biobehav Rev*. 2000;24(1):157–160.
64. Papa M, Sellitti S, Sadile AG. Remodeling of neural networks in the anterior forebrain of an animal model of hyperactivity and attention deficits as monitored by molecular imaging probes. *Neurosci Biobehav Rev*. 2000;24(1):149–156.
65. Sadile AG, Lamberti C, Siegfried B, Welzl H. Circadian activity, nociceptive thresholds, nigrostriatal and mesolimbic dopaminergic activity in the Naples high- and low-excitability rat lines. *Behav Brain Res*. 1993;55(1):17–27.

66. Sadile AG, Pellicano MP, Sagvolden T, Sergeant JA. NMDA and non-NMDA sensitive [L-3H] glutamate receptor binding in the brain of the Naples high- and low-excitability rats: An autoradiographic study. *Behav Brain Res*. 1996;78(2):163–174.
67. Hess EJ, Collins KA, Wilson MC. Mouse model of hyperkinesia implicates SNAP-25 in behavioral regulation. *J Neurosci*. 1996;16(9):3104–3111.
68. Steffensen SC, Henriksen SJ, Wilson MC. Transgenic rescue of SNAP-25 restores dopamine-modulated synaptic transmission in the coloboma mutant. *Brain Res*. 1999;847(2):186–195.
69. Gonen F. The dopaminergic hypothesis of attention-deficit/hyperactivity disorder needs re-examining. *Trends Neurosci*. 2009;32(1):2–8.
70. Cheon KA, Ryu YH, Kim YK, Namkoong K, Kim CH, Lee JD. Dopamine transporter density in the basal ganglia assessed with [123I]IPT SPET in children with attention deficit hyperactivity disorder. *Eur J Nucl Med Mol Imaging*. 2003;30(2):306–311.
71. Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ. Dopamine transporter density in patients with attention deficit hyperactivity disorder. *Lancet*. 1999;354(9196):2132–2133.
72. Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: Effects of methylphenidate as measured by single photon emission computed tomography. *Neurosci Lett*. 2000;285(2):107–110.
73. Larisch R, Sitte W, Antke C, et al. Striatal dopamine transporter density in drug naive patients with attention-deficit/hyperactivity disorder. *Nucl Med Commun*. 2006;27(3):267–270.
74. van Dyck CH, Quinlan DM, Cretella LM, et al. Unaltered dopamine transporter availability in adult attention deficit hyperactivity disorder. *Am J Psychiatry*. 2002;159(2):309–312.
75. Hesse S, Ballaschke O, Barthel H, Sabri O. Dopamine transporter imaging in adult patients with attention-deficit/hyperactivity disorder. *Psychiatry Res*. 2009;171(2):120–128.
76. Madras BK, Miller GM, Fischman AJ. The dopamine transporter: Relevance to attention deficit hyperactivity disorder (ADHD). *Behav Brain Res*. 2002;130(1–2):57–63.
77. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet*. 2005;366(9481):237–248.
78. Stevenson J. Evidence for a genetic etiology in hyperactivity in children. *Behav Genet*. 1992;22(3):337–344.
79. Swanson JM, Sergeant JA, Taylor E, Sonuga-Barke EJ, Jensen PS, Cantwell DP. Attention-deficit hyperactivity disorder and hyperkinetic disorder. *Lancet*. 1998;351(9100):429–433.
80. Nadder TS, Silberg JL, Eaves LJ, Maes HH, Meyer JM. Genetic effects on ADHD symptomatology in 7- to 13-year-old twins: Results from a telephone survey. *Behav Genet*. 1998;28(2):83–99.
81. Saudino KJ, Ronald A, Plomin R. The etiology of behavior problems in 7-year-old twins: Substantial genetic influence and negligible shared environmental influence for parent ratings and ratings by same and different teachers. *J Abnorm Child Psychol*. 2005;33(1):113–130.
82. Larsson JO, Larsson H, Lichtenstein P. Genetic and environmental contributions to stability and change of ADHD symptoms between 8 and 13 years of age: A longitudinal twin study. *J Am Acad Child Adolesc Psychiatry*. 2004;43(10):1267–1275.
83. Thapar A, Harrington R, McGuffin P. Examining the comorbidity of ADHD-related behaviours and conduct problems using a twin study design. *Br J Psychiatry*. 2001;179:224–229.
84. Polderman TJ, de Geus EJ, Hoekstra RA, et al. Attention problems, inhibitory control, and intelligence index overlapping genetic factors: A study in 9-, 12-, and 18-year-old twins. *Neuropsychology*. 2009;23(3):381–391.
85. Purcell S. Statistical methods in behavioral genetics. In: Plomin R, DeFries J, McClearn G, McGuffin P, editors. *Behavioral Genetics*. New York, NY: Worth; 2001.
86. Rutter M. Gene-environment interdependence. *Dev Sci*. 2007;10(1):12–18.
87. Spielman RS, McGinnis RE, Ewens WJ. Transmission test for linkage disequilibrium: The insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am J Hum Genet*. 1993;52(3):506–516.
88. Spielman RS, Ewens WJ. The TDT and other family-based tests for linkage disequilibrium and association. *Am J Hum Genet*. 1996;59(5):983–989.
89. Clayton D. A generalization of the transmission/disequilibrium test for uncertain-haplotype transmission. *Am J Hum Genet*. 1999;65(4):1170–1177.
