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Low Dopamine Function in Attention Deficit/Hyperactivity Disorder: Should Genotyping Signify Early Diagnosis in Children?

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Abstract

Attention deficit/hyperactivity disorder (ADHD) is present in 8% to 12% of children, and 4% of adults worldwide. Children with ADHD can have learning impairments, poor self-esteem, social dysfunction, and an increased risk of substance abuse, including cigarette smoking. Overall, the rate of treatment with medication for patients with ADHD has been increasing since 2008, with > 2 million children now being treated with stimulants. The rise of adolescent prescription ADHD medication abuse has occurred along with a concomitant increase of stimulant medication availability. Of adults presenting with a substance use disorder (SUD), 20% to 30% have concurrent ADHD, and 20% to 40% of adults with ADHD have a history of SUD. Following a brief review of the etiology of ADHD, its diagnosis and treatment, we focus on the benefits of early and appropriate testing for a predisposition to ADHD. We suggest that by genotyping patients for a number of known, associated dopaminergic polymorphisms, especially at an early age, misdiagnoses and/or over-diagnosis can be reduced. Ethical and legal issues of early genotyping are considered. As many as 30% of individuals with ADHD are estimated to either have secondary side-effects or are not responsive to stimulant medication. We also consider the benefits of non-stimulant medication and alternative treatment modalities, which include diet, herbal medications, iron supplementation, and neurofeedback. With the goals of improving treatment of patients with ADHD and SUD prevention, we encourage further work in both genetic diagnosis and novel treatment approaches.

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Conflict of Interest Statement

Mark S. Gold, MD, discloses no conflicts of interest. Kenneth Blum, PhD, discloses that he is the owner of and employed by Synaptamine Inc; and owns 100% of stock and all patents issued and pending. He also owns 80% of the stock for Igene LLC; 50% of Impact Genomics, LLC; 10% of Victory Nutrition, LLC; and 25% of Kenber LLC. Marlene Oscar-Berman, PhD, discloses no conflicts of interest. Eric R. Braverman, MD, is the owner of Total Health Nutrients, Inc.

Keywords

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Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with onset of symptoms and impairments during childhood.[1] Epidemiologic data suggest that the onset of ADHD may occur as early as 3 years of age, although the disorder is most often identified during the elementary school years. A recent paper by Setlik et al[2] review the American Association of Poison Control Center's National Poison Data System for the years 1998 to 2005 for all cases involving adolescents aged 13 to 19 years. The authors found calls related to abuse by teenagers with prescription ADHD medication rose 76%, which is faster than calls for substance abuse generally, and teen-aged substance abuse. Moreover, during the 8 years of surveyed cases, Setlik et al estimated that prescriptions for teens and pre-teens had increased 133% for amphetamine products, 52% for methylphenidate products, and 80% for both together. Additionally, substance-related abuse calls per million adolescent prescriptions rose 140%.[2] The findings prompted our own review and hypothesis.

Attention deficit/hyperactivity disorder is distinguished by a multitude of interacting multifaceted neurobiological and environmental factors that impact the onset and severity of the disease. Complex polygenic and heterogenic mechanisms contribute to variability in the phenotypic manifestation, comorbidities, and the severity of symptoms in neuropsychiatric and developmental disorders.[3] The persistence of childhood ADHD into adolescence and adulthood has been recognized so that the criterion for what constitutes ADHD has been expanded to include more female adolescents and adults. The larger demographic is being diagnosed earlier and treated for longer periods of time with stimulant medication. Although approximately 3% of US youth are being treated, epidemiologic studies that use standardized diagnostic criteria suggest that as much as 6% of the elementary through high school population may have ADHD.[4] Currently, the number of children who may meet standardized diagnostic criteria could be as high as 9.5%.[4]

Pharmacologic treatment with stimulant medication has provided significant short-term symptomatic relief for patients, which has resulted in academic improvement.[5] Although there are some cases of ADHD diagnosis made with inadequate evaluation, and some cases where stimulant medication is prescribed although alternatives treatment exist, there is little evidence of widespread over-prescription of methylphenidate by physicians, or over-diagnosis, or misdiagnoses of ADHD.[4]

The existence of a problem of stimulant abuse and diversion among ADHD patients is controversial, although, with the expanding use and production of stimulants abuse and diversion could increase.[4] Moreover, the Council of Scientific Affairs of the American Medical Association identified several factors that contribute to existing controversies related to the diagnosis and treatment of ADHD in children.[4] The diagnostic criteria for ADHD are similar to those used for most psychiatric disorders, based on patient history and

behavioral assessment; however, with ADHD: 1) there are no specific radiologic or laboratory tests that can definitively confirm the diagnosis; 2) ADHD is a chronic disorder and requires extended treatment; and 3) treatment includes potentially abusable medications.[2]

The purpose of treatment has extended from a focus on the behavioral aspects of ADHD, to concern about underlying cognitive dysregulation. Stimulants have been studied extensively for the enhancement of executive functions, particularly in scholastic settings.[6–8] There is also a substantial body of literature regarding a role in treatment for other psychopharmacologic agents that can modulate noradrenergic and dopaminergic pathways/processes.[5] In addition, there is promising evidence that newer cholinergic agents may provide other useful treatment alternatives.[9] Patient comorbidities can increase social and psychiatric disabilities if not treated. For example, the presence of ADHD is known to increase patient risk for development of substance use and antisocial disorders in adolescence, and consequently, increases the risk for criminal behavior in both adolescence and adulthood;[10] therefore, to achieve an effective response, sometimes it is necessary to use several medications to treat comorbidities. In any case, appropriate intervention is facilitated by early identification of the disorder to interrupt such consequences of ADHD.

Although there are safe and effective treatment options for school-aged children who have ADHD, little is known about the long-term effects of use of these modalities in preschoolers. Recognition of the developmental course and potential outcomes for preschool children presenting for identification, differential diagnosis, and treatment of ADHD and comorbid conditions will help clinicians. Additionally, knowledge of the safety and efficacy of psychosocial interventions and pharmacotherapy for preschoolers who have ADHD may guide treatment planning for very young children and their families.

Misdiagnosis and Challenges

Discrepancies exist between pediatricians' practice patterns and guidelines of the American Academy of Pediatrics (AAP)[11] for assessing and treating children with ADHD. Additional concerns can be raised regarding access to ADHD treatment for girls, African Americans, and impoverished individuals. Barriers occur at multiple levels, including identification and referral by school personnel because of lack of familiarity with *Diagnostic and Statistical Manual of Mental Disorders* IV[12] (DSM-IV) criteria, and difficulty identifying comorbidities, parents' help-seeking behavior, and acceptance of diagnosis and treatment decisions by the medical provider. Other very serious concerns range from erratic recognition and treatment referral among schools in the same system, pressure to prescribe stimulants from parents and schools, and cultural biases that may deter families from seeking help, or prevent schools from assessing children for ADHD. Publication of the American Association of Pediatrics (AAP) ADHD toolkit[11] provides a resource to assist with implementing the ADHD guidelines in clinical practice; however, even with adherence to the AAP guidelines, misdiagnoses still exist in school systems.[9,11] In sum, establishing appropriate mechanisms to ensure that all children receive appropriate assessment and treatment is an important goal, confirmed by the variety and extent of these challenges.

Psychological Testing and Rating Scales: an Unresolved Path

Throughout the world, millions of people are impaired by ADHD; meanwhile, both the disorder and its prevalence are being reevaluated at the phenotypic level. Pervasive impairment, meaning impairment in > 1 setting, is one of the diagnostic criteria for ADHD set out in DSM-IV[12] classification of ADHD; however, the DSM-IV[12] has undergone extensive reevaluation and formal revision (now, DSM-V[13]).

There are a number of validated evidence-based methods for assessing ADHD, including symptom rating scales based on the DSM-V, ADHD rating scales derived from the DSM, global impairment measures, structured interviews, and behavioral observations.[14] According to Pelham et al,[15] the best assessment method is to obtain both teacher and parent rating scales for each child. When parent and teacher ratings are utilized, there is no further benefit gained by using structured interviews. Additionally, non—DSM-based rating scales correlate highly with DSM scales, are brief, more efficient, and just as effective for diagnosing patients with ADHD. Observational procedures are not practical for clinical use, although they have both validity and treatment utility for individualized assessments of specific target behaviors. It has been correctly suggested that measures that assess impairment and report on functioning in the areas of family, school, and peer group are more useful than nonspecific global measures of impairment, as suggested in the DSM-IV.[12]

Other researchers have evaluated a number of psychological and screening techniques used to diagnose ADHD in children and adults. One group has suggested that the best approach for diagnosing ADHD in children is to incorporate an assessment of health-related quality of life (QoL). Klassen et al[16] pointed out that the current method of treatment for children with ADHD generally ignores the individual's QoL while focusing on decreasing symptoms, enhancing functionality, and improving child and family well-being—because assessment of treatment response to measure symptoms is often limited to using behavior-rating scales and checklists, which are completed by parents and teachers. So much of the focus has been on symptom reduction that less is known about other possible health problems. Questionnaires can be used to gather information across a range of health domains about health-related QoL. In their study, Klassen et al[16] found that children with numerous symptoms of ADHD, as well as children with multiple comorbid disorders had worse psychosocial health-related QoL across a range of domains compared with children without or with only 1 comorbid disorder. In addition, when compared with children with no comorbidity, although psychosocial health-related QoL was significantly worse in children with other comorbidities or oppositional defiant disorder (ODD), it was not worse in children with a learning disorder. The impact of ADHD on health and well-being, symptom severity, and comorbidity has policy consequences for supportive services, including eligibility for special educational instruction.

Barkley[17] correctly pointed out that while ADHD is viewed as a disorder primarily of hyperactive-impulsive behavior and inattention, new theories focus on lack of self-regulation, poor inhibition, and deficient executive functioning as being fundamental to the disorder. Interestingly, poor executive functioning is tied to dopaminergic genetics.[18] Wild-Wall et al[8] showed that children with ADHD were more impaired scholastically in

controlled-response than in automatic-response processing and inhibition. Although deficient error processing may not be a cardinal feature of adolescents with ADHD, it was particularly evident in reduced frontal brain activity in general, and especially in a task that required inhibition of a preferred response.[8]

Studies have revealed that diagnosis of ADHD should include associated behavioral impairments, such as a poor stress response. King et al[19] showed that subjects who maintained their ADHD diagnosis past year 1 of their study, had a blunted response to a stressor compared with subjects who were no longer considered ADHD-disordered 1 year later. The data suggested that simple psychometric testing should be amplified to gather information on an individual's ability to cope with stressful events, as a stress-response deficit may indicate a more developmentally persistent form of the disorder. There are a number of studies that have associated dopaminergic genetics and inability to cope with stressful situations.[20] To assist in the diagnosis of poor executive functioning in adult ADHD, Biederman's group[21] found that a set of 8 empirically derived questions from a 99-item Current Behavior Scale correlated with negative outcomes, raising the possibility of using the subset to identify executive function deficits.

