Mol Neurobiol (2012) 45:605–620
DOI 10.1007/s12035-012-8278-5

Role of Dopamine Receptors in ADHD: A Systematic Meta-analysis

Jing Wu · Haifan Xiao · Hongjuan Sun · Li Zou · Ling-Qiang Zhu

Received: 6 May 2012 / Accepted: 7 May 2012 / Published online: 19 May 2012

Abstract The dopaminergic system plays a pivotal role in the central nervous system via its five diverse receptors (D1–D5). Dysfunction of dopaminergic system is implicated in many neuropsychological diseases, including attention deficit hyperactivity disorder (ADHD), a common mental disorder that prevalent in childhood. Understanding the relationship of five different dopamine (DA) receptors with ADHD will help us to elucidate different roles of these receptors and to develop therapeutic approaches of ADHD. This review summarized the ongoing research of DA receptor genes in ADHD pathogenesis and gathered the past published data with meta-analysis and revealed the high risk of DRD5, DRD2, and DRD4 polymorphisms in ADHD.

Keywords ADHD · Dopamine receptor · Meta-analysis

Electronic supplementary material The online version of this article (doi:10.1007/s12035-012-8278-5) contains supplementary material, which is available to authorized users.

J. Wu · H. Xiao · H. Sun · L. Zou
Department of Epidemiology and Biostatistics and Ministry of Education Key Lab of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

L.-Q. Zhu (✉)
Department of Pathophysiology and Key Lab of Neurological Disease of Education Ministry, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
e-mail: zhulq1979@yahoo.cn

L.-Q. Zhu
e-mail: zhulq@mail.hust.edu.cn

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders in children characterized by age-inappropriate persistent and pervasive symptoms of inattention, hyperactivity, and impulsivity. It occurs in about 3 %–6 % of school-aged children [1] and is more common in boys than girls with a ratio of 3:1 or even higher [2, 3]. The onset of some symptoms of ADHD is usually before age 7 and tends to persist throughout childhood. A number of longitudinal studies suggest that nearly 30 %–60 % of children with ADHD go on to have significant behavioral and psychiatric problems in adolescence and adulthood [4–10]. Compared with children without the disorder, ADHD children have lower income, lower educational attainment, and underemployment as well as higher rates of school dropout, adult criminality, and substance abuse [11–14]. It also results in distinct educational, social, and family difficulties for patients and their relatives. Furthermore, about 50 % to 80 % of ADHD patients have comorbid psychiatric disorders, such as conduct disorders, depressive disorders, anxiety disorders, and learning disorders including dyslexia as well as dyscalculia [5, 15–17]. Until now, the exact cause of ADHD is unknown, while a lot of twin and adoption studies have provided evidence that ADHD has genetic basis and heritability of ADHD to be around 0.76, as high as 0.9, which is the highest among psychiatric disorders [18–22]. Thus, quantitative molecular genetic studies are attempting to discover specific genes [23], such as dopaminergic receptors.

It is widely recognized that dopamine (DA) transporter and receptor genes are the most important components in the etiology of ADHD among a large number of candidate genes [24]. Gene association studies also implicated several genes within DA-signaling pathways to be involved in the

pathogenesis of ADHD. The two approved drugs that had been used for the treatment of ADHD, methylphenidate (MP) and amphetamine, also affect the DA signaling in the brain. Since DA receptors and their downstream signals are important for ADHD, it is highly necessary to comprehensively collect data, thus reaching large clinical samples to achieve adequate statistical power and replicable results to address the association of DA receptor genes and signals with ADHD, combining our meta-analysis of all subjected polymorphisms of DA receptor genes with data available from at least three independent case–control or family-based samples for childhood ADHD. This review will summarize recent studies linking abnormal DA receptors and its downstream signals with the pathogenesis of ADHD and substantially facilitates the interpretation of the family genuine susceptibility of this disorder (see Table 1 for a summary of these findings).

Physiology of Dopamine Receptors

DA receptors belong to the G protein-coupled receptor superfamily which has seven highly conserved hydrophobic transmembrane domains (TMD) coupled with intracellular signal transduction systems via different G proteins as general traits [25, 26]. According to their different biochemical, pharmacological, and physiologically attribution, the five different DA receptors could be divided into two distinct subtypes: D1-like receptor family including dopamine D1 and D5 receptors, which are coupled with G protein $G_{\alpha s}$ and activate adenylyl cyclase, and D2-like receptor family including dopamine D2, D3, and D4 receptors, which are coupled with G protein $G_{\alpha i}$ and inhibit adenylyl cyclase [25, 27, 28]. In addition, two isoforms of the D2 receptor (the long isoform (D2L) and the short isoform (D2S)) are generated by alternative splicing with the difference of an insertion of 29 aa located in the third intracellular loop [29]. All the DA receptors are encoded by different genes at disparate chromosomal loci and share a considerable homology in their protein structure and function, especially in their transmembrane domains (TMD) [28]. The D1-like receptor genes are lacking introns, and D1 and D5 receptors share 80 % homology in their TMDs. The D2-like receptor genes are interrupted by introns, and D2 receptor shares 75 % homology with D3 and 53 % homology with D4 (Fig. 1) [30].

As mentioned above, the most important downstream signal pathway of DA receptors is modulation of adenylyl cyclase activity and changing cAMP concentration [28], which is mediated by the activation of different types G proteins, stimulatory $G_{\alpha s,}$ and inhibitory $G_{\alpha i}$ to activate and inhibit adenylyl cyclase [28]. In most cases, the result of the stimulation or inhibition of cyclic AMP accumulation is regulation protein kinase A activity (activation or inactivation), which is responsible for multiple downstream effectors via phosphorylation or dephosphorylation [31]. An alternative substrate of cAMP is Exchange Protein Activated by Cyclic AMP (EPAC), a GTP exchange factor for Rap1, a member of the Ras family of small GTP-binding proteins. EPAC activation promotes the binding of GTP with Rap1 and initiates Rap1 downstream signals [32]. In addition to cAMP pathway, DA receptors can also modulate the activity of phospholipase C, the release of arachidonic acid, as well as the activity of calcium or potassium channels and Na/H exchangers or the Na–KATPases [30]. Moreover, DA receptors play a vital role in the mediation of the hypothalamus–pituitary–adrenal axis, physiologically and pathologically [28].

Dopamine Receptors in ADHD

Under the action of these two kinds of receptors, DA plays a critical role in mediating neuronal motor control, cognition, emotion, vascular function, and event prediction [33–38]. Dysfunction of dopaminergic system in the brain has been implicated in a lot of neuropsychological diseases, such as Parkinson's disease, Tourette's syndrome, ADHD, addiction, and schizophrenia [39–46]. The DA hypothesis in ADHD was proposed as: (i) the critical role of the DA systems in motor, motivational, and reward processes, which are abnormal in ADHD patients; (ii) application of drugs that target DA receptor sites ameliorate some of the symptoms of ADHD [47, 48], such as MP, a DA reuptake blocker for the treatment of ADHD approved in North America and North Europe [49]; and (iii) regional cross-correlative analyses suggested an alteration of modulatory influence of DA receptors in the cross-talk within the anterior forebrain in the spontaneously hypertensive rat (SHR), a widely used animal model for ADHD. Thus, disequilibrium of D1- and D2-like receptors leading to perturbations in dopaminergic system may exert a major role in the pathogenesis of ADHD during brain development and maturation [50].