90. Weinberg CR. Allowing for missing parents in genetic studies of case-parent triads. *Am J Hum Genet*. 1999;64(4):1186–1193.
91. Morton NE, Collins A. Tests and estimates of allelic association in complex inheritance. *Proc Natl Acad Sci U S A*. 1998;95(19):11389–11393.
92. Mitchell AA, Cutler DJ, Chakravarti A. Undetected genotyping errors cause apparent overtransmission of common alleles in the transmission/disequilibrium test. *Am J Hum Genet*. 2003;72(3):598–610.
93. Risch N, Merikangas K. The future of genetic studies of complex human diseases. *Science*. 1996;273(5281):1516–1517.
94. Lander ES, Schork NJ. Genetic dissection of complex traits. *Science*. 1994;265(5181):2037–2048.
95. Clark AG, Li J. Conjuring SNPs to detect associations. *Nat Genet*. 2007;39(7):815–816.
96. Fisher R. The correlation between relatives on the supposition of Mendelian inheritance. *Trans Roy Soc Edin*. 1918;52:399–433.
97. Hirschhorn JN, Lettre G. Progress in genome-wide association studies of human height. *Horm Res*. 2009;71 Suppl 2:5–13.
98. Goldstein DB. Common genetic variation and human traits. *N Engl J Med*. 2009;360(17):1696–1698.
99. Burns GL, Walsh JA, Owen SM, Snell J. Internal validity of attention deficit hyperactivity disorder, oppositional defiant disorder, and overt conduct disorder symptoms in young children: Implications from teacher ratings for a dimensional approach to symptom validity. *J Clin Child Psychol*. 1997;26(3):266–275.
100. Pinto LP, Tryon WW. Activity measurements support dimensional assessment. *Behav Modif*. 1996;20(3):243–258.
101. Hudziak JJ, Achenbach TM, Althoff RR, Pine DS. A dimensional approach to developmental psychopathology. *Int J Methods Psychiatr Res*. 2007;16 Suppl 1:S16–S23.
102. Swanson JM, Wigal T, Lakes K. DSM-V and the future diagnosis of attention-deficit/hyperactivity disorder. *Curr Psychiatry Rep*. 2009;11(5):399–406.
103. Asherson P. Attention-deficit hyperactivity disorder in the post-genomic era. *Eur Child Adolesc Psychiatry*. 2004;13 Suppl 1:150–170.
104. Spence JP, Liang T, Liu L, et al. From QTL to candidate gene: A genetic approach to alcoholism research. *Curr Drug Abuse Rev*. 2009;2(2):127–134.
105. Cornish KM, Manly T, Savage R, et al. Association of the dopamine transporter (DAT1) 10/10-repeat genotype with ADHD symptoms and response inhibition in a general population sample. *Mol Psychiatry*. 2005;10(7):686–698.
106. Fisher SE, Francks C, McCracken JT, et al. A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. *Am J Hum Genet*. 2002;70(5):1183–1196.
107. Arcos-Burgos M, Castellanos FX, Pineda D, et al. Attention-deficit/hyperactivity disorder in a population isolate: Linkage to loci at 4q13.2, 5q33.3, 11q22, and 17p11. *Am J Hum Genet*. 2004;75(6):998–1014.
108. Amin N, Aulchenko YS, Dekker MC, et al. Suggestive linkage of ADHD to chromosome 18q22 in a young genetically isolated Dutch population. *Eur J Hum Genet*. 2009;17(7):958–966.
109. Zhou K, Dempfle A, Arcos-Burgos M, et al. Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(8):1392–1398.
110. Asherson P, Zhou K, Anney RJ, et al. A high-density SNP linkage scan with 142 combined subtype ADHD sib pairs identifies linkage regions on chromosomes 9 and 16. *Mol Psychiatry*. 2008;13(5):514–521.
111. Bakker SC, van der Meulen EM, Buitelaar JK, et al. A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: Suggestive evidence for linkage on chromosomes 7p and 15q. *Am J Hum Genet*. 2003;72(5):1251–1260.

112. Faraone SV, Doyle AE, Lasky-Su J, et al. Linkage analysis of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet.* 2008;147B(8):1387–1391.
113. Hebebrand J, Dempfle A, Saar K, et al. A genome-wide scan for attention-deficit/hyperactivity disorder in 155 German sib-pairs. *Mol Psychiatry.* 2006;11(2):196–205.
114. Ogdie MN, Macphie IL, Minassian SL, et al. A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample: Suggestive linkage on 17p11. *Am J Hum Genet.* 2003;72(5):1268–1279.
115. Romanos M, Freitag C, Jacob C, et al. Genome-wide linkage analysis of ADHD using high-density SNP arrays: Novel loci at 5q13.1 and 14q12. *Mol Psychiatry.* 2008;13(5):522–530.
116. Doyle AE, Ferreira MA, Sklar PB, et al. Multivariate genome-wide linkage scan of neurocognitive traits and ADHD symptoms: Suggestive linkage to 3q13. *Am J Med Genet B Neuropsychiatr Genet.* 2008;147B(8):1399–1411.
117. Neale BM, Lasky-Su J, Anney R, et al. Genome-wide association scan of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet.* 2008;147B(8):1337–1344.