It is noteworthy that the diagnosis of ADHD, both in children and adults, presents a number of difficulties, and many scientists have attempted to investigate and improve current screening and psychometric testing with varying results. One such attempt resulted in a positive outcome using the well-known Rorschach inkblot test.[22] Utilizing the Exner system, the responses of 24 children with a rigorous diagnosis of ADHD were scored and then compared with normative data. Given their greater impulsiveness, poor attention span, and increased responsiveness to external stimuli, the authors predicted that responses by the ADHD group would differ considerably from the controls.[22] However, Rorschach responses of the ADHD group turned out to be similar in many ways to the normative data, but comparisons between small subgroups with and without ODD suggested differences in the frequency of generalized human responses but not aggressive responses.[22]

The quest for new and better diagnostic methods includes the work of Re and Cornoldi,[23] who found that despite the "good" psychometric properties of 2 new scales, parent and teacher agreement was poor. Parents endorsed more symptomatic behaviors in their children than teachers, especially for the hyperactive dimension, although they did not necessarily associate the symptomatic behaviors with the presence of a potential problem. Re and Cornoldi concluded that the low correspondence between teachers and parents demonstrated that ADHD rating scales, although useful screening instruments, are not sufficient for diagnosis and must be combined with other tools.[23] One example of the importance of combining psychometric testing and other measures, such as QoL, is best exemplified by the work of Escobar et al.[24] They found that the subtype of patients with hyperactivity/impulsivity (ADHD-HI) predominance had less disorder severity, fewer comorbid psychiatric disorders, and better quality of life than the predominantly inattentive (ADHD-PI) subtype or the subtype with combined (ADHD-C) symptomatology.

Interestingly, evaluation of the validity and classification utility of the Conner's Continuous Performance Test (CPT) in the assessment of inattentive and hyperactive-impulsive

behaviors in children was unhelpful. Edwards et al[25] found no significant, positive correlations between the CPT parameters and behavioral ratings of ADHD, and teacher and parent ratings of inattentive and hyperactive-impulsive behaviors. In fact, receiver operating characteristic analyses showed the accuracy of CPT to be low.[25] Additionally, according to Schatz et al,[26] ADHD is difficult to diagnose because the symptoms are subjective and precise assessment measures are lacking. Specifically, results from Schatz et al showed that both the Test of Variables of Attention (TOVA) and CPT indicated significant problem areas. The combination of tests found an attention deficit in approximately 85% of children who had been clinically diagnosed with ADHD. The TOVA alone found attention problems in approximately 30% of control children, and no abnormal scores in the controls on the CPT. There may be a risk of over-diagnosis and treatment for ADHD in children generally as the use of computerized testing increases.

Although possibly premature, we propose that truly accurate assessment of patients with ADHD would benefit from a combined approach using questionnaires, clinical evaluation, including genotyping, and new or modified computerized tests of attention. Taking all discussed assessment methods under consideration, the information leaves us uncertain about diagnostic and screening accuracy and favors the emerging concept of *personalized medicine*, using gene testing.

Are Children Over-Diagnosed and Over-Medicated for ADHD?

An estimated 3% to 10% of school children meet the DSM-IV TR criteria for ADHD,[12] however, to be over-diagnosed, the rate of children inappropriately diagnosed with ADHD (false positives) would have to be considerably larger than the number of children with ADHD who are under-identified and not diagnosed (false negatives). Based on the review of recent research on factors that affect diagnostic accuracy and prevalence studies, Sciutto and Eisenberg[27] concluded that claims that ADHD is systematically over-diagnosed cannot be justified. Along similar lines, Froehlich et al[28] provided some interesting prevalence data on ADHD in the United States. Of an estimated 2.4 million US children, aged 8 to 15 years, 8.7% met the DSM-IV TR[12] criteria for ADHD. Of those, 47.9% had been diagnosed previously, and 32.0% of those were consistently treated with ADHD medications during the preceding year. Boys were more likely than girls to be identified, and the wealthiest children from the highest quintile were significantly less likely than children from the lowest quintile to fulfill ADHD criteria. Poor children were less likely to receive consistent pharmacotherapy and less than half of the children who met the criteria reported having received either a diagnosis or treatment.[28]

With Sciutto and Eisenberg's results in mind, Wilens et al[29] conducted a PubMed search and found that while there is misuse of stimulant medication, especially in adolescents—probably due to street diversion and high risk for drug-seeking behavior—other surprising facts supported under-medication and lack of treatment of ADHD. In terms of diversion, there have been variable reports as to the extent, demographics, risk factors, and legal implications. Wilens et al[29] identified 21 studies representing 113 104 subjects. The studies reported rates of past-year non-prescribed stimulant use. In grade-school to high-school aged children, 5% to 9% and in college-aged individuals, 5% to 35% used non-prescribed

stimulants. Diversion rates ranged from 16% to 29% over lifetime use, with students asked to give, trade, or sell their stimulant medications.[29] Recent work suggests that students have reported using stimulants to improve concentration, increase alertness, or to experiment and "get high." Students who have low grade-point averages, are white, and members of fraternities and sororities, use immediate-release compared with extended-release preparations. Individuals who are at highest risk for misuse and diversion of stimulant medication report having symptoms of ADHD.[29]

The question of over-prescription of stimulant medication to patients with ADHD has been evaluated in a non-biased study by Jensen et al.[30] The researchers examined epidemiologic survey data obtained from 1285 children and their parents from 4 US communities. Across the pooled sample of children, 5.1% met full DSM-III-R ADHD criteria. During the previous 12 months, 12.5% of those children who met the criteria had been treated with stimulants. Stimulants had also been prescribed for some children who, although they did not fully meet ADHD diagnostic criteria, presented with high levels of ADHD symptoms, suggesting that treatment with prescription stimulants had been appropriate. Accordingly, from the study data, under-treatment with stimulant medication of certain patient populations needs to be scientifically addressed.[31]

Recent investigations have established that in individuals with continuing ADHD symptoms, up to half have a SUD; a consequence of ADHD is that having the disorder is an independent risk factor for substance abuse·[31] For example, 40% of adults with ADHD are nicotine dependent compared with 26% of the general adult population. It is known that nicotine increases focus[32]; indeed, a variety of the symptoms of ADHD may be similarly ameliorated by other classes of substances of abuse. Impulsive behavior and poor judgment in social settings also increase vulnerability to substance use in individuals with ADHD. The development of substance abuse in adolescents with ADHD is accelerated by an earlier age of onset, more rapid progress from alcohol to another drug of abuse, longer duration of abuse, and a shorter interval between the onset of abuse and drug dependence. The dys-functional and disruptive behavior of individuals with ADHD puts them at greater risk for treatment failure and can interfere with treatment access and response.[31,33]

Taken together these study results raise questions about whom should be prescribed stimulant medication and if there is a population at risk for subsequent drug abuse, how should that population be identified? Early identification of children at risk for psychoactive SUD (PSUD) or Reward Deficiency Syndrome (RDS) by genotyping for "reward" gene(s) polymorphisms seems reasonable.[33] It is important that physicians, parents, and teachers become educated about the risks of stimulant medication and be provided with alternative non-stimulant, effective new medications or non-addicting nutrition-based therapies.

In order to reduce spurious diagnosis and over-prescription of stimulant medication for ADHD in young children (as early as preschool), researchers have sought to subtype ADHD into viable classifications; however, even this logical approach has met with poor diagnostic outcomes. Lahey et al[34] found that although children with the ADHD-C and PI (persistently inattentive) subtypes may be stable enough while young to separate into groups for research, the subtypes were not stable enough to be used to clinically assess individual children.

Lahey and associates[34] observed that over time, children rarely remain in the ADHD-HI subtype; rather, most moved to the C subtype in later years, although some would not remain in either subgroup. The authors concluded that using continuous ratings of hyperactivity-impulsivity symptoms should be considered as an alternative diagnostic qualifier to classifying the nominal subtypes of ADHD in DSM-V. Moreover Lahey's group also reported that both the World Health Organization's International Diseases HyperKinetic Disorder (ICD-10 HKD) and the DSM-IV classifications of ADHD exhibited predictive validity over 6 years; however, children with impairment related to persistent ADHD symptoms appear to be under-identified by the ICD-10 HKD and children who meet DSM-IV criteria for ADHD but not ICD-10 HKD, over time exhibited at least as much impairment as children diagnosed as hyperkinetic.[35]

It is well established that ADHD is a clinically heterogeneous disorder of impulsivity, inattention, and hyperactivity with early-age onset. Based on a consensus in the literature, there is a real need to improve methods for early diagnosis of ADHD and to move toward assessment methods that are less subjective and more biologically objective. Tools available today have come a long way towards recognizing ADHD as a disease in the United States and other countries,[36] but non-subjective means for diagnosis await further research. As family, twin, adoption, segregation analysis, and molecular genetic studies have shown that ADHD has a substantial genetic component; it would be beneficial to provide the clinician and patient with an informative prediction of a potential predisposition to ADHD by developing a validated ADHD gene panel. Sullivan and Rudnik-Levin[31] reviewed genetic studies examining the role of the dopamine (DA) D^2 receptor gene (*DRD2)*—highly associated with drug-seeking behavior[37]—in the etiology of ADHD. Additionally, according to results from molecular genetic studies, Faraone and Biederman[38] cautiously suggested that susceptibility to ADHD may be increased by 3 genes: *DRD4*; the dopamine (DA) transporter (*DAT1)*; and the *DRD2*[33]; however, other genes also have been associated with a predisposition for ADHD. Although controversial, genetic identification of ADHD predisposition represents the possibility of a helpful direction to be taken in the future, along with recognizing the impact of environmental adversity, including low socioeconomic status, marital distress, and complications during pregnancy and delivery on gene expression.[38]

We now focus on a number of candidate genes as putative noninvasive markers for an acceptable gene panel to diagnose a predisposition for ADHD at all age levels in children, even infancy. The most relevant question is whether early identification through genotyping will significantly increase scientific understanding of the neurobiologic components associated with inattention, hyperactivity, and impulsivity? Would such knowledge translate to preventive modalities without stimulant medication side effects, especially during early ontogenetic development? Perhaps insights can be gained through an understanding of neurogenetic aspects of ADHD derived from both human and nonhuman animal studies. Neurogenetic aspects of the disorder are receiving important attention, especially in light of "the rejection of DSM-V by the National Institutes of Mental Health" (NIMH).[39]

Animal Models of Neurobiologic and Neurogenetic Antecedents

The search for the biologic equivalent of ADHD in animals has resulted in numerous interesting and important correlates to behavior and genetics that mimic the human condition. Viggiano, Vallone, and Sadile[40] proposed 3 groups of animal models for characterizing neural substrates for the study of ADHD. The first group was comprised of animals bred to have genetic hyperactivity/inattention; the second group of animal models showed cases of reduced symptoms following pharmacologic intervention; and the third group consisted of spontaneous variations in a random population.[40] The work of Sagvolden et al[41] in 1993 paved the way for finding an ADHD counterpart in nonhuman animals by showing that lever pressing by spontaneously hypertensive rats (SHR) was markedly different from that of 4 other rat strains; SHR pressed the lever more than any of the other groups.