D1-like Receptors

Dopamine D1 Receptor Gene (*DRD1*)

The dopamine D1 receptor gene (*DRD1*) is located in chromosome 5q35.1 [51]. It is the most abundant subtype in the brain and regulates adenylyl cyclase activation and phosphoinositide hydrolysis via coupling to heterotrimeric G proteins, G_s, and G_q [52, 53]. D1 receptor is highly expressed in the brain, including the striatum, cerebral cortex, olfactory bulb, and to a lesser extent, in the hippocampus and amygdale [54]. At the cellular level, D1 receptor is

Table 1 Molecular characteristics of human dopamine receptors

Molecular characteristics	D1-like		D2-like			
	D1	D5	D2S	D2L	D3	D4
Chromosome localization	5q35.1	4p15.3	11q23.1		3q13.3	11p15.5
G coupling protein	G_s, G_o, G_{i1}, G_{i2}	G_s, G_z	$G_{i1} > G_{i2}$[a], G_z, G_o	G_{i2}, G_{i3}, G_z, G_o	G_s, G_{i1}, G_{i2}, G_{i3}, G_q, G_z	G_z, G_{oB}, G_{t2}
Exons	2	1	8	8	7	4
Introns	0	0	5	6	5	3
Effector pathway	↑cAMP	↑cAMP	↓cAMP, ↑K^+ channel, ↓Ca^{2+} channel		↓cAMP	↓cAMP
Pseudogenes	None	DRD5P1, DRD5P2	None	None	None	None
Amino acids	446	477	414	443	400	387–515[b]
Amino acids in the 3rd cytoplasmic loop	57	50	134	443	120	101–261[b]
Molecular weight	49,300	52,951	47,347	50,619	44,225	41,487
mRNA distribution in the brain	Caudate-putamen, nucleus accumbens, olfactory tubercle	Hippocampus, hypothalamus	Caudate-putamen, nucleus accumbens, olfactory tubercle		Olfactory tubercle, hypothalamus, nucleus accumbens	Frontal cortex, medulla, midbrain
Reference	[25, 30, 51, 97, 213–215]	[25, 30, 72, 73, 97, 215, 216]	[25, 30, 96, 97, 217–221]		[25, 30, 31, 97, 217, 222–224]	[25, 30, 97, 141, 142, 217, 221, 225, 226]

[a] $G_{i1} > G_{i2}$: D2S receptors were found to couple with higher efficacy to G_{i1} than they did to G_{i2}

[b] The number of amino acids in human D4 receptor depends on the number of repeats in 3rd intracellular loop

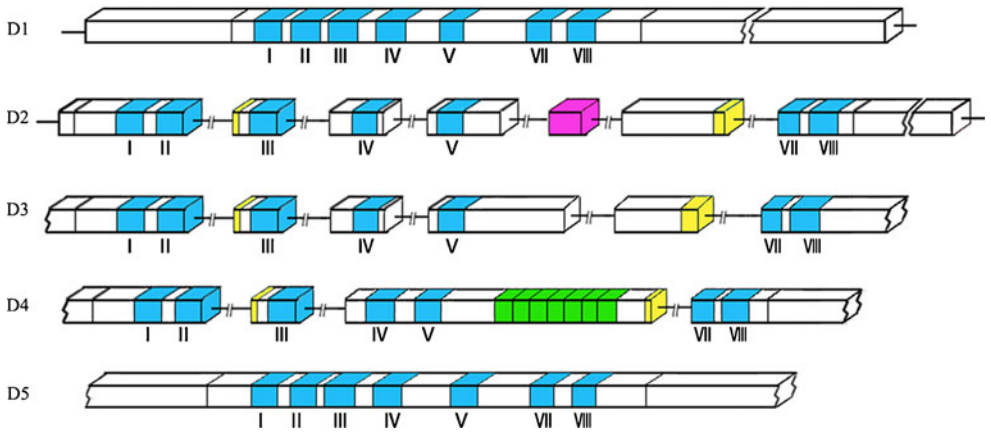

Fig. 1 Genetic schematic of human dopamine receptors. *Lines* introns, *boxes* exons, *blue boxes* the putative transmembrane domains, *yellow boxes* the untranslated region of the corresponding mRNA; the watery *red exon* of the D2 receptor gene indicates the alternatively spliced exon (D2S and D2L); the *green part* of the exon reflects 48-bp VNTR polymorphism in D4 receptor, and this figure takes 7-repeat as an example

mostly located in axon terminals and dendrites with a higher level at the dendritic spines [54]. The broad distribution in central nervous system indicates its plentiful physiological functions, such as regulating neuronal growth and development, mediating some behavioral responses, and modulating DA receptor D2-mediated events [55]. D1 receptor knockout mice exhibits reduced striatum volume [56], greater locomotor activity [57], hyperactivity, lack of psychostimulant effects of cocaine and amphetamine [57–59], less substance P, dynorphin and *N*-methyl-D-aspartate (NMDA) receptor [60–62], and poorer performance and slower learning ability in the Morris water maze task [63].

As DRD1 is highly expressed in prefrontal cortex (PFC) and striatum, numerous neuropsychological studies show that dysfunction of the PFC could account for fundamental difficulty in ADHD to a large extent, and individuals with impaired PFC perform ADHD-like behavior [64, 65]. D1 receptor in PFC is not only present in the pyramidal neurons but also in the GABAergic interneurons so as to form a feed-forward inhibition microcircuit to regulate working memory [66], which is highly correlated to attention and severely impaired in ADHD patients [67, 68].

Several population studies attempted to explore the association between ADHD and genetic variations of DRD1, such as single nucleotide polymorphisms (SNPs) in D1.7 maker (rs686) located in the 3′-untranslated region [69–71], D1P.6 maker (rs265981) located in the 5′-untranslated region [22, 27, 70], and D1P.5 maker (−1251 G/C) located ~0.2 kb upstream of one of two promoter regions [27, 70], but all returned negative results. Recently, more attention has been paid to the G–A transition in D1.1 maker (rs4532) which located in the 5′-untranslated region [71]. We tried to conduct a meta-analysis to summarize the association between this variation and childhood ADHD [22, 69, 70]. However, the results did not support the association (OR= 1.07, 95 % CI=0.55–2.09, P=0.8404) with high heterogeneity in effect size (Q-statistic χ^2=18.09, P=0.0001, I^2= 89.94). Due to insufficient sample size, all of the above negative results still need to be replicated in more population samples (Supplementary Fig. 1).

Dopamine D5 Receptor Gene (*DRD5*)

The dopamine D5 receptor gene (*DRD5*) is the last cloned DA receptor and mapped to chromosome 4p15.3 [72]. It also belongs to G protein-coupled receptors and stimulates adenyl cyclase activity [73]. D5 receptor exhibits a much more widespread expression in the central nervous system including the amygdala, frontal cortex, hippocampus, striatum, basal forebrain, hypothalamus, cerebellum, and thalamus [74] and a tenfold higher affinity for DA than the D1 subtype. At the cellular level, the large aspiny neurons of neostriatum in primates, which are typically cholinergic interneurons, only express D5 receptors [54]. Subcellularly, D5 receptors are located in neuronal perikarya and proximal dendrites, and occasionally, in the neuropil in the neuron of olfactory bulb, cerebral cortex, superior colliculus, and molecular layer of cerebellum [75].

Functionally coupled to the activation of adenylate cyclase, D5 DAR also interacts with Gamma-aminobutyric acid receptor subunitgamma-2 (GABRG2), which suggests that it may modulate $GABA_A$ receptor-mediated activity through both second messenger cascades and direct receptor–receptor interaction [76]. D5R-absent mice are less active in baseline locomotor exploration [77] than wide type littermates while their exploratory activity increases, clewing its inhibitory effect on locomotion. Based on antisense oligonucleotide studies, the D5 receptor has been implicated in modulating hypothalamic function [78, 79] and some forms of motor control [80, 81].