118. Cook EH Jr, Stein MA, Krasowski MD, et al. Association of attention-deficit disorder and the dopamine transporter gene. *Am J Hum Genet.* 1995;56(4):993–998.
119. Payton A, Holmes J, Barrett JH, et al. Examining for association between candidate gene polymorphisms in the dopamine pathway and attention-deficit hyperactivity disorder: A family-based study. *Am J Med Genet.* 2001;105(5):464–470.
120. Hawi Z, Dring M, Kirley A, et al. Serotonergic system and attention deficit hyperactivity disorder (ADHD): A potential susceptibility locus at the 5-HT(1B) receptor gene in 273 nuclear families from a multi-centre sample. *Mol Psychiatry.* 2002;7(7):718–725.
121. Turic D, Langley K, Williams H, et al. A family based study implicates solute carrier family 1-member 3 (SLC1A3) gene in attention-deficit/hyperactivity disorder. *Biol Psychiatry.* 2005;57(11):1461–1466.
122. Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry.* 2005;57(11):1313–1323.
123. Purper-Ouakil D, Wohl M, Mouren MC, Verpillat P, Ades J, Gorwood P. Meta-analysis of family-based association studies between the dopamine transporter gene and attention deficit hyperactivity disorder. *Psychiatr Genet.* 2005;15(1):53–59.
124. Yang B, Chan RC, Jing J, Li T, Sham P, Chen RY. A meta-analysis of association studies between the 10-repeat allele of a VNTR polymorphism in the 3'-UTR of dopamine transporter gene and attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet.* 2007;144B(4):541–550.
125. Jaber M, Robinson SW, Missale C, Caron MG. Dopamine receptors and brain function. *Neuropharmacology.* 1996;35(11):1503–1519.
126. Neve KA, Seamans JK, Trantham-Davidson H. Dopamine receptor signaling. *J Recept Signal Transduct Res.* 2004;24(3):165–205.
127. Oak JN, Oldenhof J, Van Tol HH. The dopamine D(4) receptor: One decade of research. *Eur J Pharmacol.* 2000;405(1–3):303–327.
128. Tarazi FI, Zhang K, Baldessarini RJ. Dopamine D4 receptors: Beyond schizophrenia. *J Recept Signal Transduct Res.* 2004;24(3):131–147.
129. Van Tol HH, Bunzow JR, Guan HC, et al. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature.* 1991;350(6319):610–614.
130. Ariano MA, Wang J, Noblett KL, Larson ER, Sibley DR. Cellular distribution of the rat D4 dopamine receptor protein in the CNS using anti-receptor antisera. *Brain Res.* 1997;752(1–2):26–34.
131. Gan L, Falzone TL, Zhang K, Rubinstein M, Baldessarini RJ, Tarazi FI. Enhanced expression of dopamine D(1) and glutamate NMDA receptors in dopamine D(4) receptor knockout mice. *J Mol Neurosci.* 2004;22(3):167–178.
132. Mrzljak L, Bergson C, Pappy M, Huff R, Levenson R, Goldman-Rakic PS. Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. *Nature.* 1996;381(6579):245–248.
133. Noain D, Avale ME, Wedemeyer C, Calvo D, Peper M, Rubinstein M. Identification of brain neurons expressing the dopamine D4 receptor gene using BAC transgenic mice. *Eur J Neurosci.* 2006;24(9):2429–2438.
134. Van Tol HH, Wu CM, Guan HC, et al. Multiple dopamine D4 receptor variants in the human population. *Nature.* 1992;358(6382):149–152.
135. Chang FM, Kidd JR, Livak KJ, Pakstis AJ, Kidd KK. The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Hum Genet.* 1996;98(1):91–101.
136. Ding YC, Chi HC, Grady DL, et al. Evidence of positive selection acting at the human dopamine receptor D4 gene locus. *Proc Natl Acad Sci U S A.* 2002;99(1):309–314.
137. Lichter JB, Barr CL, Kennedy JL, Van Tol HH, Kidd KK, Livak KJ. A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. *Hum Mol Genet.* 1993;2(6):767–773.
138. Wang E, Ding YC, Flodman P, et al. The genetic architecture of selection at the human dopamine receptor D4 (DRD4) gene locus. *Am J Hum Genet.* 2004;74(5):931–944.
139. Wang ET, Kodama G, Baldi P, Moyzis RK. Global landscape of recent inferred Darwinian selection for Homo sapiens. *Proc Natl Acad Sci U S A.* 2006;103(1):135–140.
140. Chen C, Burton M, Greenberger E, Dmitrieva J. Population migration and the variation of dopamine receptor (DRD4) allele frequencies around the globe. *Evol Hum Behav.* 1999;20:309–324.
141. Harpending H, Cochran G. In our genes. *Proc Natl Acad Sci U S A.* 2002;99(1):10–12.
142. Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *J Neurochem.* 1995;65(3):1157–1165.
143. De La Garza R 2nd, Madras BK. [(3H)]PNU-101958, a D(4) dopamine receptor probe, accumulates in prefrontal cortex and hippocampus of non-human primate brain. *Synapse.* 2000;37(3):232–244.
144. Primus RJ, Thurkauf A, Xu J, et al. II. Localization and characterization of dopamine D4 binding sites in rat and human brain by use of the novel, D4 receptor-selective ligand [3H]NGD 94-1. *J Pharmacol Exp Ther.* 1997;282(2):1020–1027.