In terms of understanding molecular mechanisms involved in human ADHD, the hypodopaminergic hypothesis, as observed in addictive disorders,[33,41,42] is predictive of associated ADHD behaviors in humans. This work has been further supported by the research of Zimmer et al,[43] using positron emission tomography (PET). To understand the onset and the molecular mechanisms triggering dopaminergic dysregulation in animal ADHD, Leo et al[44] used the SHR animal model, the most widely studied for the disorder. Their results showed that postnatally, tyrosine hydroxylase and *DAT1* expression were significantly reduced in the SHR midbrain and transiently during the first month of development. In addition, when compared with controls, high-affinity DA uptake activity was significantly reduced in synaptosomes obtained from the striatum of 1-month-old SHR. The data suggested that down-regulation of dopaminergic neurotransmission in the midbrain of SHR occurred within a developmentally regulated temporal window. The finding underscored the hypodopaminergic hypothesis in the pathogenesis of ADHD.[45]

For more than a decade, scientists have performed intensive investigations using a number of animal ADHD models in addition to the SHR rat, including Naples High Excitability (NHE) rats,[40] a lesion mouse model,[45] Wistar-Kyoto (WKY)/NCrl and WKY/NHsd rats,[46] and the genetically hypertensive rat.[47] Characterizations of these models have led to an understanding of differential genetic expression of specific dopaminergic genes linked to subtype behaviors observed in the animal models and potential correlates to the human condition. Specifically, the enzyme tyrosine hydroxylase is hyper-expressed in NHE rats and in SHR.[40] The *DAT1* was hyper-expressed in both lines, although DA uptake was reduced due to low *DAT1* activity in the SHR rats. In the striatum and prefrontal cortex of juvenile SHR, DA levels were increased, however, in handled young and non-handled older animals, DA levels were decreased. In the prefrontal cortex of SHR, messenger RNA (mRNA) of the *DRD1* was up-regulated; it was, however, down-regulated in NHE rats. Although the experimental evidence is not conclusive, *DRD1* is likely to be hypo-functioning in SHR, whereas the D_2 DA receptor mRNA is hyper-expressed in NHE rats. Thus, in NHE rats only, the mesocortical system is involved, whereas the mesocortical and mesolimbic DA pathways both appear to be involved in SHR.[41] Moreover, comparisons of SHR with genetically matched controls were investigated by others.[48] Magnetic resonance imaging (MRI) studies of the brains of SHR revealed that they had significantly smaller vermis

cerebelli and caudate putamen. Similar to data seen when patients with ADHD are compared with non-ADHD volunteers, the levels of *DRD4* gene expression and protein synthesis were significantly lower in the prefrontal cortex of SHR. It is possible that rather than a general down-regulation of catecholamine synthesis, the hypo-dopaminergic state in those with ADHD involves down-regulation of DRD4.[48]

The *DRD4* gene is well known as a candidate gene for ADHD from genetic studies that have reported the presence of particular polymorphisms at greater frequency in affected children. A mouse model generated by Avale et al[45] used 6-hydroxydopamine to disrupt neonatal central dopaminergic pathways. The lesioned mice showed signs of hyperactivity that faded after puberty; symptoms of hyperactivity included deficits in continuously performed motor coordination tasks, reduced inhibition in approach/avoidance conflict tests, and paradoxical hypo-locomotor responses to amphetamine and methylphenidate. To determine whether *DRD4* plays a role in these behavioral phenotypes, Avale et al performed 6-hydroxydopamine lesions in neonatal mice lacking *DRD4* (*DRD4*[−/−]). Although tyrosine hydroxylase-positive mid-brain neurons and striatal DA contents were reduced to the same extent in both genotypes, (*DRD4*[−/−]) mice lesioned with 6-hydroxydopamine did not develop hyperactivity. Similarly, the *DRD4* antagonist, PNU-101387 G, prevented hyperactivity in wild-type 6-hydroxydopamine-lesioned mice. These results, a combination of genetic and pharmacologic approaches, demonstrated that the expression of juvenile hyperactivity and impaired behavioral inhibition rely on *DRD4* signaling, which is essential for the manifestation of the features present in the ADHD-like mouse model.[46]

According to the DSM-IV,[12] the 3 subtypes of ADHD each may have unique etiologies and represent separate childhood-onset neurobehavioral disorders. To assess the validity of behavioral responses by subtype in animal models, Sagvolden et al[46] used the WKY/NHsd and WKY/NCrl rats as models for discrete substrains. Behavioral features of the WKY/NCrl rat indicated that it should be a useful model for the ADHD-PI subtype of ADHD. Sagvolden et al supported the conclusion that the best validated animal model of ADHD-C, is the SHR/NCrl; that exhibits impulsiveness, over-activity, and lack of sustained attention.

Altered-reinforcement response is a mechanism that may underlie many of the symptoms of ADHD. Sensitivity to delay of reinforcement was measured by Sutherland et al[47] in two animal models of ADHD, using SHR and a newly proposed model, genetically hypersensitive rats. Wistar- Kyoto and Wistar rats were used as genetic control strains for comparison with SHR and genetically hypersensitive rats. Compared to the genetic control strains, both the SHR and genetically hypersensitive strains assigned significantly more responses to the immediately reinforced lever, demonstrating the applicability of immediate reinforcement in children with ADHD.[48]

Finally, Carey et al,[49] following cross-correlative analyses (connectivity), revealed a modulatory influence of *DRDA* in cross-talk within the anterior forebrain of SHR. Thus, the regulation and differential distribution of *DRDA* subtypes following administration of a DA re-uptake blocker, as well as the different regional connectivity in the target sites—mesolimbic and nigrostriatal DA systems of animal models of ADHD—lend support to the hypodopaminergic hypothesis in the pathogenesis of ADHD in children.

A Case for ADHD-Predisposing Genes

A promising area of research involves the neurogenetics of ADHD, and more specifically, gene polymorphisms associated with various ADHD-related behaviors. Understanding the genetic correlation between certain candidate genes and their association and/or linkage to ADHD should improve diagnosis.

Two main behaviors highly associated with individuals diagnosed with ADHD are disruptive behaviors (ie, criminality) and drug seeking.[50] A Mayo Clinic study revealed that an estimated hazard risk (HR) score, using Cox proportional hazard models adjusted for child's sex, and mother's age and education, resulted in a corresponding HR score for substance-related disorders as high as 4.03.[50] Drug seeking is uniquely important in patients with ADHD due to the acceptable treatment modality of employing stimulant medication, such as methylphenidate, which raises the risk for street diversion and subsequent stimulant-seeking behavior in adolescents. We propose firstly, that genotyping for dopaminergic and other gene polymorphisms coupled with other diagnostic instruments would enhance diagnostic accuracy in patients with ADHD. Secondly, for early prevention, genotyping should be required for specific candidate genes that already have been significantly associated with high-risk drug-seeking behavior, prior to prescribing stimulant medication for children and young adults with ADHD. Ethical and legal issues for gene testing at birth are later discussed in our review.

Ideally, implementation of personalized medicine based on the identification of genes with specific factors that can herald epigenetic changes is in the future. Identification of specific diagnostic biologic markers, target genes, and polymorphisms is the first step in the development of novel drug therapies to treat patients with ADHD and prevent impairment and comorbidity. Using genetic markers to identify at-risk individuals early on and implement treatment sooner would decrease both duration and severity of ADHD symptoms and comorbidities, like SUD. Although more research is needed, we believe that a number of important candidate markers exist and should be considered in the ongoing quest to develop an informative gene map for ADHD predisposition.

Attention deficit/hyperactivity disorder is highly heritable and candidate genes for which an association has been confirmed include *DRD2*, *DAT1*, *DRD4*, *SNAP25*, *DRD5*, *5HTT*, *HTR1B*, *DBH*, *IL2*, *IL6*, *TNF-α*, *BDNF*, *TPH2*, *ARRB2*, *SYP*, *DAT1*, *ADRB2*, *HES1*, *MAOA*, and *PNMT*.[33] These genes independently; confer relatively small risk for development of ADHD; however, a genetic map could be developed that incorporates these candidate genes and possibly others. For example, a number of chromosomal regions containing potential ADHD-predisposing loci including 5p, 6q, 7p, 11q, 12q, 13q, and 17p, some overlapping ≥ 2 studies, have been identified in family-based linkage studies.[51]

The *DRD2* Gene

In 1996, our laboratory first described RDS to define common genetic variants involving the D_2 DA receptor gene (*DRD2*) polymorphisms as a putative predictor of impulsive and addictive behaviors. Our most recent PubMed search found > 3400 published reports on the subject. The A1 allele of the *DRD2* gene, ***Taq1 A1*** allele, may also be involved in comorbid

antisocial personality disorder symptoms,[52] high novelty seeking,[53–56] alcoholism,[37] and addictive behaviors.[20,33] Addictions are increasingly recognized as sharing a common neuroanatomy and neurobiology. Reinforcement of natural rewards, like food and sex, and unnatural rewards, like drugs of abuse, are mediated, in part, in the mesocorticolimbic dopaminergic pathway. The neuronal circuitry involved in multiple addictions also is implicated in a number of neuropsychiatric disorders, including ADHD.[57]

Comings et al[58] reported an association between the ***Taq1 A1*** allele in subjects and their diagnoses of ADHD as early as 1991. However, since then, there have been both positive and negative findings related to the putative association of the *DRD2* A1 allele as a critical polymorphism linked to ADHD and related behaviors. Careful dissection of the existing literature seems to support an association of this gene with specific behavioral subsets in patients with ADHD. In a follow-up to their initial research, Comings et al[59] showed an association of polymorphisms of 3 different dopaminergic genes, *DRD2*, *DBH*, and *DAT1*, in ADHD probands. Each gene correlated significantly with behavioral variables in subjects with ADHD and the 3 genes were examined for additive and subtractive effects, resulting in a linear progressive decrease with less loading in the mean score for each of the 3 gene markers, suggesting that ADHD is polygenic.