In human studies, the association between ADHD and a highly polymorphic dinucleotide repeat of DRD5 ((CA)n), which located in 18.5 kb at the end of 5′ flank, has been the most concerned about. The variation comprises 12 alleles ranging from 134 to 156 bps in length [72], among which the 148-bp and 136-bp alleles are the most common. In this review, we conducted comprehensive meta-analyses between ADHD and the dinucleotide repeats in 136 bp, 138 bp, 140 bp, 146 bp, 148 bp, and 150 bp [22, 82–94]. The results indicated that most of the SNPs were not associated with ADHD, except for the 148-bp and 136-bp alleles which showed significant associations. The dinucleotide repeat of 148-bp allele was a risk factor (OR=1.26, 95 % CI=1.08–1.47, P=0.0036) (Fig. 2), which is consistent with previous report [90], while that of 136-bp allele was a protective factor (OR=0.58, 95 % CI=0.35–0.96, P=0.0329) for ADHD (Fig. 2). In addition, based on a unidimensional cluster analysis [95], Kim et al. classified the alleles shorter than or equal to 148 bp as short allele while those longer than 148 bp as long allele to test associations between the two types of variation and ADHD [91]. We also summarized these studies and performed meta-analyses. The results showed a significant association between ADHD and short allele (OR=0.81, 95 % CI=0.67–0.98, P=0.0314) [84, 87, 92], whereas no association was found between ADHD and long allele (OR=1.16, 95 % CI=0.99–1.35, P=0.0617), which also needs reduplication in larger populations resulting from insufficient sample size (Supplementary Fig. 2 and Supplementary Fig. 3).

D2-like Receptors

Dopamine D2 Receptor Gene (*DRD2*)

The dopamine D2 receptor gene is located at chromosome 11q23.1 [96], and alternative splicing of *DRD2* results in two different transcript variants that encode two isoforms (D2L isoform and D2S isoform). Besides the inhibitory effect to adenylyl cyclase by coupling to $G_{\alpha i/o}$, it is shown that D2R could regulate the calcium channel and initiate the PLC and β-arrestin-2/Akt/glycogen synthase kinase 3 pathways by targeting Gβγ subunit [97]. Additionally, direct interaction of D2 receptor with Adenosine A2A receptor [98], Band 4.1-like protein 1 (EPB41L1) [99], Neurabin-2 (PPP1R9B) [100], and Neuronal calcium sensor-1 (NCS-1) [101] are also reported. The dopamine receptor D2 is also highly distributed throughout the brain with DA contained or projected. The highest expression of D2 had been found in neostriatum, olfactory tubercle, substantia nigra, ventral tegmental area, and nucleus accumbens by autoradiography [102] and in situ hybridization [103, 104]. At the subcellular level, D2 is distributed in both presynaptic and postsynaptic compartments, including dendrites and spines, and the axon

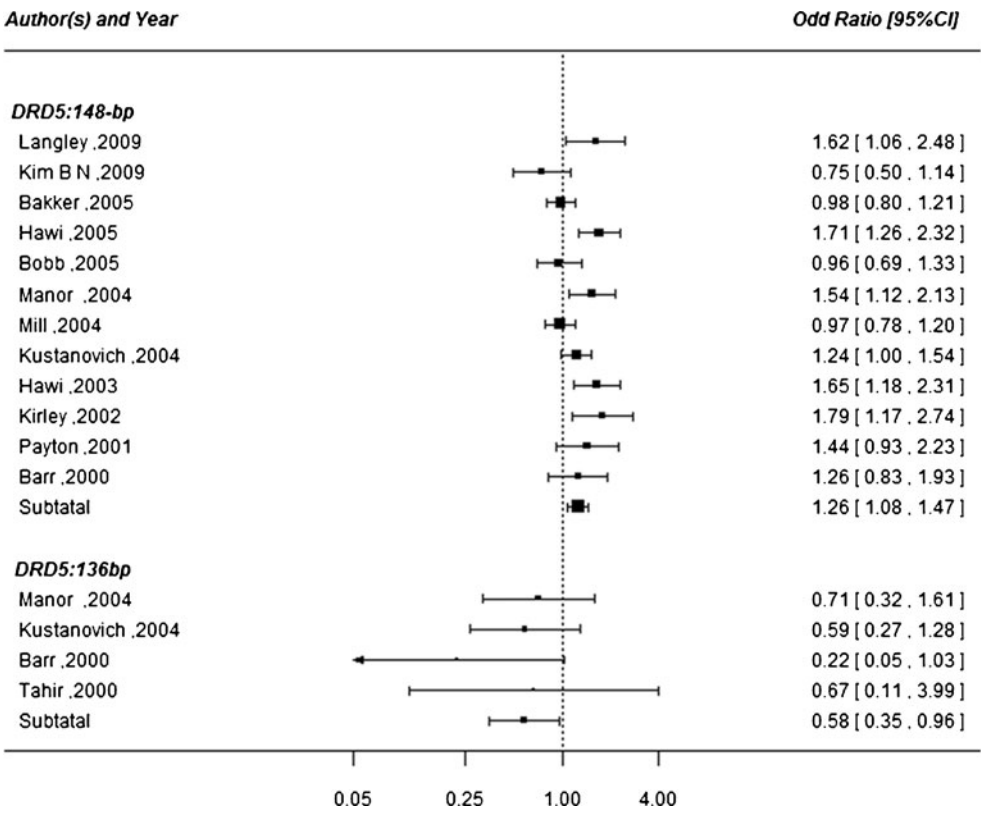

Fig. 2 Summary estimates for risk of ADHD associated with 148-bp and 136-bp of microsatellite flanking DRD5 from meta-analysis. Summary statistics: 148-bp (pooled OR=1.26, 95 % CI=1.08–1.47, P=0.0036; Q-statistic χ^2=.04, Pheterogeneity=0.0011, I^2=65.74); 136-bp (pooled OR=0.58, 95 % CI=0.35–0.96, P=0.0329; Q-statistic χ^2=1.78, Pheterogeneity=0.6187, I^2=0).*CI* confidence interval

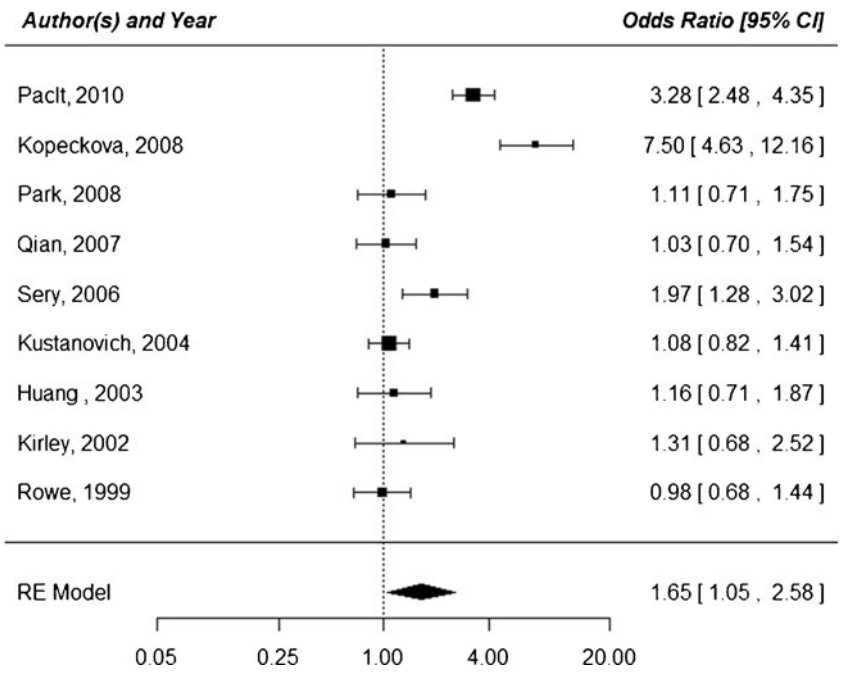

Fig. 3 Summary estimates for risk of ADHD associated with DRD2-TaqI (rs1800497) from meta-analysis (pooled OR= 1.65, 95 % CI=1.05–2.58, P= 0.0294; Q-statistic χ^2=89.12, Pheterogeneity<0.0001, I^2= 91.42). *CI* confidence interval, *RE Model* random effects model