145. Dolan RJ. Emotion, cognition, and behavior. *Science.* 2002;298(5596):1191–1194.
146. Durston S, de Zeeuw P, Staal WG. Imaging genetics in ADHD: A focus on cognitive control. *Neurosci Biobehav Rev.* 2009;33(5):674–689.
147. Rubinstein M, Phillips TJ, Bunzow JR, et al. Mice lacking dopamine D4 receptors are supersensitive to ethanol, cocaine, and methamphetamine. *Cell.* 1997;90(6):991–1001.
148. Avale ME, Falzone TL, Gelman DM, Low MJ, Grandy DK, Rubinstein M. The dopamine D4 receptor is essential for hyperactivity and impaired behavioral inhibition in a mouse model of attention deficit/hyperactivity disorder. *Mol Psychiatry.* 2004;9(7):718–726.
149. Rubinstein M, Cepeda C, Hurst RS, et al. Dopamine D4 receptor-deficient mice display cortical hyperexcitability. *J Neurosci.* 2001;21(11):3756–3763.
150. Seaman MI, Fisher JB, Chang F, Kidd KK. Tandem duplication polymorphism upstream of the dopamine D4 receptor gene (DRD4). *Am J Med Genet.* 1999;88(6):705–709.
151. Kereszturi E, Kiraly O, Csapo Z, et al. Association between the 120-bp duplication of the dopamine D4 receptor gene and attention deficit hyperactivity disorder: Genetic and molecular analyses. *Am J Med Genet B Neuropsychiatr Genet.* 2007;144B(2):231–236.
152. Yang JW, Jang WS, Hong SD, et al. A case-control association study of the polymorphism at the promoter region of the DRD4 gene in Korean boys with attention deficit-hyperactivity disorder: Evidence of association with the -521 C/T SNP. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(1):243–248.
153. Grady DL, Harxhi A, Smith M, et al. Sequence variants of the DRD4 gene in autism: Further evidence that rare DRD4 7R haplotypes are ADHD specific. *Am J Med Genet B Neuropsychiatr Genet.* 2005;136B(1):33–35.

154. LaHoste GJ, Swanson JM, Wigal SB, et al. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. *Mol Psychiatry*. 1996;1(2):121–124.
155. Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *Am J Psychiatry*. 2001;158(7):1052–1057.
156. Li D, Sham PC, Owen MJ, He L. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Hum Mol Genet*. 2006;15(14):2276–2284.
157. Maher BS, Marazita ML, Ferrell RE, Vanyukov MM. Dopamine system genes and attention deficit hyperactivity disorder: A meta-analysis. *Psychiatr Genet*. 2002;12(4):207–215.
158. Wohl M, Purper-Ouakil D, Mouren MC, Ades J, Gorwood P. Meta-analysis of candidate genes in attention-deficit hyperactivity disorder. *Encephale*. 2005;31(4 Pt 1):437–447. French.
159. Curran S, Mill J, Sham P, et al. QTL association analysis of the DRD4 exon 3 VNTR polymorphism in a population sample of children screened with a parent rating scale for ADHD symptoms. *Am J Med Genet*. 2001;105(4):387–393.
160. Lasky-Su J, Lange C, Biederman J, et al. Family-based association analysis of a statistically derived quantitative traits for ADHD reveal an association in DRD4 with inattentive symptoms in ADHD individuals. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(1):100–106.
161. Mill J, Xu X, Ronald A, et al. Quantitative trait locus analysis of candidate gene alleles associated with attention deficit hyperactivity disorder (ADHD) in five genes: DRD4, DAT1, DRD5, SNAP-25, and 5HT1B. *Am J Med Genet B Neuropsychiatr Genet*. 2005;133B(1):68–73.
162. Todd RD, Neuman RJ, Lobos EA, Jong YJ, Reich W, Heath AC. Lack of association of dopamine D4 receptor gene polymorphisms with ADHD subtypes in a population sample of twins. *Am J Med Genet*. 2001;105(5):432–438.
163. Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am J Psychiatry*. 2003;160(4):636–5.
164. Flint J, Munafò MR. The endophenotype concept in psychiatric genetics. *Psychol Med*. 2007;37(2):163–180.
165. Doyle AE, Willcutt EG, Seidman LJ, et al. Attention-deficit/hyperactivity disorder endophenotypes. *Biol Psychiatry*. 2005;57(11):1324–1335.
166. Rommelse NN. Endophenotypes in the genetic research of ADHD over the last decade: Have they lived up to their expectations? *Expert Rev Neurother*. 2008;8(10):1425–1429.
167. Slaats-Willems D, Swaab-Barneveld H, de Sonneville L, van der Meulen E, Buitelaar J. Deficient response inhibition as a cognitive endophenotype of ADHD. *J Am Acad Child Adolesc Psychiatry*. 2003;42(10):1242–1248.
168. Bidwell LC, Willcutt EG, Defries JC, Pennington BF. Testing for neuropsychological endophenotypes in siblings discordant for attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2007;62(9):991–998.
169. Bitsakou P, Psychogiou L, Thompson M, Sonuga-Barke EJ. Delay aversion in attention deficit/hyperactivity disorder: An empirical investigation of the broader phenotype. *Neuropsychologia*. 2009;47(2):446–456.