Further support for the association of the ***Taq1 A1*** allele and ADHD and related behaviors is derived from a number of studies. Serý et al[60] confirmed that in male subjects, the pathogenesis of childhood ADHD involves the polymorphism ***Taq1 A1*** of the *DRD2* gene. They found an association between the genotype A1/A1 in male subjects with ADHD. Furthermore, Kopecková et al[61] also confirmed the work of Comings et al.[59] Kopecková and colleagues[61] found that in the presence of 1 risk allele in the genes *DRD2*, *5HTT*, and *DAT1*, there was significantly increased ADHD predisposition. The risk for ADHD was also significantly increased at homozygotes for risk alleles in genes *DRD2*, *5HTT*, and *DAT1*. For polymorphisms G444A and C1603T in *DBH*, which were detected by univariant analyses, haplotype analysis was performed and resulted in the conclusion that the risk of ADHD is significantly increased in the presence of allele *DBH* +444A, as well as in the presence of allele *DBH* +1603 T. In fact, when compared with *DAT1*, *HTT*, *5HTT*, and *DBH* genes, 2 A1 alleles of the *DRD2* gene demonstrated the highest risk.

To test the hypothesis that an association with gene variants that code for the DA system would be found in a homogeneous sample of cocaine addicts, particularly those with comorbid childhood ADHD or high impulsivity scores, Ballon and associates[62] genotyped African-Caribbean men who smoked crack cocaine and were dependent on the drug. The investigators studied a potential association of ADHD, impulsivity, and cocaine addiction with the 3 prime untranslated region (3′-UTR) variable number tandem repeats (VNTR) of the *DAT1* gene, the ***Taq1 A1*** variant of the *DRD2* gene, the BalI variant of the *DRD3* gene, and the exon III repeat variant of the *DRD4* gene. They used the Wender Utah rating scale for childhood ADHD, the Barratt Impulsivity Scale, and a Diagnostic Interview of Genetic Studies to assess each subject. Consequently, a positive association with the *DRD2* and *DRD4* polymorphisms was found in the subgroups of patients with childhood ADHD at 53.3%, or with a high impulsivity score at 73%.[58] Genetic studies have associated similar candidate genes with ADHD and tobacco-smoking phenotypes, and individuals with ADHD

symptoms are at increased risk for smoking. McClernon et al[63] used multiple logistic regression analyses to examine relationships between genotype, lifetime history of habitual smoking, and self-reported ADHD symptoms in 1900 unrelated young adults. Polymorphisms in the *DRD2* gene and, among females, in the *MAOA* gene, are also associated with retrospective reports of ADHD symptoms and risk for smoking. The findings suggested that an interaction of ADHD symptoms with genotypes associated with catecholamine neurotransmission contribute to smoking risk.[64]

While not all study results would agree with the assertion of the *DRD2* A1 allele as a risk factor for ADHD in children,[64–66] a study by Nyman et al[67] provided clear genetic evidence for the association of the allele and the *DBH* gene with ADHD risk. Unlike other studies, to minimize genetic heterogeneity, Nyman et al[62] used an adolescent population sample from the Northern Finland Birth Cohort 1986 of > 9000 individuals diagnosed with ADHD (188 cases), characterized by founder effect and isolation. Thus, these investigators genotyped markers in 13 candidate genes, including critical components of DA and serotonin pathways, and reported evidence for the association of ADHD with allelic variants of the *DBH* and *DRD2* genes. Their work has been confirmed by others involved in polygenic investigations resulting in *DRD2* gene positive associations with ADHD and related behaviors.[37,38,68–71]

The DA Transporter Gene

The response of patients with ADHD to medications that inhibit *DAT1*, including methylphenidate, amphetamine, pemoline, and bupropion, led Cook et al[72] to consider *DAT1* as a primary candidate gene for ADHD. Theirs was the first association study to obtain a positive association between VNTR polymorphisms at the *DAT1* locus and DSM-III-R-diagnosed ADHD. Cook et al[72] examined a 3′-VNTR polymorphism at the *DAT1* gene in a sample of 49 patients with ADHD, along with the subjects' parents, using the haplotype relative risk method and observed a significant association between ADHD and the 480-base pair (bp) *DAT1* VNTR allele. The first replication of their work came from Gill et al,[73] who found that the 480-bp allele was significantly and preferentially transmitted to ADHD probands.

Moreover, Vandenbergh et al[74] reported on approximately 60 000 bp of genomic sequence containing the entire *DAT1* gene. The sequence was used to amplify each of the 15 *DAT1* gene exons and several introns. The amplification products were analyzed by single-stranded sequence conformation and/or direct sequencing. Results defined silent-allelic single-nucleotide sequence variants in *DAT1* gene exons 2, 6, 9, and 15. Rare, conservative mutations are identified in amino acids encoded by *DAT1* exons 2 and 8. As the study failed to identify any common protein coding of the *DAT1* sequence variant, Vandenbergh et al[74] suggested that associations between *DAT1* gene markers and ADHD, and with other neuropsychiatric disorders are best reported using other variations that alter *DAT1* expression. Barr et al[75] confirmed linkage of the *DAT1* gene 480-bp VNTR allele and ADHD.

An 8-year longitudinal study examined associations between *DAT1* VNTR, genotypes, and disruptive behavior in 183 children.[76] Half the children at 4-to-6-year follow-up continued to meet the criteria for ADHD; the others were non-referred children included for comparison. The non-additive association for the 10-repeat allele, consistent with several studies, was significant for hyperactivity-impulsivity symptoms. However, also consistent with other studies, hyperactivity-impulsivity and ODD symptoms were also significant in an exploratory analysis of the non-additive association of the 9-repeat allele of *DAT1*. The joint influence of the 9-repeat and 10-repeat alleles may account for the inconsistent association between *DAT1* and child behavior problems in this and other samples.[76] Understanding allelic influences increases the potential of finding risk behaviors associated with ADHD.

It is beneficial to associate specific gene polymorphisms with specific subset behaviors in patients with ADHD. Barkley et al[77] found that the *DAT1* 40-bp VNTR heterozygous 9/10-repeat and the 10/10-repeat pair differed in many respects. At all 3 study follow-ups, presence of the 9/10 repeat in patients was associated with more diagnoses of ADHD and externalizing (oppositional, aggressive) symptoms, lower class rankings in high school, more cross-situational behavioral problems in childhood and adolescence, and poorer mother-teen relations at adolescence. In the control group, participants with the 9/10 pair also had a poorer grade-point average in high school; more teachers rated externalizing symptoms during adolescence, lower work performance, and greater omission errors on a continuous performance test in adulthood.[73] There appears to be reliable association of the *DAT1* 440-bp VNTR 9/10 polymorphism pairing with greater symptoms of ADHD, externalizing behavior from childhood to adulthood, and with family, educational, and occupational impairments.

There are clear associations with ADHD and drug-seeking behavior. In addition, exposure to smoking and alcohol in utero are risk factors that have been often associated with ADHD in human beings and nonhuman animal models. Neuman et al[78] found that the odds of a diagnosis of the DSM-IV ADHD-C subtype were 2.9 times greater in twins who had inherited the *DAT1* 440-bp allele and who were exposed prenatally to cigarette smoking than in unexposed twins without the risk allele. The odds ratios (OR) for the *DRD4* 7-repeat allele were 3.0 for twins who were exposed prenatally to cigarette smoking compared with 2.8 for those who were not exposed in the population-defined ADHD-C subtype. The OR for exposed children with both alleles was 9.0 (95% CI, 2.0–41.5) for the population-defined ADHD-C subtype.[79] Subsequent to the findings by Neumann et al, results from many other studies confirmed the correlation of the *DAT1* gene and ADHD and related behaviors using genome-wide scans and other techniques[61,68,69,78–87]; however, there have also been reports[62,63,82] of no association involving *DAT1* and ADHD.

The DAD4 Receptor Gene

The *DRD4* gene is prominent in psychiatric genetics because it is involved in pharmacologic responses, the physiology of behavior, and psychopathology. The sequence of the gene includes some polymorphisms from class VNTR, including the exon 3, constituted from 2 to 10 copies of repetitive sequences of 48 bp. In the exon 1, another gene variant presents polymorphisms to 12-bp VNTR; and from the promoter region, a C to T transition at

position −521 (C-521T). When compared with the C allele, the −521 T allele can reduce the gene expression efficiency. The *DRD4* gene codes a protein that is distributed in the frontal cortex, striatum, hypothalamus, and hippocampus and is transmembranal of 7 domains.[86]

The *DRD4* polymorphism has been studied in association with schizophrenia, obsessive-compulsive disorder with tics, bipolar manic-depressive disorder, abnormal novelty seeking, and ADHD. The *DRD4* gene is a genetic marker that may have a role in the etiology of different behavioral traits and mental illnesses. The polymorphism of the *DRD4* gene can be a marker used in association and epigenetic studies, and in pharmacogenomics analyses to understand the genetic basis of both mental disorders and traits.[86]

Moreover, in terms of ADHD, the *DRD4* gene is currently of great interest because of variability that is highly functional and has a relevant association with novelty-seeking behavior.[86] La Hoste et al[87] was the first to examine *DRD4* variations in the length of a region containing a 48-bp repeat sequence. In children with ADHD and controls matched for ethnicity, variation of *DRD4* with a 7-fold repeat occurred significantly more often in those with ADHD than in the control sample. Variation of the receptor had formerly been shown to mediate a blunted intracellular response to DA.[88]

One intriguing question relates to the persistence of ADHD from childhood to adulthood. A study that addressed this important question was carried out by Langley et al[89] in ADHD probands and controls. Participants who carried the *DRD4* 7-fold repeat allele showed greater symptom severity at reassessment and follow-up; and over time, decreased ADHD symptom reduction. The hypothesis that certain genes that carry a susceptibility for developing ADHD also influence the developmental course of the disorder is supported by these findings.

It has been suggested that parenting may be pivotal in terms of expression of certain behaviors associated with ADHD in children. One such behavior is aggression manifest as externalizing behavior. Maternal insensitivity predicts externalizing behavior in preschoolers; however, the question of gene—environment having an impact on expression of aggression in children with ADHD prompted Bakermans- Kranenburg and van Ijzendoorn[90] to investigate, with their results pointing to a gene—environment interaction, with the combination of maternal insensitivity and the *DRD4* 7-repeat polymorphism predicting significantly increased risk. The risk was 6-fold compared with controls, and maternal insensitivity was associated with externalizing behaviors, but only in the presence of the *DRD4* 7-repeat polymorphism. The data indicated that susceptibility to insensitive parenting depended on the presence in the offspring of the *DRD4* 7-repeat allele.[91] It is noteworthy that this study provides impetus to physicians and parents to know whether the preschooler has the *DRD4* 7-repeat polymorphism. Having this genetic information has the potential to prompt therapeutic intervention toward an increase in maternal sensitivity in order to reduce preschooler stress.

Although several studies have shown an association between ADHD and the 7-repeat allele of the *DRD4* gene, several studies have not. Thus, the status of the ADHD–*DRD4* association is uncertain. In a meta-analysis of existing data, Faraone et al[91] found support

for the association between ADHD and *DRD4*, although there was no evidence that the association was accounted for by any one study, nor was there evidence for publication bias. In 2009, a meta-analysis performed by Gizer et al[92] further confirmed results of the earlier work and reported that the *DRD4* gene 7-repeat polymorphism was significantly associated with development of ADHD.