terminal of in both excitatory- and inhibitory-like synapses [105]. In transfected NG108-15 cells, it was shown that D2S isoform is mostly localized at the plasma membrane, whereas D2L isoform is predominantly expressed in the perinuclear region that surrounds the Golgi apparatus. Among the five subtypes, D2 dopamine receptors seem to be the predominant type that regulates the firing rate, synthesis of DA, and release of DA in presynapse [106]. Signaling through D2 receptors governs locomotor behavior, hormone production, drug abuse, and antipsychiatric target in schizophrenia [37, 107, 108]. The different neuronal distributions of two variants at synapse (D2L in the postsynapse and D2S in the presynapse) indicate their different contributions to the biological events that D2 receptor participated in [107]. In a mice lacking D2 receptor, LB-like inclusions and axonal degeneration of dopaminergic neurons are augmented and locomotor activity with delayed initiations of movements were found to be decreased, which are similar in Parkinson's disease [109, 110].

In an experimental mice model of ADHD, the hyperactivity in locomotion and extremely increased reward behavior with deletion of DRD2 polymorphism were reported [111]. By position emission tomotraphy (PET) examination with F-deoxyglucose, the DRD2 A1 allele carriers show significantly lowered glucose metabolism in putamen, temporal, frontal, central, prefrontal, orbital, and occipitotemporal cortices [1, 112]. Moreover, a meta-analysis supported the association of impulsive–addictive–compulsive behavior with DRD2 [113]. Notably, the TaqIA (rs1800497) polymorphism of DRD2 was believed to connect with urinary level of the DA metabolite homovanillic acid [114] and expression levels [115, 116], which turned it into the most interesting variation in DRD2 association studies [82, 94]. Ser–Cys polymorphism was studied only in two articles showing identical but statistically nonsignificant results [82, 117].

Here, we conducted a meta-analysis to identify the association between ADHD and TaqIA polymorphism of DRD2, and the results reflected a significant association (OR=1.65, 95 % CI=1.05–2.58, P<0.0001) [82, 94, 117–123], which is inconsistent with the meta-analysis results reported in 2009 (OR=1.65, 95 % CI=0.89–3.06, P=0.110) [24]. However, due to the excessive heterogeneity (Q-statistic χ^2=89.12, P< 0.0001, I^2=91.42) (Fig. 3, Table 2), this positive result is invalid and the sources of heterogeneity need to be sought.

Dopamine D3 Receptor Gene (*DRD3*)

The dopamine D3 receptor gene is located on chromosome 3q13.3 [124] and inhibits adenylyl cyclase by coupling to G_i/G_o in appropriate expression systems [31]. In rats, D3 receptors are distributed in the islands of Calleja and olfactory bulb, the nucleus accumbens, vestibulocerebellum, and substantia nigra pars compacta. It also expressed in the superficial layers of the dorsal horn in spinal cord [125]. In humans, D3 receptors are much higher in striatal regions than in rats [126]. At the subcellular level, some of the D3 receptors are localized in the presynapse, acting as autoreceptors that modulate neuronal firing and DA synthesis and release [127]. The major biological function of D3 receptors is modulating hydrolysis of phosphinositide, regulating the activity of potassium channel and P/Q calcium channels

Table 2 Meta-analytic results for associations between dopamine receptor gene polymorphisms and childhood ADHD

Gene	Location	Polymorphism	Risk allele	Studies (TDT/CC or HHRR)	Results		Q-statistic	
					OR (95 % CI)	*Z* (*P* value)	χ^2 (*P* value)	I^2
DRD1	5′UTR	rs4532	G allele	3 (1/2)	1.07 (0.55–2.09)	0.20 (0.8404)	18.09 (0.001)	89.94
DRD5	**5′Flank**	**Dinucleotide repeat**	**136 bp**	**4 (4/0)**	**0.58 (0.35–0.96)**	**−2.13 (0.0329)**	**1.78 (0.6187)**	**0**
	5′Flank	Dinucleotide repeat	138 bp	3 (3/0)	0.96 (0.65–1.44)	−0.18 (0.8544)	1.42 (0.4901)	0
	5′Flank	Dinucleotide repeat	140 bp	3 (3/0)	0.69 (0.45–1.06)	−1.71 (0.0866)	0.05 (0.9752)	0
	5′Flank	Dinucleotide repeat	146 bp	3 (3/0)	0.67 (0.40–1.11)	−1.55 (0.1208)	4.26 (0.1186)	53.74
	5′Flank	**Dinucleotide repeat**	**148 bp**	**12 (9/3)**	**1.26 (1.08–1.47)**	**2.91 (0.0036)**	**31.04 (0.0011)**	**65.74**
	5′Flank	Dinucleotide repeat	150 bp	3 (2/1)	0.91 (0.72–1.15)	−0.77 (0.4428)	0.25 (0.8813)	0
	5′Flank	**Dinucleotide repeat**	**Short allele**	**3 (3/0)**	**0.81 (0.67–0.98)**	**−2.15 (0.0314)**	**0.22 (0.8961)**	**0**
	5′Flank	Dinucleotide repeat	Long allele	3 (3/0)	1.16 (0.99–1.35)	1.86 (0.0617)	0.27 (0.873)	0
DRD2	**3′Flank**	**TaqI**	**A1 allele**	**9 (2/7)**	**1.65 (1.05–2.58)**	**2.18 (0.0294)**	**89.12 (<0.0001)**	**91.42**
DRD3	Exon 1	rs6280	Unknown	6 (4/2)	1.08 (0.96–1.21)	1.31 (0.1905)	1.01 (0.961)	0
DRD4	Exon 3	VNTR	2-repeat	28 (10/18)	0.99 (0.87–1.13)	−0.18 (0.8605)	32.47 (0.2127)	10.74
	Exon 3	VNTR	3-repeat	19 (5/14)	0.94 (0.69–1.28)	−0.38 (0.7071)	26.73 (0.0842)	32.88
	Exon 3	VNTR	4-repeat	27 (10/17)	0.92 (0.85–1.00)	−2.03 (0.0422)	32.69 (0.1715)	15.57
	Exon 3	VNTR	5-repeat	14 (3/11)	1.32 (0.80–2.16)	1.09 (0.2762)	16.42 (0.2271)	28.92
	Exon 3	VNTR	6-repeat	10 (3/7)	1.23 (0.62–2.44)	0.60 (0.5456)	11.51 (0.2423)	26.16
	Exon 3	**VNTR**	**7-repeat**	**38 (15/23)**	**1.35 (1.20–1.51)**	**5.10 (<0.0001)**	**75.2 (0.0002)**	**50.92**
	Exon 3	VNTR	8-repeat	4 (2/2)	0.50 (0.20–1.28)	−1.44 (0.1485)	2.71 (0.4389)	0
	Exon 3	**VNTR**	**Short allele**	**24 (8/16)**	**0.83 (0.73–0.94)**	**−2.95 (0.0032)**	**41.9 (0.0093)**	**41.01**
	Exon 3	**VNTR**	**Long allele**	**24 (8/16)**	**1.28 (1.10–1.48)**	**3.29 (0.001)**	**36.14 (0.0399)**	**36.05**
	Promoter	In/Del	1-repeat	9 (7/2)	1.09 (0.91–1.30)	0.93 (0.3506)	16.88 (0.0314)	50.61
	Promoter	rs1800955	T allele	8 (4/4)	1.09 (0.90–1.30)	0.89 (0.3750)	15.00 (0.036)	53.89
	Promoter	rs747302	C allele	4 (3/1)	1.35 (0.99–1.82)	1.93 (0.0542)	9.72 (0.0211)	65.89

Bold text indicates significant result at $P<0.05$. I^2 describes the proportion of total variation in study effect sizes due to heterogeneity

[128], and stimulating the activity of mitogen-activated protein kinase (MAPK) [129], which in turn induce the c-Fos expression [130]. D3 receptors also initiate some phosphorylation events independent of G protein but relying on the PKC activity [131].