170. Kebir O, Tabbane K, Sengupta S, Joobar R. Candidate genes and neuropsychological phenotypes in children with ADHD: Review of association studies. *J Psychiatry Neurosci*. 2009;34(2):88–101.
171. Swanson J, Oosterlaan J, Murias M, et al. Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention. *Proc Natl Acad Sci U S A*. 2000;97(9):4754–4759.
172. Langley K, Marshall L, van den Bree M, et al. Association of the dopamine D4 receptor gene 7-repeat allele with neuropsychological test performance of children with ADHD. *Am J Psychiatry*. 2004;161(1):133–138.
173. Manor I, Tyano S, Eisenberg J, Bachner-Melman R, Kotler M, Ebstein RP. The short DRD4 repeats confer risk to attention deficit hyperactivity disorder in a family-based design and impair performance on a continuous performance test (TOVA). *Mol Psychiatry*. 2002;7(7):790–794.
174. Waldman ID. Statistical approaches to complex phenotypes: Evaluating neuropsychological endophenotypes for attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2005;57(11):1347–1356.
175. Sheese BE, Voelker PM, Rothbart MK, Posner MI. Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Dev Psychopathol*. 2007;19(4):1039–1046.
176. Moffitt TE, Caspi A, Rutter M. Strategy for investigating interactions between measured genes and measured environments. *Arch Gen Psychiatry*. 2005;62(5):473–481.
177. Rutter M, Silberg J. Gene-environment interplay in relation to emotional and behavioral disturbance. *Annu Rev Psychol*. 2002;53:463–490.
178. Brookes KJ, Mill J, Guindalini C, et al. A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. *Arch Gen Psychiatry*. 2006;63(1):74–81.
179. Weindrich D, Laucht M, Esser G, Schmidt MH. Marital discord and early child development. *Acta Paedopsychiatr*. 1992;55(4):187–192.
180. Neuman RJ, Lobos E, Reich W, Henderson CA, Sun LW, Todd RD. Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. *Biol Psychiatry*. 2007;61(12):1320–1328.
181. Langley K, Turic D, Rice F, et al. Testing for gene x environment interaction effects in attention deficit hyperactivity disorder and associated antisocial behavior. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(1):49–53.
182. Seeger G, Schloss P, Schmidt MH, Ruter-Jungfleisch A, Henn FA. Gene-environment interaction in hyperkinetic conduct disorder (HD + CD) as indicated by season of birth variations in dopamine receptor (DRD4) gene polymorphism. *Neurosci Lett*. 2004;366(3):282–286.
183. Bakermans-Kranenburg MJ, Van IMH, Pijlman FT, Mesman J, Juffer F. Experimental evidence for differential susceptibility: Dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Dev Psychol*. 2008;44(1):293–300.
184. Amara SG, Kuhar MJ. Neurotransmitter transporters: Recent progress. *Annu Rev Neurosci*. 1993;16:73–93.
185. Frazer A, Gerhardt GA, Daws LC. New views of biogenic amine transporter function: Implications for neuropsychopharmacology. *Int J Neuropsychopharmacol*. 1999;2(4):305–320.
186. Gainetdinov RR, Jones SR, Fumagalli F, Wightman RM, Caron MG. Re-evaluation of the role of the dopamine transporter in dopamine system homeostasis. *Brain Res Brain Res Rev*. 1998;26(2–3):148–153.
187. Ciliax BJ, Heilman C, Demchishyn LL, et al. The dopamine transporter: immunochemical characterization and localization in brain. *J Neurosci*. 1995;15(3 Pt 1):1714–1723.
188. Freed C, Revay R, Vaughan RA, et al. Dopamine transporter immunoreactivity in rat brain. *J Comp Neurol*. 1995;359(2):340–349.
189. Vandenberg DJ, Persico AM, Hawkins AL, et al. Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. *Genomics*. 1992;14(4):1104–1106.
190. Mitchell RJ, Howlett S, Earl L, et al. Distribution of the 3' VNTR polymorphism in the human dopamine transporter gene in world populations. *Hum Biol*. 2000;72(2):295–304.
191. Fuke S, Suo S, Takahashi N, Koike H, Sasagawa N, Ishiura S. The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. *Pharmacogenomics J*. 2001;1(2):152–156.
192. Mill J, Asherson P, Browes C, D'Souza U, Craig I. Expression of the dopamine transporter gene is regulated by the 3' UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. *Am J Med Genet*. 2002;114(8):975–979.
193. Miller GM, Madras BK. Polymorphisms in the 3'-untranslated region of human and monkey dopamine transporter genes affect reporter gene expression. *Mol Psychiatry*. 2002;7(1):44–55.
194. Greenwood TA, Kelsoe JR. Promoter and intronic variants affect the transcriptional regulation of the human dopamine transporter gene. *Genomics*. 2003;82(5):511–520.

195. Heinz A, Goldman D, Jones DW, et al. Genotype influences in vivo dopamine transporter availability in human striatum. *Neuropsychopharmacology*. 2000;22(2):133–139.
196. van Dyck CH, Malison RT, Jacobsen LK, et al. Increased dopamine transporter availability associated with the 9-repeat allele of the SLC6A3 gene. *J Nucl Med*. 2005;46(5):745–751.
197. Kimmel HL, Carroll FI, Kuhar MJ. Dopamine transporter synthesis and degradation rate in rat striatum and nucleus accumbens using RTI-76. *Neuropharmacology*. 2000;39(4):578–585.