Indeed it is noteworthy that the polymorphisms of the *DAT1* gene have been associated with hyperactive re- uptake of DA; however, a sub-sensitive postsynaptic D4 receptor may be associated with the 7-repeat allele of the *DRD4* gene.[79] The 2 factors suggest a neurogenetic mechanism, supporting the hypodopaminergic reward deficiency hypothesis,[33] especially when coupled with the A1 allele of *DRD2* (low number of receptors) in children.[93] It is well established that certain genes code for enzymes involved in the synthesis or metabolism of the catecholamines, DA, and norepinephrine.

Dopamine β-Hydroxylase

Dopamine β-hydroxylase (DBH) is a 290 kDa oxygenase that contains copper, consists of 4 identical subunits, and requires ascorbate as a cofactor for activation.[94] It is a membrane-bound enzyme involved in synthesizing norepinephrine and epinephrine, the only neurotransmitters with molecules small enough to be synthesized inside the vesicles. It is expressed in the chromaffin cells of the adrenal medulla and the nor-adrenergic nerve terminals in the peripheral and central and nervous systems.

Candidate gene analysis was begun in 1988 before neuropsychogenetics emerged as a scientific discipline. Initially, Egeland[95] identified a possible association between the tyrosine hydroxylase enzyme and manic-depressive disorder in the Amish of Pennsylvania.[95] This work was followed by the work of Blum et al (reviewed in[33]) and others. Rogeness et al[96] compared red blood cell (RBC) catechol-O-methyltransferase (COMT), plasma DBH, whole blood serotonin, and platelet monoamine oxidase (MAO) in 2 subgroups of children (undersocialized and socialized) with conduct disorder compared with control children. They found that children diagnosed as having conduct disorder-socialized had significantly higher DBH and COMT activity than children diagnosed as having conduct disorder-undersocialized. The control group also had significantly higher DBH activity than children with conduct disorder-undersocialized.[97]

The first findings associating *DBH* gene polymorphism with ADHD came from the laboratory of Comings et al.[57] They examined polymorphisms of the *DRD2*, *DBH*, and *DAT1* genes in controls, Tourette syndrome probands, and their families. A significant correlation with behavioral variables and each gene was shown in the subjects and additive and subtractive effects were examined. A significant linear association was found between the degree of loading for markers of the 3 genes and the mean behavior scores for 9 of the 20 participants with Tourette syndrome-associated comorbid behaviors. Behaviors that comprise the majority of overt clinical aspects of Tourette syndrome had significant linear associations. The power of each behavioral association was, in order: ADHD, stuttering, ODD, tics, conduct disorder, obsessive-compulsive disorder, mania, alcohol abuse, and

general anxiety.[59] There was a linear progression in the decreased mean score for 16 of the 20 behavior scores, with progressively diminished loading for the 3 gene markers.[60]

In our PubMed search while writing this article, we coupled the terms *DBH* and *ADHD*, and found 39 citations, with both positive and negative findings. One interesting example is the work of Hess et al[97]; although *DBH* C-1021 T polymorphism was not implicated in their findings regarding the pathophysiology of depressive or personality disorders, they did find that homozygosity at that locus appeared to increase risk for impulsive and aggressive personality traits and related disease states, including adult ADHD.

In 2008, Kopecková et al,[61] following a univariant analysis by haplotype, reported that ADHD risk was significantly increased in the presence of allele *DBH* +1603 T (OR, 15) and the allele *DBH* +444A for polymorphisms G444A and C1603T. Barkley et al[77] later found that when homozygous, the *DBH* ***Taq1 A2*** allele was associated with increased hyperactivity in childhood, earning less money performing a card-playing task in adulthood, and pervasive behavior problems during adolescence. Poorer test scores were also found in adolescence, but only in the hyperactive group of participants who were homozygous for the allele. A recent meta-analysis reported the association of *DBH* and ADHD etiology,[92] and others[67,81,85] have reported similar associations.

Catechol-O-Methyl Transferase Gene

Catechol-O-methyl transferase (COMT) is an enzyme that deactivates catecholamines like DA, epinephrine, and norepinephrine. First discovered by Nobel Laureate Julius Axelrod in 1957,[98] COMT is the target of several pharmaceutical drugs, as catecholamine regulation is impaired in a number of medical conditions. An intracellular enzyme, COMT is involved in the inactivation of the catecholamine neurotransmitters (DA, norepinephrine, and epinephrine) in the postsynaptic neuron. The catecholamine is degraded when a methyl group, donated by S-adenosyl methionine, is introduced.

Compounds including catecholestrogens and catechol-containing flavonoids, which have a catechol structure, are substrates of COMT. Levodopa is a catecholamine precursor, an important substrate of COMT. The action of levodopa can be prolonged by COMT inhibitors, such as entacapone. For this reason, entacapone is widely used as an adjunct to levodopa therapy. Levodopa therapy is further optimized with the addition of an inhibitor of dopa decarboxylase (carbidopa or benserazide) and this triple therapy is becoming standard treatment for patients with Parkinson’s disease. Fortunately, because of the many side effects of the drug, levodopa has never been prescribed to treat ADHD.

Specific reactions catalyzed by COMT include norepinephrine to normetanephrine; epinephrine to metanephrine; dihydroxyphenylethylene glycol to methoxyhydroxyphenyl-glycol; and 3,4-dihydroxymandelic acid to vanillylmandelic acid. The gene *COMT* codes the COMT protein and is associated with allelic polymorphism, such as the well-studied Val158Met; others are rs737865 and rs165599, which have been studied to determine an association with personality traits.[99]

Val158Met Polymorphism

A common normal variant of the *COMT* gene, Val158Met (rs4680) is a functional single-nucleotide polymorphism that has been shown to affect cognitive task performance broadly related to executive functioning,[100] including abstract thought, set shifting, the acquisition of rules or task structure, and response inhibition.[101] The polymorphism in the *COMT* gene called Val158Met is named for the amino acid valine substituted for methionine at codon 158. The valine variant has been shown to catabolize DA ≤ 4 times faster than the methionine variant; thus following neurotransmitter release, the presence of Val158Met will result in a significant reduction of synaptic DA and reduced dopaminergic stimulation of the post-synaptic neuron. A consequence is that during certain cognitive tasks, to achieve enough postsynaptic activation, neurons with valine-variant *COMT* demonstrate higher levels of neuron firing. Impairments in types of cognitive tasks linked to the *COMT* gene are thought to be mediated by an effect on DA signaling in the frontal lobes.

Such findings led a number of investigators to perform various association and linkage studies in an attempt to determine the role of COMT in ADHD and related behaviors. One important caveat in studies involving ADHD may reside in mixing of subset behaviors into the same generalized category called the “ADHD phenotype.” It is well known, for example, that aggressive and covert conduct disorder symptom subtypes are etiologically distinct. The results of studies by Qian et al[102] highlight the potential etiologic role of COMT in ADHD with comorbid ODD and its predominately inattentive subtype in male Chinese subjects. The low-activity Met allele was associated with the ADHD-IA subtype, whereas ADHD with comorbid ODD was associated with homozygosity of the high-activity Val58Met allele. There was no evidence of association between ADHD with comorbid ODD or the ADHD-1A subtype and the *MAOA*-upstream (u)VNTR variant. Moreover, the etiologic role of COMT for children with ADHD and potentially for substance-seeking behavior as highlighted by the Lahey’s study.[35] The failure to observe an interaction between COMT and MAOA[31] suggests that epistasis between *COMT* and *MAOA* genes and the phenotype of ADHD-IA with comorbid ODD is not influenced in a clinical sample of Chinese male subjects, supporting the notion of distinct subsets of behavior associated with the ADHD phenotype.[32]

Monoamine Oxidases

Monoamine oxidases were discovered in the liver by Mary Hare and named *tyramine oxidase*.[103] The MAOs are enzymes that catalyze the oxidation of monoamines found in mitochondria in most cell types bound to the outer mitochondrial membrane. There are 2 types of MAOs in humans, MAO-A and MAO-B; both are found in neurons and astroglia and outside of the central nervous system. The enzyme MAO-A is found in the gastrointestinal tract, liver, and placenta and is particularly important for the catabolism of monoamines in ingested food. The enzyme MAO-B is found mostly in blood platelets. When MAOs catalyze the oxidative deaminate of monoamines, oxygen removes an amine group from a molecule and forms aldehyde and ammonia. Monoamine oxidases are classified as flavoproteins because they contain amine oxidoreductases and the covalently bound cofactor flavin adenine dinucleotide (FAD). The MAOs display different specificities

to accomplish the inactivation of monoamine neurotransmitters. Specific reactions catalyzed by MAO include epinephrine or norepinephrine to 3,4 dihydroxymandelic acid; metanephrine or normetanephrine to vanillylmandelic acid; dopamine to dihydroxyphenylacetic acid; and 3-methoxytyramine to homovanillic acid. Additionally, serotonin, epinephrine (adrenaline), and (noradrenaline) are mostly broken down by MAO-A; phenethylamine is mainly broken down by MAO-B, and both forms break down dopamine equally.

The MAOs play a vital role in the inactivation of neurotransmitters and MAO dysfunction is considered to be the culprit in the pathoneurology of numerous psychiatric disorders. Abnormalities that result in too little or too much MAO activity have been associated with depression,[104] migraines, substance abuse, schizophrenia, ADD,[105] and inconsistent sexual maturation.[3,33,37,38,57,58] The MAO inhibitors are, therefore, one of the major drug classes prescribed for treating depression, although the risk of MAO interaction with other drugs or diet make them a last-line treatment. Excessive levels of serotonin may lead to serotonin syndrome; excessive levels of catecholamines may lead to a hypertensive crisis. Researchers using PET have seen that tobacco use heavily depletes MAO.[106]

The locus for genes that encode MAO-A and MAO-B is the short arm of the X chromosome; the genes are side-by-side and have about a 70% sequence similarity. With a mean heritability of 0.75, ADHD is generally deemed to be a highly heritable disorder. Both the A and B types of MAO have long been considered candidate pathological substrates for ADHD, and recently, *MAO* genes that code for both enzymes A and B have been examined as moderators of the disorder.[107]

A study based on the Dunedin cohort of maltreated children reported in *Science* (August 2002) concluded that maltreated children with the high-activity polymorphism of the *MAOA* gene were less likely to develop antisocial conduct disorders than maltreated children with the low-activity variant.[108] The low-activity variant was present in a total of 37% of 442 total males studied (maltreated or not); however, 11 of the 13 maltreated males with the *MAOA* gene low-activity variant had adolescent conduct disorder diagnoses, and 4 had been convicted for violent offenses. This suggested a mechanism whereby the *MAOA* gene low-activity variant decreased ability to quickly degrade the synaptic neurotransmitter norepinephrine, resulting in prolonged sympathetic arousal and rage, which is further supported by the other work related to dopaminergic genetics, catabolism, and pathological aggression.[109] Researchers have also uncovered a possible link between the *MAOA* genotype and a predisposition to novelty seeking.[110]