Highly expressed in the mesolimbic brain areas, especially in the nucleus accumbens, D3 receptors play primary function in the reward process of addictive behaviors [132] and incentive-based learning [133]. Regulating DA-related prefrontal neurocognition [134], D3 receptors have been associated with addictive behaviors and impulsive personality—pivotal features of both obesity and ADHD in adults [135]. Also, the D3 receptor contributed an inhibitory effect on motor response via an army of evidence [136]. Moreover, an anatomical study supported for a role in motivation and motor behavior for D3 receptor, which distribution in the ventral striatum implicated it probably could regulate the process of locomotion than that of attention. Limbic distribution also exerted a function in motivation and regulation of emotion (e.g., nucleus accumbens) [137]. Especially, in a study from Chinese Han population, Guan et al. suggested a distinct significant association of DRD3 with ADHD [138], and a later study also indicated the relationship of DRD3 with the manifestation of hyperactive/impulsive symptoms of ADHD [139].

Regarding the association of genetic variation of DRD3 with ADHD, it has focused on the SNP in rs6280 (Ser9Gly) located in exon 1. We did a meta-analysis [82, 89, 119, 137, 138, 140] and got a negative result (OR=1.08, 95 % CI=0.96–1.21, *P*=0.1905), which is the same as a previous meta-analysis conducted by Gizer et al. in 2009 [24] (Supplementary Fig. 4).

Dopamine D4 Receptor Gene (DRD4)

The dopamine D4 receptor is located at chromosome 11p15.5 [141, 142]. It is widely expressed in the brain, especially in the hippocampus (CA1, CA2, CA3, and

dentate gyrus), frontal cortex, entorhinal cortex, caudate putamen, nucleus accumbens, olfactory tubercle, cerebellum, supraoptic nucleus, and sustantia nigra pars compacta [143]. In the subcellular level, D4 receptor is distributed predominantly on the periphery of the cell body but not in a certain population of neurons with clear cytoplasmatic localization [144]. Other immunohistochemical studies demonstrated that the D4 receptor is found mainly in dendritic shafts and spines (postsynaptically) of mammalian striatum [145] with projecting back to the substantia nigra. D4 receptor plays multiple important roles in the CNS, such as, mediating corticostriatal neurotransmission by controlling the activity of glutamate receptors (two major subtypes are NMDA and AMPA receptors), carrying out phospholipid methylation, and affecting the kinetics of ion channels [146, 147], which are important for the synaptic strength and the modulation of neuronal firing activity that is impaired in ADHD. It is also linked to many neuropsychological disorders including schizophrenia, Parkinson's disease, bipolar disorder, addictive behaviors, and eating disorders. Mice with *DRD4* gene knockout have lowered responses to novel stimuli [148] but are enhanced to stimulants, such as, methamphetamine and cocaine, suggesting that it is heightened in locomotor behavior [149].

DRD4 contains quite a large number of polymorphisms in its nucleotide sequence. The most extensive one was found in exon 3, the region that encodes the third intracellular loop (IC3) domain. The length of this polymorphism varies from 2916 amino acids to 11916 amino acids, in which a 48-bp sequence exists as a two- to 11-fold variable number of tandem repeats (VNTR), denoted as D4.2 to D4.11. In this review we conducted comprehensive meta-analyses between ADHD and the VNTR of DRD4 from two- to eight-repeat allele. Our results indicated that most of the SNPs (two-, three-, four-, four-, six-, and eight-repeat allele) were not associated with ADHD (Supplementary Figs. 5, 6, 7, and 8) [83, 92, 117, 150–173], except for the seven-repeat allele which showed a significant association as a risk factor for ADHD (OR=1.35, 95 % CI=1.20–1.51, $P<0.0001$) (Fig. 4, Supplementary Fig. 9) [83, 90, 92–94, 140, 150–154, 160–185]. Particularly, functional studies on VNTR seem to produce evidence in support of the results. Asghari et al. had reported that the seven-repeat allele is slightly different from the two- and four-repeat alleles in secondary messenger (i.e., cAMP) activity, therefore, probably as well as in the response to DA-mediated antipsychotics, such as, emonapride, clozapine, haloperidol, raclopride, and so on [186, 187].

Moreover, based on different pharmacological characteristics [188, 189], quite a few studies divided these repeat alleles into two categories: short repeat (two to four) allele and long repeat (five to eight) allele [168,

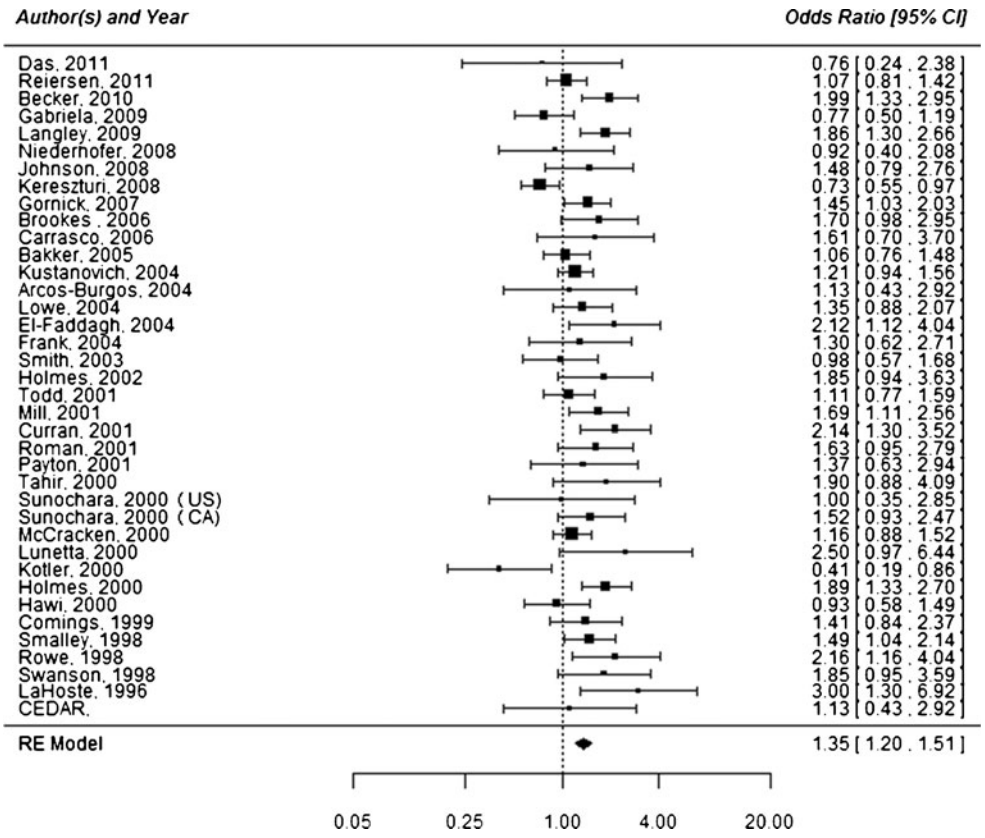

Fig. 4 Summary estimates for risk of ADHD associated with 7-repeat of DRD4 exon 3 VNTR from meta-analysis (pooled OR=1.35, 95 % CI=1.20–1.51, $P<0.0001$; Q-statistic $\chi^2=75.2$, Pheterogeneity=0.0002, $I^2=50.92$). *CI* confidence interval, *RE Model* random effects model