198. Xia Y, Goebel DJ, Kapatos G, Bannon MJ. Quantitation of rat dopamine transporter mRNA: Effects of cocaine treatment and withdrawal. *J Neurochem*. 1992;59(3):1179–1182.
199. Chen CK, Chen SL, Mill J, et al. The dopamine transporter gene is associated with attention deficit hyperactivity disorder in a Taiwanese sample. *Mol Psychiatry*. 2003;8(4):393–396.
200. Gill M, Daly G, Heron S, Hawi Z, Fitzgerald M. Confirmation of association between attention deficit hyperactivity disorder and a dopamine transporter polymorphism. *Mol Psychiatry*. 1997;2(4):311–313.
201. Roman T, Schmitz M, Polanczyk G, Eizirik M, Rohde LA, Hutz MH. Attention-deficit hyperactivity disorder: A study of association with both the dopamine transporter gene and the dopamine D4 receptor gene. *Am J Med Genet*. 2001;105(5):471–478.
202. Todd RD, Jong YJ, Lobos EA, Reich W, Heath AC, Neuman RJ. No association of the dopamine transporter gene 3' VNTR polymorphism with ADHD subtypes in a population sample of twins. *Am J Med Genet*. 2001;105(8):745–748.
203. Curran S, Mill J, Tahir E, et al. Association study of a dopamine transporter polymorphism and attention deficit hyperactivity disorder in UK and Turkish samples. *Mol Psychiatry*. 2001;6(4):425–428.
204. Asherson P, Brookes K, Franke B, et al. Confirmation that a specific haplotype of the dopamine transporter gene is associated with combined-type ADHD. *Am J Psychiatry*. 2007;164(4):674–677.
205. Muglia P, Jain U, Inkster B, Kennedy JL. A quantitative trait locus analysis of the dopamine transporter gene in adults with ADHD. *Neuropsychopharmacology*. 2002;27(4):655–662.
206. Cornish KM, Wilding JM, Hollis C. Visual search performance in children rated as good or poor attenders: The differential impact of DAT1 genotype, IQ, and chronological age. *Neuropsychology*. 2008;22(2):217–225.
207. Todd RD, Huang H, Smalley SL, et al. Collaborative analysis of DRD4 and DAT genotypes in population-defined ADHD subtypes. *J Child Psychol Psychiatry*. 2005;46(10):1067–1073.
208. Loo SK, Specter E, Smolen A, Hopfer C, Teale PD, Reite ML. Functional effects of the DAT1 polymorphism on EEG measures in ADHD. *J Am Acad Child Adolesc Psychiatry*. 2003;42(8):986–993.
209. Sonuga-Barke EJ, Sergeant JA, Nigg J, Willcutt E. Executive dysfunction and delay aversion in attention deficit hyperactivity disorder: Nosologic and diagnostic implications. *Child Adolesc Psychiatr Clin N Am*. 2008;17(2):367–384.
210. Rommelse NN, Altink ME, Arias-Vasquez A, et al. A review and analysis of the relationship between neuropsychological measures and DAT1 in ADHD. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(8):1536–1546.
211. Kahn RS, Khoury J, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. *J Pediatr*. 2003;143(1):104–110.
212. Becker K, El-Faddagh M, Schmidt MH, Esser G, Laucht M. Interaction of dopamine transporter genotype with prenatal smoke exposure on ADHD symptoms. *J Pediatr*. 2008;152(2):263–269.
213. Laucht M, Skowronek MH, Becker K, et al. Interacting effects of the dopamine transporter gene and psychosocial adversity on attention-deficit/hyperactivity disorder symptoms among 15-year-olds from a high-risk community sample. *Arch Gen Psychiatry*. 2007;64(5):585–590.
214. Sonuga-Barke EJ, Oades RD, Psychogiou L, et al. Dopamine and serotonin transporter genotypes moderate sensitivity to maternal expressed emotion: The case of conduct and emotional problems in attention deficit/hyperactivity disorder. *J Child Psychol Psychiatry*. 2009;50(9):1052–1063.
215. Stevens SE, Kumsta R, Kreppner JM, Brookes KJ, Rutter M, Sonuga-Barke EJ. Dopamine transporter gene polymorphism moderates the effects of severe deprivation on ADHD symptoms: Developmental continuities in gene-environment interplay. *Am J Med Genet B Neuropsychiatr Genet*. 2009;150B(6):753–761.
216. Bradley C. The behavior of children receiving benzedrine. *Am J Psychiatry*. 1937;94:577–585.
217. Chavez B, Sopko MA Jr, Ehret MJ, et al. An update on central nervous system stimulant formulations in children and adolescents with attention-deficit/hyperactivity disorder. *Ann Pharmacother*. 2009;43(6):1084–1095.
218. Malone MA, Swanson JM. Effects of methylphenidate on impulsive responding in children with attention-deficit hyperactivity disorder. *J Child Neurol*. 1993;8(2):157–163.
219. Patrick KS, Straughn AB, Perkins JS, Gonzalez MA. Evolution of stimulants to treat ADHD: Transdermal methylphenidate. *Hum Psychopharmacol*. 2009;24(1):1–17.