In 2006, a New Zealand researcher, Dr Rod Lea, said that a particular variant of *MAOA* gene called “the warrior gene” was over-represented in the Maori populations.[111] Earlier studies also found that the proportion of gene polymorphisms differ within ethnic groups, such as the case of the low-activity *MAOA* promoter variant carried by 33% of whites/non-Hispanics and in 61% of Asians/Pacific Islanders.[112] Pathological aggression may also be associated with polymorphisms of the *COMT* gene.[113]

Other researchers have studied *MAO* gene polymorphisms and associations with ADHD. Interestingly, Li et al[107] examined an association between outcomes for adolescents with ADHD and *MAO* gene polymorphisms. They included the 1460 C > T polymorphism in exon 14 (rs1137070) and the 941 T > G polymorphism in exon 8 (rs1799835) of the *MAOA* gene. Li et al also examined the 2327 T > C polymorphism in exon 15, the A > G polymorphism in intron 13 (rs1799836), and the C > T polymorphism in the 3′UTR (rs1040399) of the *MAOB* gene. Significant associations were observed between the *MAOA* gene polymorphisms and ADHD remission. Others have also replicated this work and have favored the association of both the *MAOA* and *MAOB* genes as potential high-risk predisposing genes for ADHD pathology.[114,115] Finally, Malmberg et al[116] found an association in girls, between symptoms of ODD and low-platelet MAO-B activity. In boys, disruptive behavior was associated with hemizygosity for the short *MAOA* VNTR allele.

Proposed ADHD-Risk Gene Map

Since Blum et al[117] in 1990, many candidate genes have been associated with ADHD and related behaviors. We believe that major inconsistencies among the findings have to do with understanding the endophenotype (or intermediate phenotypes that are heritable, quantitative biologic variations, or deficits embedded within biologic disease markers). Non-disease phenotypes need to be used as controls, especially for comparative results in association studies. A good example of spurious results can be seen in studies concerning the association of the DRD2 gene polymorphisms and RDS.[118]

Our laboratory, in agreement with others, has called for super controls to end the potential for controls having the same condition (RDS behaviors) that one is trying to associate with specific gene polymorphisms in study subjects.[109] Despite technologic advances in genetic mapping, the field of psychiatric genetics has been fraught with inconsistencies. The ADHD phenotype is complex to dissect with respect to the existence of phenocopies, genetic heterogeneity, and the difficulties associated with defining the disorder in a way that covers all ages and both sexes adequately. To have strong genetic studies, the controls utilized in studies must be disease-free. Until now, this has not been easily accomplished and has caused quite a dilemma.

The reward pathways of the brain, dopaminergic and opioidergic, are critical for survival as they provide the pleasure that is derived from natural rewards, like eating and reproduction, and involve the release of DA in the frontal lobes and the nucleus accumbens core (NAc). The same DA production and release that results in pleasure sensations can be produced by unnatural rewards, like alcohol, cocaine, heroin, methamphetamine, nicotine, marijuana, and other drugs, and by other risk-taking behaviors and compulsive activities, such as overeating, and harmful sex. Not all individuals become addicted to substances or behaviors, so the question is: What are the elements that separate those who become addicted from those who do not? In the past, it was assumed that the behaviors were voluntary and that environmental factors played a role. Following the advent of psychiatric genetics, researchers found a significant genetic component associating such behaviors with ≥ 1 genes or genetic variables. Plausibly, genetic associations can map individual genetic risk for such behaviors.

The primary neurotransmitter of the reward pathway is DA, therefore, logical marker candidates for such a map would be genes that code for the synthesis, degradation, receptor formation, and transport of DA. Dopamine metabolism and DA neurons are, however, modified by serotonin, norepinephrine, GABA, opioid, and cannabinoid signaling. Archer et al[3] proposed that individuals are at risk for RDS (abuse of substances or behaviors to make up for DA deficiency) if they have defects in any of the genes needed for normal functioning of the DA neurotransmitters. The gene *DRD2* is an important reward gene candidate. Since its discovery, research studies have shown that the ***Taq1 A1*** allele of the *DRD2* gene is associated in a variety of disease states, including alcoholism and other substance abuse, obesity, and compulsive behaviors. Several personality traits, including those seen with ADHD, have been associated with the ***Taq1 A1*** allele of the *DRD2* gene. A range of other DA, opioid, cannabinoid, norepinephrine, inflammatory pro genes, and related genes have since been added to the list. Attention deficit/hyperactivity disorder is inherited and polygenetic, and, like other behavioral disorders, each gene is responsible for a small percentage of the variance (Table 1[119]).

In ADHD, the many genes that affect DA include norepinephrine, serotonin, GABA, and other neurotransmitters; their respective synergistic interaction means that ADHD is a polygenic disorder. Some of the specific loci involved include DA genes—*DRD2*, *DRD4*, *DRD5*, and *DAT1*; norepinephrine and epinephrine genes—*DBH*, norepinephrine transporter; *MAOA*, *COMT*, *ADRA2A*, *ADRA2C*, *PNMT*; serotonin genes—*TDO2*, *HTR1A*, *HTR1DA*, serotonin transporter; GABA genes—*GABRB3*; opioid receptor(s)—*MOR*, *KOR*, and the androgen receptor. The following model is consistent with present knowledge about ADHD and includes: 1) the existence of a broad range of comorbid behaviors (depression, anxiety, substance abuse, learning, conduct, and oppositional-defiant disorders) in ADHD probands and their parents; 2) a greater incidence of ADHD in the families of ADHD probands; 3) lack of success in the search to find associated genes for Tourette syndrome using linkage analysis, despite the close relationship of the syndrome with ADHD; 4) the correlation between tics and D_2 DA receptor density in Tourette syndrome; 5) brain imaging studies showing hypometabolism of the frontal lobes; 6) the relationship between D_2 DA receptor density and regional blood flow; 7) the motor hyperactivity of DA transporter and *DRD3*; 8) the LeMoal and Shaywitz DA deficiency animal models of ADHD; 9) the norepinephrine models of ADHD; 10) the inability to explain ADHD based on a single defective neurotransmitter; 11) the response of ADHD to DA and alpha 2-adrenergic agonists; 12) the small percentage of the variance of specific behaviors accounted for by each gene, and numerous other aspects of ADHD; and 13) increased susceptibility to substance seeking behavior linked to D2 gene polymorphisms.

All behaviors, socially acceptable or not, originate from an individual's genetic makeup at birth; this genetic predisposition interacts with the environment.[3] Combinations of genes and polymorphisms are expressed differently based on numerous environmental factors, including contaminant exposure, nurturing, family, friends, educational and socioeconomic status, the availability of psychoactive substances, and compulsive and impulsive behaviors. Genes and mRNA modify neurotransmitter interaction at the brain reward center located in the mesolimbic system and result in the release of DA.[3]

Individuals with ADHD carry the core of predisposition to these behaviors, a set of polymorphic dopaminergic genes that result in hypodopaminergic function.[57] The mechanisms of hypodopaminergic function in ADHD include 1) reduced number of D^2 DA receptors; 2) reduced synthesis of DA (by *DBH*); 3) reduced net release of presynaptic DA (from, eg, *DRD1*); and 4) increased synaptic DA clearance as a result of extra DA transporter sites (*DAT1*). Hypodopaminergic function causes people with ADHD to be more vulnerable to addictive behaviors. The presence of ADHD involves shared genes and their expression via mRNA, along with behavioral tendencies that can induce presynaptic DA release. Such behaviors include dependence on alcohol and psychoactive drugs, altered opiate receptor function, carbohydrate bingeing, obesity, pathological gambling, pathological aggression, vulnerability to stress, and certain personality disorders, including novelty seeking and sex addiction. Dopamine dysregulation is also associated with spectrum disorders, such as Tourette syndrome and autism. Both Tourette syndrome and autism have been associated with other rare gene mutations; one such association is with neuroligin 4 (NL1GN4), a member of a cell-adhesion protein family that has maturation and functional roles in the neuronal synapses.

Future Perspective: Extending Genotyping for Predisposing Risk of ADHD and Genomics of Treatment

First, it must be understood that a major risk for society is the link between ADHD and substance-seeking vulnerability. Biederman et al[21] and others,[77,81,102] provided insight into this known, associated risk. A robust and bi-directional comorbidity between ADHD and PSUD, including alcohol or drug abuse, has been reported consistently in the literature, based almost exclusively on male-only samples. Accordingly, Biederman et al[21] found that the risk for ADHD in relatives of ADHD female probands was significantly increased, independent of the comorbidity with PSUD. Similarly, female PSUD probands had a significantly increased risk for PSUD in relatives, regardless of ADHD status. Although the variable expressivity as a possible hypothesis could not be ruled out, the hypothesis that these disorders are independently transmitted is suggested by familial risk analysis that looked at the association between ADHD and PSUD in adolescent females.[120] This finding is not consistent with previously reported patterns of familial associations between ADHD and PSUD found in adolescent males, and continues to be a real risk.[120]

It is equally important to provide evidence for and against stimulant treatment of ADHD in preschoolers, children, adolescents, and adults. The literature is exhaustive and includes pharmacogenetic and pharmacogenomic solutions. A number of published reports provide a sampling of the current consensus on the subject.[121–125] Certainly the question of dopaminergic-agonist therapy has intrigued many scientists. In fact, recently, Ruocco and associates[126] have addressed this precise question using juvenile NHE rats treated intranasally (both nares) with either vehicle or DA (0.075 mg/kg, 0.15 mg/kg, and 0.3 mg/kg) daily for 15 days. One hour after treatment, the rats were tested in the Làt maze on Day 14, and 1 day later, in an 8-arm radial maze. In the Làt maze, the highest dose of DA (0.3 mg/kg) decreased horizontal and vertical activity during the first 10 minutes of the test. In the radial maze, an index of selective spatial attention, at the intermediate dose of DA

(0.15 mg/kg), the number of arms visited before the first repetitive arm entry significantly improved. Thus, in an animal model of ADHD, intranasal application of DA at the highest dose reduced hyperactivity, whereas attention improved at the intermediate dose. The authors suggested that their results highlighted the potential of employing intranasal DA for therapeutic purposes.[126]

Recent advances in the treatment of patients with ADHD have involved expanding pharmacologic perspectives to include both noradrenergic and dopaminergic agents. Therapeutic directions in ADHD, indicated by a review of animal and human pharmacologic studies,[127] suggest that the D1 receptor is a specific site for dopaminergic regulation of the prefrontal cortex, but that for beneficial effects on working memory to occur, optimal levels of DA are required. Other studies[128] in human and nonhuman animal models indicate that the alpha-2A receptor is another important target for prefrontal regulation.