170, 190]. We also summarized these studies and performed meta-analyses [92, 150–155, 157, 159–165, 167–173, 190]. The results demonstrated that the short allele as a protective factor (OR=0.83, 95 % CI=0.73–0.94, P=0.0032) (Table 2, Supplementary Fig. 10) and the long allele as a risk factor (OR=1.28, 95 % CI=1.10–1.48, P=0.0399) were all significantly associated with ADHD (Table 2, Supplementary Fig. 11). Asghari et al. also had shown that DA is twice as potent with respect to blockage of forskolin-stimulated cAMP increment on the D4.2 and D4.4 receptors in CHO cells as the D4.7 receptor [187]. Thus, the short alleles of DRD4 are more likely gain of function, while the long alleles are loss of function. Accordingly, we suppose that this difference induces differential biological functions and, in turn, produce opposite effects in ADHD. Moreover, DRD4 seven-repeat allele carriers have a thinner right orbitofrontal/inferior prefrontal and posterior parietal cortex, and distinct trajectory of cortical development with a normalization of right parietal cortical thickening during adolescence, which are highly similar with ADHD [191]. Some ADHD patients without a seven-repeat allele (noncarriers) displayed longer reaction times, suggesting the seven-repeat allele might be associated with behavioral features but not cognitive deficits [192].

Other mutations in the promoter region has been also widely studied, focusing on 120-base pair duplication (120-bp dup), −521 C/T (rs1800955), −616 C/G (rs747302), −615A/G, and −376 C/T (rs916455), which are located in the 5′ untranslated region [179, 193, 194]. The 120-bp duplication is located at 1.2 kb of the transcription start site recognized by Seaman et al. who also found the sequence contained several transcription factor-binding sites, such as, MEP-1, CEB/P, and Sp1 [195], and one-repeat (120-bps) and two-repeat (240-bps) alleles are the most common. The two-repeat allele appeared to heighten binding ability for Sp1 in a mobility shift assay [196]. A function study on 120-bp dup revealed that the one-repeat allele posses higher promoter activity than the two-repeat allele [197]. Hence, the 120-bp dup exerted a role in transcriptional regulation of the *DRD4* gene. Moreover, in view of an association between the 120-bp allele and novelty seeking [198], the one-repeat allele may be a risk allele in ADHD. In our meta-analysis [94, 140, 160, 164, 179, 190, 194, 199, 200] of this insertion/deletion with ADHD, we got a negative result (OR=1.09, 95 % CI=0.91–1.30, P=0.3506) (Supplementary Fig. 12), thus replicating the results of previous reviews [24].

The −521 C/T allele is located at 521 bp upstream of the transcription start site in the DRD4 promoter region. This SNP has been studied in association with quite a few disorders such as substance abuse [201], schizophrenia [202], attachment disorganization [203] as well as in behavioral traits such as novelty seeking [204]. Furthermore, compared to the C allele in transitorily transfected human retinoblastoma Y79 cells, the −521 T allele was deemed to lower promoter activity by 40 % [202]. However, our meta-analysis showed that the T allele of rs1800955 [89, 117, 150, 179, 193, 194, 199, 205] had no association with ADHD (OR=1.09, 95 % CI=0.90–1.30, P=0.3750) (Supplementary Fig. 12), which is contrary to the previous review [24].

The C to G substitution at the −616 SNP potentially heightened an AP-2 binding site [206]. With activation and repression effects, the inducible AP-2 developmentally regulated transcription factor family and is involved in the induction of genes via innumerable factors containing cAMP, protein kinase C, retinoic acid, and phorbol esters [206–208]. Therefore, it is supposed that the −616 SNP can influence the transcription level of DRD4, which has not yet been verified at the functional level [195, 199]. Our results indicated that the C allele of rs747302 was not associated with ADHD (OR=1.35, 95 % CI=0.99–1.82, P=0.0542) (Supplementary Fig. 12) [86, 179, 194, 199].

In addition, a small number of association studies focused on other SNPs in the promoter region of DRD4, such as, −615A/G [194, 209] and −376 C/T [179, 193], but all obtained nonsignificant results. Besides the above variations in exon 3 and promoter, several studies explored the association of the 12-bp repeat located in exon 1 [210], especially the rarer single-repeat (one-repeat) allele, with psychiatric disorders. However, no association was found in ADHD [190, 211] and schizophrenics [212] and a positive association with delusional disorder [210].

Conclusions and Future Directions

Converging evidences implicated the association of DA receptors genes in ADHD, especially DRD4.7 DRD5. Comprehensive studies to understanding the possible underlying mechanisms are necessary, which is beneficial to the future diagnosis and therapy of ADHD.

We assessed the evidence from this meta-analysis by Egger's regression test, sensitivity analysis, and meta-regression (Supplementary Table 1). The methods and other results of our meta-analysis are summarized in supplementary files available online.

Acknowledgments The manuscript is supported by the National Nature Science Foundation of China (NSFC) (81101016), New Century Excellent Talents in University (NCET-10-0421), and the Ministry of Science and Technology of China (2011DFG33250).

Conflicts of interest The authors declared no conflicts of interest.