220. Wilens TE, Biederman J, Prince J, et al. Six-week, double-blind, placebo-controlled study of desipramine for adult attention deficit hyperactivity disorder. *Am J Psychiatry*. 1996;153(9):1147–1153.
221. Spencer T, Biederman J, Heiligenstein J, et al. An open-label, dose-ranging study of atomoxetine in children with attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2001;11(3):251–265.
222. Sonuga-Barke EJ, Van Lier P, Swanson JM, et al. Heterogeneity in the pharmacodynamics of two long-acting methylphenidate formulations for children with attention deficit/hyperactivity disorder. A growth mixture modelling analysis. *Eur Child Adolesc Psychiatry*. 2008;17(4):245–254.
223. Coghill DR, Rhodes SM, Matthews K. The neuropsychological effects of chronic methylphenidate on drug-naïve boys with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2007;62(9):954–962.
224. Cornforth C, Coghill D, Sonuga-Barke E. Sex and age effects in MPH response in ADHD. *Psychopharmacology (Berl)*. 2010; In press.
225. Sonuga-Barke EJ, Coghill D, Markowitz JS, Swanson JM, Vandenbergh M, Hatch SJ. Sex differences in the response of children with ADHD to once-daily formulations of methylphenidate. *J Am Acad Child Adolesc Psychiatry*. 2007;46(6):701–710.
226. Stein MA, McGough JJ. The pharmacogenomic era: Promise for personalizing attention deficit hyperactivity disorder therapy. *Child Adolesc Psychiatr Clin N Am*. 2008;17(2):475–490.
227. Levy F. What do dopamine transporter and catechol-o-methyltransferase tell us about attention deficit-hyperactivity disorder? Pharmacogenomic implications. *Aust N Z J Psychiatry*. 2007;41(1):10–16.
228. Winsberg BG, Comings DE. Association of the dopamine transporter gene (DAT1) with poor methylphenidate response. *J Am Acad Child Adolesc Psychiatry*. 1999;38(12):1474–1477.
229. Roman T, Szobot C, Martins S, Biederman J, Rohde LA, Hutz MH. Dopamine transporter gene and response to methylphenidate in attention-deficit/hyperactivity disorder. *Pharmacogenetics*. 2002;12(6):497–499.
230. Cheon KA, Ryu YH, Kim JW, Cho DY. The homozygosity for 10-repeat allele at dopamine transporter gene and dopamine transporter density in Korean children with attention deficit hyperactivity disorder: Relating to treatment response to methylphenidate. *Eur Neuropsychopharmacol*. 2005;15(1):95–101.
231. Kirley A, Lowe N, Hawi Z, et al. Association of the 480 bp DAT1 allele with methylphenidate response in a sample of Irish children with ADHD. *Am J Med Genet B Neuropsychiatr Genet*. 2003;121B(1):50–54.
232. Stein MA, Waldman ID, Sarampote CS, et al. Dopamine transporter genotype and methylphenidate dose response in children with ADHD. *Neuropsychopharmacology*. 2005;30(7):1374–1382.
233. Joobar R, Grizenko N, Sengupta S, et al. Dopamine transporter 3'-UTR VNTR genotype and ADHD: A pharmacogenomic study with methylphenidate. *Neuropsychopharmacology*. 2007;32(6):1370–1376.

234. Langley K, Turic D, Peirce TR, et al. No support for association between the dopamine transporter (DAT1) gene and ADHD. *Am J Med Genet B Neuropsychiatr Genet.* 2005;139B(1):7–10.
235. McGough J, McCracken J, Swanson J, et al. Pharmacogenetics of methylphenidate response in preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry.* 2006;45(11):1314–1322.
236. Tharoor H, Lobos EA, Todd RD, Reiersen AM. Association of dopamine, serotonin, and nicotinic gene polymorphisms with methylphenidate response in ADHD. *Am J Med Genet B Neuropsychiatr Genet.* 2008;147B(4):527–530.
237. van der Meulen EM, Bakker SC, Pauls DL, et al. High sibling correlation on methylphenidate response but no association with DAT1-10R homozygosity in Dutch sibpairs with ADHD. *J Child Psychol Psychiatry.* 2005;46(10):1074–1080.
238. Zeni CP, Guimaraes AP, Polanczyk GV, et al. No significant association between response to methylphenidate and genes of the dopaminergic and serotonergic systems in a sample of Brazilian children with attention-deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet.* 2007;144B(3):391–394.
239. Hamarman S, Fossella J, Ulger C, Brimacombe M, Dermody J. Dopamine receptor 4 (DRD4) 7-repeat allele predicts methylphenidate dose response in children with attention deficit hyperactivity disorder: A pharmacogenetic study. *J Child Adolesc Psychopharmacol.* 2004;14(4):564–574.
240. Cheon KA, Kim BN, Cho SC. Association of 4-repeat allele of the dopamine D4 receptor gene exon III polymorphism and response to methylphenidate treatment in Korean ADHD children. *Neuropsychopharmacology.* 2007;32(6):1377–1383.
241. Froehlich TE, McGough JJ, Stein MA. Progress and promise of attention-deficit hyperactivity disorder pharmacogenetics. *CNS Drugs.* 2010;24(2):99–117.
242. McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: Consensus, uncertainty and challenges. *Nat Rev Genet.* 2008;9(5):356–369.