Currently, available dopaminergic and noradrenergic agents for treating patients with ADHD have overlapping but different actions in the subcortical centers and prefrontal cortex. Stimulants act on D1 receptors in the dorsolateral prefrontal cortex; they may also effect D2 receptors in the corpus striatum, and have serotonergic effects at orbitofrontal areas. At therapeutic levels, DA stimulation (through *DAT1* inhibition), decreases noise level by acting on subcortical D2 receptors, while norepinephrine stimulation (through alpha-2A agonists) increases signal by acting preferentially in the prefrontal cortex, probably at *DRD1* sites.

Alpha-2A noradrenergic transmission is mostly limited to the prefrontal cortex, whereas alpha-2B and alpha-2C agonists may have broader effects; the latter 2, however, are more likely to have motor or stereotypic side effects. According to Levy,[129] data suggest a possible hierarchy of specificity in medications used for ADHD treatment, with guanfacine probably being the best treatment for working memory and prefrontal attention deficits. Stimulants may have broader dose-dependent effects on both motor impulsivity and vigilance, while atomoxetine, via noradrenergic transmission, may affect attention, anxiety, social affect, and sedation.

We do not agree with the use of DA (ie, levodopa) as a therapeutic agent, however, research does support the potential administration of natural dopaminergic agonistic therapy. For example, the Synaptamine Complex (KB220 and KB220Z) and other non-stimulant agents have been observed to reduce stress, PSUD, and relapse, among other ADHD-associated behaviors in patients.[21,34,107] It is reasonable to theorize, awaiting further double-blind comparisons to standard stimulant medication(s), that the use of natural dopaminergic agonist therapy could be beneficial, especially when coupled with early diagnosis, using both candidate gene polymorphisms and psychometric testing.[130–152] Because of the potential for misdiagnosis of ADHD in children when employing only the clinically standardized tools of ADHD diagnosis (eg, interviews), we propose serious consideration be given to genotyping (Table 1[119]).

The next question is: If early diagnosis is beneficial for positive treatment outcomes, then when should the scientific community adopt the proposed paradigm shift using genotyping?

There are laws and federal and state mandates that require gene testing at birth. The reasoning behind use of genotyping for diagnosing ADHD is that, unlike certain rare diseases where there are limited treatment options (ie, Huntington's disease, phenylketonuria, congenital hypothyroidism, galactosemia, sickle cell anemia), ADHD does have effective treatment options. Although having ADHD is not life-threatening, related gene testing could allow for early diagnosis and non-pharmacologic interventions. We might find that exercise, diet, parent-training, computer-assisted learning, or a safe non-stimulant nutraceutical dopaminergic agonist therapy reduces the impact of the gene abnormality. We would have to weigh the stigma and other factors, but it may be realistic to ask whether it is prudent to use such techniques to clarify the diagnosis and follow outcomes. It is known that ADHD diagnosed in children extends into adult ADHD, and if not treated appropriately, will result in PSUD, among other behaviors. To suggest that children, even at birth should be screened for potential ADHD risk alleles may seem too bold and premature. It may, however, be intelligent to at least explore the possibility in the future. In this regard, Bill Moyers of PBS has done some excellent work investigating the plight of future America, suggesting that we should diagnose ADHD very early in life (if not at birth), and couple diagnosis with a safe side-effect-free treatment.

Gene Testing at Birth

State newborn screening tests are performed within the first few days of life to screen for serious, life-threatening diseases. Every baby born in every US state is tested, even if the baby seems healthy and has no symptoms of health problems. State laws mandate that babies be tested between 2 and 7 days of age. Recessive diseases usually occur when both healthy parents naively carry a gene for a recessive disorder and both pass the gene to their baby. The baby who inherits 2 copies of the recessive gene is born with the condition. The resulting diseases are often treatable with special diets and/or medications. Early detection of these diseases can prevent mental retardation, other disabilities, and mortality. Pediatric metabolic specialists and nutritionists are required for conditions that necessitate specified diets, like phenylketonuria (PKU) and galactosemia. Parents require education regarding appropriate foods and blood and urine monitoring to ensure that the infant remains unharmed by the disease. Could this same level of expertise be adopted in testing for and treating infants with ADHD predisposition, as well?

Genetic Testing and Screening

Human medical genetics deals with the role of genes in illness. Traditional analysis of the genetic contribution to human characteristics and illness and has involved 3 types of disorders: 1) disorders due to changes in single genes; 2) polygenic disorders influenced by > 1 gene; and 3) chromosomal disorders. Genetic screening[153] differs from genetic testing. Although the terms are used interchangeably, genetic screening is carried out on a defined (by age, sex, or other risk factor) section or a subgroup of the population, in which certain disabilities may be the result of genetic factors. *Genetic screening* has been defined as: "… a search in a population to identify individuals who may have, or be susceptible to, a serious genetic disease, or who, though not at risk themselves, as gene carriers may be at risk of having children with that genetic disease."[154] On the other hand, *genetic testing* has been

defined as: "… the analysis of a specific gene, its product or function, or other DNA and chromosome analysis, to detect or exclude an alteration likely to be associated with a genetic disorder," and results in a definitive diagnosis for the individual involved.[152,153]

Screening programs are crucial in public health care systems where they can identify individuals at serious risk and prevent morbidity by timely treatment. In this regard, the goals are: 1) to improve the health of persons with genetic disorders; 2) to facilitate informed choices regarding reproduction for the carriers of abnormal genes; 3) to alleviate the concerns of families and communities about serious genetic disease: and 4) reduce public health costs. For those institutions seeking to reduce cost and better manage their public health exposure, genetic screening is a good option. There are some concerns that genetic testing of the human population could slide into eugenics. Eugenics was a social movement that sought to improve the genetic features of human populations through sterilization and selective breeding (for example, sterilization of the mentally "unfit" practiced in some states until the 1970s).[154] This is not the case for genetic screening and testing for the ADHD phenotype, suggested in order to facilitate early and accurate diagnosis and preventive treatment.[26,155,156] Nonetheless, it is noteworthy that the negative impacts of genetic screening have ethical implications—they can be separated into personal and societal categories of harm.

Personal harm concerns the psychological well-being of the individual and may include increased personal anxiety about labeling, health, and decisions related to infant and prenatal testing. Societal harm, perhaps with more powerful ethical considerations, involves the interaction of society with the individual, with regard to employment prospects, access to health insurance, life insurance, and other benefits, as well as eugenics.

Ethical Considerations

A variety of ethical issues will need to be confronted following the advent of psychiatric genetics. As knowledge grows regarding the genetic basis of psychiatric disorders, the accepted etiology of most psychiatric disorders will be that environmental factors interact with multiple predisposing genes. As tests for the genes involved have become more readily available for screening in adults, children, and for prenatal testing, aside from using genetic screening to diagnose predisposition and design treatment for psychiatric illnesses, pressures to use such testing for premarital screening and selection of potential adoptees may develop.

Challenges of genetic testing include the impact that such knowledge can have on the individual, on one's sense of self; misunderstanding of the consequences of genetic predisposition and discrimination; and using genetic information to deny persons access to, for example, employment and insurance. Most states have some legislation aimed at preventing discrimination, however, coverage by most state law is spotty. Now with the US Genetic Information Non-Discrimination Act (GINA) of 2008 in place, individuals are protected by federal law. Physicians may find that they have new duties created by reports of genetic test results, including addressing common misunderstandings of the consequences of possessing an affected allele and alerting third parties who may share the patient's genetic endowment.

Some questions about appropriate disclosure of information to individuals and their family members during the process of genetic research have risen. Germane information about the genes that are being studied, how the subjects of the research are defined, and how information is collected from the proband's family members should be addressed. In the near-term, medical professionals will need to attend to and resolve these dilemmas, as neglecting them will leave others to make rules to control medical psychiatric practice, including psychiatric genetic research.[157]

Ethical concerns arise over the genetic testing of children, such as disclosure to the child and informed consent. Even if future research confirms the need to test preschoolers for ADHD risk behaviors, certain laws now in place would govern the subsequent testing in children. If the provider's view is that the potential for harm would outweigh the potential benefit of the test, or if no benefit from medical intervention would be possible until adulthood, the test would be deferred until adulthood. The test can be conducted only when it is in the child's best interest, the justification being that the test should be timely and medically beneficial to the child.[158]

There is a continued need for gene-directed research in terms of identification, prevention, and treatment of ADHD, and our hypothesis, based on existing scientific evidence as reviewed, suggests that parents, pediatricians, psychiatrists, and primary care physicians think about the potential importance of appropriate genotyping of at least dopaminergic genes as part of the overall assessment for identifying children at risk for ADHD and related risk behaviors (eg, PSUD). We are cognizant that in pediatrics, it may be dangerous to worry families unnecessarily with data showing risk alleles in their offspring. We want to emphasize that our intent is not to genotype children at a young age for purposes of labeling them and influencing their future successes and failures, but instead to suggest careful and appropriate use of the information obtained from postnatal genotyping for preventive and treatment options, which could ultimately lead to appropriate, safe treatment, early on, to reduce behavioral risk, including poor scholastic performance and SUD.

Prevention of SUD

It is noteworthy that tobacco smoke may be a gateway to other drugs of abuse, including marijuana use, especially in children with ADHD.[159] It has been argued that among current college smokers, 40% started smoking by learning to inhale marijuana, and then started using tobacco, or they started using tobacco at the same time.[160] The conundrum here is, without a clear diagnosis of early-onset ADHD, it is difficult to ascribe the concept of the gateway theory generalized to any specific drug because the abuse of any particular psychoactive drug, such as marijuana or tobacco, may occur with or without the ADHD phenotype.[161,162] However, that said, gene testing, as we propose, will provide additional and pertinent information regarding the connection between ADHD symptomatology and marijuana or tobacco use and other risk behaviors. More importantly, existing polymorphisms could then be targeted to provide personalized medicine to the individual child, especially in carriers of the *DRD2* A1 allele (among other gene polymorphisms).

Volkow et al[163] evaluated DA reward pathways in individuals with ADHD using PET radioligands for DA for DAT using [11C] cocaine, and for D2/D3 receptors using [11C] raclopride, quantified as binding potential (distribution volume ratio-1). The investigators found a lower D2/D3 postsynaptic availability in participants with ADHD than in control participants, in the left brain hemisphere. Similar findings were obtained for the DAT presynaptic receptor. The analyzed cluster included the left ventral caudate, accumbal, midbrain, and hypothalamic regions. The importance of the findings, coupled with the findings of reduced caudate DA release in ADHD,[164] and high risk for drug abuse in D2/D3 deficits in the NAc,[165] confirm the relevance of dopaminergic genetic analysis in ADHD. It is noteworthy that the *DRD3* gene has been associated with ADHD by a number of investigators; specifically, Davis et al[165] found scores that were significantly higher on the symptom scale for ADHD-HI in 3 *DRD3* genotypes that included Ser/Ser.