References

1. Tannock R (1998) Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. J Child Psychol Psychiatry 39(1):65–99
2. Baumgartel A, Wolraich ML, Dietrich M (1995) Comparison of diagnostic criteria for attention deficit disorders in a German elementary school sample. J Am Acad Child Adolesc Psychiatry 34:629–638
3. Anderson JC, Williams S, McGee R, Silva PA (1987) DSMIII-R disorders in preadolescent children: prevalence in a large sample from the general population. Arch Gen Psychiatry 44:69–76
4. Barkley RA, Smith KM, Fischer M, Navia B (2006) An examination of the behavioral and neuropsychological correlates of three ADHD candidate gene polymorphisms (DRD4 7+, DBH TaqI A2, and DAT1 40 bp VNTR) in hyperactive and normal children followed to adulthood. Am J Med Genet B Neuropsychiatr Genet 141B(5):487–498
5. Biederman J, Newcorn J, Sprich S (1991) Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. Am J Psychiatry 148:564–577
6. Gittelman R, Mannuzza S, Shenker R, Bonagura N (1985) Hyperactive boys almost grown up. I. Psychiatric status. Arch Gen Psychiatry 42(10):937–947
7. Swanson JM, Sergeant JA, Taylor E, Sonuga-Barke E, Jensen PS, Cantwell DP (1998) Attention-deficit hyperactivity disorder and hyperkinetic disorder. Lancet 351(9100):429–433
8. Wilens TE, Biederman J, Spencer TJ (2002) Attention deficit/hyperactivity disorder across the lifespan. Annu Rev Med 53:113–131
9. Woodward L, Taylor E, Dowdney L (1998) The parenting and family functioning of children with hyperactivity. J Child Psychol Psychiatry 39:161–169
10. Barkley RA (1990) Attention deficit hyperactivity disorder: a handbook for diagnosis and treatment. Guilford, New York
11. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M (1993) Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. Arch Gen Psychiatry 50(7):565–576
12. Lilienfeld SO, Waldman ID (1990) The relation between childhood attention-deficit hyperactivity disorder and adult antisocial behavior reexamined: the problem of heterogeneity. Clin Psychol Rev 10(6):699–725
13. Loeber R, Dishion T (1983) Early predictors of male delinquency: a review. Psychol Bull 94(1):68–99
14. Biederman J, Faraone SV (2005) Attention-deficit hyperactivity disorder. Lancet 366:237–248
15. Spencer T, Biederman J, Wilens T (1999) Attention-deficit/hyperactivity disorder and comorbidity. Pediatr Clin N Am 46:915–927
16. Jensen PS, Martin D, Cantwel LD (1997) Comorbidity in ADHD: implications for research, practice and DSMIV. J Am Acad Child Adolesc Psychiatry 36(7):1065–1079
17. Bird HR, Gould MS, Staghezza BM (1993) Patterns of diagnostic comorbidity in a community sample of children aged 9 through 16 years. J Am Acad Child Adolesc Psychiatry 32(2):361–368
18. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P (2005) Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 57(11):1313–1323
19. Derks EM, Hudziak JJ, Dolan CV, van Beijsterveldt TC, Verhulst FC, Boomsma DI (2008) Genetic and environmental influences on the relation between attention problems and attention deficit hyperactivity disorder. Behav Genet 38(1):11–23
20. Haberstick BC, Timberlake D, Hopfer CJ, Lessem JM, Ehringer MA, Hewitt JK (2008) Genetic and environmental contributions to retrospectively reported DSM-IV childhood attention deficit hyperactivity disorder. Psychol Med 38(7):1057–1066
21. Wood AC, Rijsdijk F, Saudino KJ, Asherson P, Kuntsi J (2008) High heritability for a composite index of children's activity level measures. Behav Genet 38(3):266–276
22. Bobb AJ, Addington AM, Sidransky E, Gornick MC, Lerch JP, Greenstein DK, Clasen LS, Sharp WS, Inoff-Germain G, Wavrant-De VF, Arcos-Burgos M, Straub RE, Hardy JA, Castellanos FX, Rapoport JL (2005) Support for association between ADHD and two candidate genes: *NET1* and *DRD1*. Am J Med Genet B Neuropsychiatr Genet 134B(1):67–72
23. Banaschewski T, Becker K, Scherag S, Franke B, Coghill D (2010) Molecular genetics of attention-deficit/hyperactivity disorder: an overview. Eur Child Adolesc Psychiatry 19(3):237–257
24. Gizer IR, Ficks C, Waldman ID (2009) Candidate gene studies of ADHD: a meta-analytic review. Hum Genet 126(1):51–90
25. Sibley DR, Monsma FJ Jr (1992) Molecular biology of dopamine receptors. Trends Pharmacol Sci 13:61–69
26. Gingrich JA, Caron MG (1993) Recent advances in the molecular biology of dopamine receptors. Annu Rev Neurosci 16:299–321
27. Cichon S, Nöthen MM, Stöber G, Schroers R, Albus M, Maier W, Rietschel M, Körner J, Weigelt B, Franzek E, Wildenauer D, Fimmers R, Propping P (1996) Systematic screening for mutations in the 5′-regulatory region of the human dopamine D1 receptor (*DRD1*) gene in patients with schizophrenia and bipolar affective disorder. Am J Med Genet 67(4):424–428
28. Pivonello R, Ferone D, Lombardi G, Colao A, Lamberts SW, Hofland LJ (2007) Novel insights in dopamine receptor physiology. Eur J Endocrinol 156(Suppl 1):S13–S21
29. Fukunaga K, Shioda N (2012) Novel dopamine D2 receptor signaling through proteins interacting with the third cytoplasmic loop. Mol Neurobiol 45(1):144–152
30. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG (1998) Dopamine receptors: from structure to function. Physiol Rev 78 (1):189–225
31. Vallone D, Picetti R, Borrelli E (2000) Structure and function of dopamine receptors. Neurosci Biobehav Rev 24(1):125–132
32. Gloerich M, Bos JL (2010) Epac: defining a new mechanism for cAMP action. Annu Rev Pharmacol Toxicol 50:355–375
33. Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. Science 275(5306):1593–1599
34. Beninger RJ, Miller R (1998) Dopamine D1-like receptors and reward-related incentive learning. Neurosci Biobehav Rev 22 (2):335–345
35. Hollerman JR, Schultz W (1998) Dopamine neurons report an error in the temporal prediction of reward during learning. Nat Neurosci 1(4):304–309
36. Iversen SD (1995) Interactions between excitatory amino acids and dopamine systems in the forebrain: implications for schizophrenia and Parkinson's disease. Behav Pharmacol 6(5 And 6):478–491
37. Picetti R, Saiardi A, Abdel ST, Bozzi Y, Baik JH, Borrelli E (1997) Dopamine D2 receptors in signal transduction and behavior. Crit Rev Neurobiol 11(2–3):121–142
38. Watanabe M, Kodama T, Hikosaka K (1997) Increase of extracellular dopamine in primate prefrontal cortex during a working memory task. J Neurophysiol 78(5):2795–2798
39. Hietala J, Syvalahti E (1996) Dopamine in schizophrenia. Ann Med 28:557–561
40. Baldessarini RJ (1997) Dopamine receptors and clinical medicine. In: Neve KA, Neve RL (eds) The Dopamine Receptors. Humana Press, NJ, pp 457–498
41. Bardo MT (1998) Neuropharmacological mechanisms of drug reward: beyond dopamine in the nucleus accumbens. Crit Rev Neurobiol 12(1–2):37–67
42. Nestler EJ (1997) Molecular mechanisms of opiate and cocaine addiction. Curr Opin Neurobiol 7(5):713–719