243. McCarthy MI, Hirschhorn JN. Genome-wide association studies: Potential next steps on a genetic journey. *Hum Mol Genet.* 2008;17(R2):R156–R165.
244. Maher B. Personal genomes: The case of the missing heritability. *Nature.* 2008;456(7218):18–21.
245. Franke B, Neale BM, Faraone SV. Genome-wide association studies in ADHD. *Hum Genet.* 2009;126(1):13–50.
246. Leung PW, Lee CC, Hung SF, et al. Dopamine receptor D4 (DRD4) gene in Han Chinese children with attention-deficit/hyperactivity disorder (ADHD): Increased prevalence of the 2-repeat allele. *Am J Med Genet B Neuropsychiatr Genet.* 2005;133B(1):54–56.
247. Gabriela ML, John DG, Magadela BV, et al. Genetic interaction analysis for DRD4 and DAT1 genes in a group of Mexican ADHD patients. *Neurosci Lett.* 2009;451(3):257–260.
248. Gordon D, Haynes C, Johnnidis C, Patel SB, Bowcock AM, Ott J. A transmission disequilibrium test for general pedigrees that is robust to the presence of random genotyping errors and any number of untyped parents. *Eur J Hum Genet.* 2004;12(9):752–761.
249. Curtis D, Sham PC. A note on the application of the transmission disequilibrium test when a parent is missing. *Am J Hum Genet.* 1995;56(3):811–812.
250. Swanson JM, Moyzis RK, McGough JJ, et al. Effects of source of DNA on genotyping success rates and allele percentages in the Preschoolers with Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS). *J Child Adolesc Psychopharmacol.* 2007;17(5):635–646.
251. West A, Langley K, Hamshere ML, et al. Evidence to suggest biased phenotypes in children with attention deficit hyperactivity disorder from completely ascertained trios. *Mol Psychiatry.* 2002;7(9):962–966.
252. Pearson TA, Manolio TA. How to interpret a genome-wide association study. *JAMA.* 2008;299(11):1335–1344.
253. Weedon MN, Lango H, Lindgren CM, et al. Genome-wide association analysis identifies 20 loci that influence adult height. *Nat Genet.* 2008;40(5):575–583.
254. Visscher PM. Sizing up human height variation. *Nat Genet.* 2008;40(5):489–490.
255. Pritchard JK, Cox NJ. The allelic architecture of human disease genes: common disease-common variant...or not? *Hum Mol Genet.* 2002;11(20):2417–2423.
256. Schork NJ, Murray SS, Frazer KA, Topol EJ. Common vs rare allele hypotheses for complex diseases. *Curr Opin Genet Dev.* 2009;19(3):212–219.
257. Robinson R. Common disease, multiple rare (and distant) variants. *PLoS Biol.* 2010;8(1):e1000293.
258. Dickson SP, Wang K, Krantz I, Hakonarson H, Goldstein DB. Rare variants create synthetic genome-wide associations. *PLoS Biol.* 2010;8(1):e1000294.
259. DeFries JC, Fulker DW. Multiple regression analysis of twin data. *Behav Genet.* 1985;15(5):467–473.
260. Swanson J, Deutsch C, Cantwell D, et al. Genes and attention-deficit hyperactivity disorder. *Clin Neurosci Res.* 2001;1:217–216.
261. Zametkin A. Dopamine reward pathway in adult ADHD (Letter to editor). *JAMA.* 2010;303(3):232–234.
262. Hay DA, Bennett KS, Levy F, Sergeant J, Swanson J. A twin study of attention-deficit/hyperactivity disorder dimensions rated by the strengths and weaknesses of ADHD-symptoms and normal-behavior (SWAN) scale. *Biol Psychiatry.* 2007;61(5):700–705.
263. Young DJ, Levy F, Martin NC, Hay DA. Attention deficit hyperactivity disorder: A Rasch analysis of the SWAN Rating Scale. *Child Psychiatry Hum Dev.* 2009;40(4):543–559.
264. Aulchenko YS, Struchalin MV, Belonogova NM, et al. Predicting human height by Victorian and genomic methods. *Eur J Hum Genet.* 2009;17(8):1070–1075.
265. Gauderman WJ. Sample size requirements for matched case-control studies of gene-environment interaction. *Stat Med.* 2002;21(1):35–50.
266. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med.* 2008;359(1):61–73.
267. Lou HC. Etiology and pathogenesis of attention-deficit hyperactivity disorder (ADHD): Significance of prematurity and perinatal hypoxic-haemodynamic encephalopathy. *Acta Paediatr.* 1996;85(11):1266–1271.
268. Rosa Neto P, Lou H, Cumming P, Pryds O, Gjedde A. Methylphenidate-evoked potentiation of extracellular dopamine in the brain of adolescents with premature birth: Correlation with attentional deficit. *Ann NY Acad Sci.* 2002;965:434–439.

Pharmacogenomics and Personalized Medicine

Publish your work in this journal

Pharmacogenomics and Personalized Medicine is an international, peer-reviewed, open access journal characterizing the influence of genotype on pharmacology leading to the development of personalized treatment programs and individualized drug selection for improved safety, efficacy and sustainability. This journal is indexed on the American Chemical

Submit your manuscript here: <http://www.dovepress.com/pharmacogenomics-and-personalized-medicine-journal>

Dovepress

Society's Chemical Abstracts Service (CAS). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.