A better general understanding and acceptance of ADHD diagnoses have been achieved and treatment medications are widely available and abused, however, the findings of Setlik et al[2] showed that although methylphenidate prescriptions had increased, exposures were lower than that of other ADHD medications. Methylphenidate is a noted performance enhancer, which has demonstrated tolerance and withdrawal. The agent has a much shorter half-life and is not as reinforcing compared with amphetamine-type ADHD medications.[166] There have been frequent reports that methylphenidate is being snorted or injected by abusers in an attempt to reap any positive effects. Patients also take these types of prescriptions when trying to control weight or appetite and boost energy.[167]

Recently, Paclt et al[168] studied 586 unrelated Czech boys, aged between 6 and 13 years. The study group consisted of 269 boys with ADHD and the control group consisted of 317 boys. The investigators found that when genotype frequencies were compared, there was a statistically significant difference between the groups studied. When the allelic frequencies were compared between the 2 groups, a significant difference was also found, with the A1 allele present having a 4.4-fold higher risk of ADHD present. The results presented a highly positive correlation between the ADHD-C subtype without comorbidities and *ANKK1* (*DRD2*) polymorphism. Once again, the results point to the emerging concept that increasing availability of D2 density seems parsimonious as a therapeutic approach.

Esposito-Smythers et al[169] found interaction effects between the *DRD2* ***Taq1 A1*** polymorphism and conduct disorder. In addition, adolescents who had the A1 allele were carriers (A1+), had impulsive behavior or conduct disorder, higher levels of problematic alcohol use, and problem drug use severity reported than those who were non-carriers (A1+). The authors suggested that a relationship between conduct disorder, the impulsivity behavioral phenotype, and problematic alcohol/drug use among adolescents and their *DRD2*A1 carrier status, is well documented.

In sum, we underscore the importance to pediatricians and the scientific community of continuing the search for accurate diagnosis of ADHD and incorporation of non-addicting prevention modalities in children at an early age. We hypothesize that it is reasonable to suggest that children with ADHD are candidates for a novel clinical approach that includes a confirmatory laboratory evaluation, incorporating gene-based diagnosis and psychometric

testing. Additionally, we suggest a multimodal treatment plan that includes the use of pharmacologic or nutrition-based agents, such as DNA-directed, non-stimulatory, natural dopaminergic agonistic therapy, parent/school counseling, neuro-biofeedback therapy, and behavioral therapy. More importantly, our review serves as a potential directive in encouraging research by practicing pediatricians and research scientists to determine the benefits of 1) coupling genotyping with psychometric testing as a combined diagnostic method; 2) evaluating the proposition that dopaminergic genotyping be used to determine high risk of future SUD prior to stimulant treatment, and to reduce subsequent PSUD in adolescents; and 3) evaluating, through systematic, randomized, double-blind, placebo-controlled studies, the use of an alternative, non-stimulatory, and natural D2 agonist (customized to specific candidate polymorphisms) to treat ADHD symptoms.

Conclusion

Unlike certain rare, single-gene disorders having no treatment options, albeit polygenetic, at least in patients with ADHD, there are multiple treatment options, including non-stimulant, safe, non-addicting modalities. Evidence points to dopaminergic agonist therapy as a standardized treatment; however, the choice of the agonist must take into account a potential for DA receptor down-regulation instead of an up-regulation of D2 receptors.[131] It is theorized, awaiting further confirmation, that the latter could be accomplished using less powerful but safe, natural D2 receptor agonists that could be administered at a rather young age without negatively affecting a child's neuronal development. In our review, and following additional confirming research findings,[170] we raise the possibility of extending governmental acts related to genetic testing at birth to include ADHD as a genetic risk. This idea will be argued against by many, especially those who believe that ADHD in the child tends to resolve and improve over time. In response, Reef et al[171] concluded that even post age 24 years, individuals are more likely to meet criteria for DSM-IV (possibly now DSM-V) diagnoses if as children they had psychopathology than individuals without childhood psychopathology. Moreover, across the lifespan, different types of continuities of children's psychopathology exist. Reef et al[169] found that children with conduct problems, ODD, and anxious children are at greater risk for psychopathology as adults. According to the authors, continuity of psychopathology into adulthood may be reduced by effective identification and treatment of children with these conditions. The authors' conclusions are further underscored by the work of Biederman et al,[172] who found at 11-year follow-up, that the majority of children with ADHD continued to have a full or a partial persistence of the disease. Predictors of persistence were exposure to maternal psychopathology at baseline, psychiatric comorbidity, and severe impairment from ADHD.[173] With regard to accurate diagnosis augmented by genetic testing, the good news is that after more than a decade of working its way through the US Congress in various forms, GINA has been passed, barring employers and health insurers from discriminating based on an individual's biologic blueprint.

Fletcher and Wolfe[174] suggested that children with ADHD symptomatology be considered at enhanced risk for impairment and poor outcomes as young adults. For that reason, a compelling case can be made for targeting this group of children with early intervention programs and developing research to test the value of genetic testing and non-stimulant

treatment agents that have been shown to improve focus,[175] reduce stress, reduce PSUD, and prevent relapse.

According to Johnson et al,[173] although the cause of ADHD is unknown, recent studies have suggested an association with disrupted dopamine signaling, whereby D_2 DA receptors in reward related brain regions are reduced. The same pattern of DA-mediated signaling reduction is observed in RDS associated with drug and food addiction[119] and obesity.[138] The marked frequency of ADHD suggests that while genetic mechanisms are likely contributory, other factors are involved in the etiology, including chronic effects of excessive sugar intake, which may lead to alterations in mesolimbic dopamine signaling and could contribute to the symptoms associated with ADHD.[173]

Development of interventional programs targeting hypodopaminergic brain function and evaluation of the program to learn how effective they are in reducing the probability that children with ADHD will commit crimes as adolescents or develop psychopathologies as adults, could be cost-effective in terms of averting crime and SUD, and allowing for normal development and the achievement of a rewarding and productive adulthood.

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Table 1

Genetic Positioning Map (GPS)[a]

Reward-dependence pathway	Candidate genes
Signal Transduction	*ADCY7*
Signal Transduction	*AVPR1A*
Signal Transduction	*AVPR1B*
Signal Transduction	*CDK5R1*
Signal Transduction	*CREB1*
Signal Transduction	*CSNKLE*
Signal Transduction	*FEV*
Signal Transduction	*FDS*
Signal Transduction	*FOSL1*
Signal Transduction	*FOSL2*
Signal Transduction	*GSK3B*
Signal Transduction	*JUN*
Signal Transduction	*MAPK1*
Signal Transduction	*MAPK3*
Signal Transduction	*MAPK14*
Signal Transduction	*MPD2*
Signal Transduction	*MGFB*
Signal Transduction	*NTRK2*
Signal Transduction	*NTSR1*
Signal Transduction	*NTSR2*
Signal Transduction	*PPP1R1B*
Signal Transduction	*PRKCE*
Serotonin	*HTRIA*
Serotonin	*HTRIB*
Serotonin	*HTR2A*
Serotonin	*HTR2C*
Serotonin	*HTR3A*
Serotonin	*HTR3B*
Serotonin	*MAOA*
Serotonin	*MAOB*
Serotonin	*SLC64A*
Serotonin	*TPH1*
Serotonin	*TPH2*
Opioid	*OPRMI*
Opioid	*OPRKI*
Opioid	*PDYN*
Opioid	*PMOC*
Opioid	*PRD1*
Opioid	*OPRL1*

Reward-dependence pathway	Candidate genes
Opioid	*PENK*
Opioid	*PNOC*
GABA	*GABRA2*
GABA	*GABRA3*
GABA	*GABRA4*
GABA	*GABRA6*
GABA	*GABRB1*
GABA	*GABRB2*
GABA	*GABRB3*
GABA	*GABRD*
GABA	*GABRE*
GABA	*GABRG2*
GABA	*GABRG3*
GABA	*GABRQ*
GABA	*SLC6A7*
GABA	*SL6A11*
GABA	*SLC32A1*
GABA	*GAD1*
GABA	*GAD2*
GABA	*DB1*
Dopamine	*COMT*
Dopamine	*DDC*
Dopamine	*DRD1*
Dopamine	*DRD2*
Dopamine	*DRD3*
Dopamine	*DRD4*
Dopamine	*DRD5*
Dopamine	*SLC18A2*
Dopamine	*SLC6A3*
Dopamine	*TH*
Cannabinoid	*CNR1*
Cannabinoid	*FAAH*
Cholinergic	*CHRMI*
Cholinergic	*CHRM2*
Cholinergic	*CHRM3*
Cholinergic	*CHRM5*
Cholinergic	*CHRNA4*
Cholinergic	*CHRNB2*
Adrenergic	*ADRA1A*
Adrenergic	*ADRA2B*
Adrenergic	*ADRB2*
Adrenergic	*SLC6A2*

Reward-dependence pathway	Candidate genes
Adrenergic	*DRA2A*
Adrenergic	*DRA2C*
Adrenergic	*ARRB2*
Adrenergic	*DBH*
Glycine	*GLRA1*
Glycine	*GLRA2*
Glycine	*GLRB*
Glycine	*GPHN*
NDMA	*GR1K1*
NDMA	*GRINI*
NDMA	*GRIN2A*
NDMA	*GRIN2B*
NDMA	*GRIN2C*
NDMA	*GRM1*
Stress	*CRH*
Stress	*CRHEP*
Stress	*CRHR1*
Stress	*CRHR2*
Stress	*GAL*
Stress	*NPY*
Stress	*NPY1R*
Stress	*NPY2R*
Stress	*NPY5R*
Drug Metabolizing	*ALDH1*
Drug Metabolizing	*ALDH2*
Drug Metabolizing	*CAT*
Drug Metabolizing	*CYPZE1*
Drug Metabolizing	*ADH1A*
Drug Metabolizing	*ADH1B*
Drug Metabolizing	*ADH1C*
Drug Metabolizing	*ADH4*
Drug Metabolizing	*ADH5*
Drug Metabolizing	*ADH6*
Drug Metabolizing	*ADH6*
Drug Metabolizing	*ADH7*
Others	*BDNF*
Others	*CART*
Others	*CCK*
Others	*CCKAR*
Others	*CLOCK*
Others	*HCRT*
Others	*LEP*

Reward-dependence pathway	Candidate genes
Others	*NR3C1*
Others	*SLC29A1*
Others	*TAC*

[a] A number of studies have validated specific genes proposed for ADHD and related behaviors in children. In some cases, the number of reports overlap, and there may be cases where a negative outcome is reported.

Modified from Blum K, Fornari F, Downs BW, et al. Genetic Addiction Risk Score (GARS): Testing for polygenetic predisposition and risk to Reward Deficiency Syndrome (RDS). In King C, ed. *Gene Therapy Applications*. Croatia: Intech Open Access; 2011: Chapter 19; 327–362.[119]