43. Self DW, Barnhart WJ, Lehman DA, Nestler EJ (1996) Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. Science 271(5255):1586–1589
44. Wise RA (1996) Neurobiology of addiction. Curr Opin Neurobiol 6(2):243–251
45. Donnan GA, Woodhouse DG, Kaczmarczyk SJ, Holder JE, Paxinos G, Chilco PJ, Churchyard AJ, Kalnins RM, Fabinyi GC, Mendelsohn FA (1991) Evidence for plasticity of the dopaminergic system in parkinsonism. Mol Neurobiol 5(2–4):421–433
46. Yu S, Ueda K, Chan P (2005) α-Synuclein and dopamine metabolism. Mol Neurobiol 31(1):243–254
47. Seiden LS, Sabol KE, Ricaurte GA (1993) Amphetamine: effects on catecholamine systems and behavior. Annu Rev Pharmacol Toxicol 33:639–677
48. Robertson SD, Matthies HJ, Galli A (2009) A closer look at amphetamine-induced reverse transport and trafficking of the dopamine and norepinephrine transporters. Mol Neurobiol 39 (2):73–80
49. Safer DJ, Krager JM (1988) A survey of medication treatment for hyperactive/inattentive students. JAMA 260(15):2256–2258
50. Sidhu A, Niznik HB (2000) Coupling of dopamine receptor subtypes to multiple and diverse G proteins. Int J Dev Neurosci 18(7):669–677
51. Grandy DK, Zhou QY, Allen L, Litt R, Magenis RE, Civelli O, Litt M (1990) A human D1 dopamine receptor gene is located on chromosome 5 at q35.1 and identifies an *Eco*RI RFLP. Am J Hum Genet 47(5):828–834
52. Jin LQ, Wang HY, Friedman E (2001) Stimulated D(1) dopamine receptors couple to multiple Galpha proteins in different brain regions. J Neurochem 78(5):981–990
53. Wang HY, Undie AS, Friedman E (1995) Evidence for the coupling of Gq protein to D1-like dopamine sites in rat striatum: possible role in dopamine-mediated inositol phosphate formation. Mol Pharmacol 48(6):988–994
54. Bergson C, Mrzljak L, Smiley JF, Pappy M, Levenson R, Goldman-Rakic PS (1995) Regional, cellular, and subcellular variations in the distribution of D1 and D5 dopamine receptors in primate brain. J Neurosci 15(12):7821–7836
55. Paul ML, Graybiel AM, David JC, Robertson HA (1992) D1-like and D2-like dopamine receptors synergistically activate rotation and c-fos expression in the dopamine-depleted striatum in a rat model of Parkinson's disease. J Neurosci 12(10):3729–3742
56. Drago J, Gerfen CR, Lachowicz JE, Steiner H, Hollon TR, Love PE, Ooi GT, Grinberg A, Lee EJ, Huang SP, Et A (1994) Altered striatal function in a mutant mouse lacking D1A dopamine receptors. Proc Natl Acad Sci USA 91(26):12564–12568
57. Xu M, Moratalla R, Gold LH, Hiroi N, Koob GF, Graybiel AM, Tonegawa S (1994) Dopamine D1 receptor mutant mice are deficient in striatal expression of dynorphin and in dopamine-mediated behavioral responses. Cell 79(4):729–742
58. Crawford CA, Drago J, Watson JB, Levine MS (1997) Effects of repeated amphetamine treatment on the locomotor activity of the dopamine D1A-deficient mouse. Neuroreport 8(11):2523–2527
59. Moratalla R, Xu M, Tonegawa S, Graybiel AM (1996) Cellular responses to psychomotor stimulant and neuroleptic drugs are abnormal in mice lacking the D1 dopamine receptor. Proc Natl Acad Sci USA 93(25):14928–14933
60. Drago J, Padungchaichot P, Accili D, Fuchs S (1998) Dopamine receptors and dopamine transporter in brain function and addictive behaviors: insights from targeted mouse mutants. Dev Neurosci 20 (2–3):188–203
61. Ariano MA, Drago J, Sibley DR, Levine MS (1998) Striatal excitatory amino acid receptor subunit expression in the D1A-dopamine receptor-deficient mouse. Dev Neurosci 20(2–3):237–241
62. Levine MS, Altemus KL, Cepeda C, Cromwell HC, Crawford C, Ariano MA, Drago J, Sibley DR, Westphal H (1996) Modulatory actions of dopamine on NMDA receptor-mediated responses are reduced in D1A-deficient mutant mice. J Neurosci 16(18):5870–5882
63. Smith DR, Striplin CD, Geller AM, Mailman RB, Drago J, Lawler CP, Gallagher M (1998) Behavioural assessment of mice lacking D1A dopamine receptors. Neuroscience 86(1):135–146
64. Arnsten AF, Steere JC, Hunt RD (1996) The contribution of alpha 2-noradrenergic mechanisms of prefrontal cortical cognitive function. Potential significance for attention-deficit hyperactivity disorder. Arch Gen Psychiatry 53(5):448–455
65. Arnsten A (2001) Dopaminergic and noradrenergic influences on cognitive functions mediated by prefrontal cortex. In: Solanto MV, Arnsten A, Castellanos FX (eds) Stimulant drugs and ADHD. basic and clinical neuroscience. Oxford University Press, New York, NY, pp 185–208
66. Goldman-Rakic PS, Muly ER, Williams GV (2000) D(1) receptors in prefrontal cells and circuits. Brain Res Brain Res Rev 31 (2–3):295–301
67. Denney CB, Rapport MD (2001) Cognitive pharmacology of stimulants in children with ADHD. Oxford University Press, Inc, New York, NY, pp 283–302
68. Castellanos FX, Tannock R (2002) Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3(8):617–628
69. Cao Y, Cui Q (2010) Association between the polymorphisms dopamine D1 receptor gene and attention deficit hyperactivity disorder. Progress in Modern Biomedicine 10(21):4039–4041
70. Misener VL, Luca P, Azeke O, Crosbie J, Waldman I, Tannock R, Roberts W, Malone M, Schachar R, Ickowicz A, Kennedy JL, Barr CL (2004) Linkage of the dopamine receptor D1 gene to attention-deficit/hyperactivity disorder. Mol Psychiatry 9(5):500–509
71. Cichon S, Nothen MM, Erdmann J, Propping P (1994) Detection of four polymorphic sites in the human dopamine D1 receptor gene (*DRD1*). Hum Mol Genet 3(1):209
72. Sherrington R, Mankoo B, Attwood J, Kalsi G, Curtis D, Buetow K, Povey S, Gurling H (1993) Cloning of the human dopamine D5 receptor gene and identification of a highly polymorphic microsatellite for the DRD5 locus that shows tight linkage to the chromosome 4p reference marker RAF1P1. Genomics 18 (2):423–425
73. Sunahara RK, Guan HC, O'Dowd BF, Seeman P, Laurier LG, Ng G, George SR, Torchia J, Van Tol HH, Niznik HB (1991) Cloning of the gene for a human dopamine D5 receptor with higher affinity for dopamine than D1. Nature 350(6319):614–619
74. Beischlag TV, Marchese A, Meador-Woodruff JH, Damask SP, O'Dowd BF, Tyndale RF, van Tol HH, Seeman P, Niznik HB (1995) The human dopamine D5 receptor gene: cloning and characterization of the 5′-flanking and promoter region. Biochemistry 34(17):5960–5970
75. Ciliax BJ, Nash N, Heilman C, Sunahara R, Hartney A, Tiberi M, Rye DB, Caron MG, Niznik HB, Levey AI (2000) Dopamine D (5) receptor immunolocalization in rat and monkey brain. Synapse 37(2):125–145
76. Liu F, Wan Q, Pristupa ZB, Yu XM, Wang YT, Niznik HB (2000) Direct protein–protein coupling enables cross-talk between dopamine D5 and gamma-aminobutyric acid A receptors. Nature 403 (6767):274–280
77. Karlsson RM, Hefner KR, Sibley DR, Holmes A (2008) Comparison of dopamine D1 and D5 receptor knockout mice for cocaine locomotor sensitization. Psychopharmacology (Berl) 200(1):117–127
78. Rivkees SA, Lachowicz JE (1997) Functional D1 and D5 dopamine receptors are expressed in the suprachiasmatic, supraoptic, and paraventricular nuclei of primates. Synapse 26(1):1–10
79. Apostolakis EM, Garai J, Clark JH, O'Malley BW (1996) In vivo regulation of central nervous system progesterone receptors:

cocaine induces steroid-dependent behavior through dopamine transporter modulation of D5 receptors in rats. Mol Endocrinol 10(12):1595–1604
80. Niznik HBSK (2000) D1-like dopamine receptors: molecular biology and pharmacolgy. Springer Verlag, Di Chiara
81. Sibley DR (1999) New insights into dopaminergic receptor function using antisense and genetically altered animals. Annu Rev Pharmacol Toxicol 39:313–341
82. Kirley A, Hawi Z, Daly G, McCarron M, Mullins C, Millar N, Waldman I, Fitzgerald M, Gill M (2002) Dopaminergic system genes in ADHD: toward a biological hypothesis. Neuropsychopharmacology 27(4):607–619
83. Bakker SC, van der Meulen EM, Oteman N, Schelleman H, Pearson PL, Buitelaar JK, Sinke RJ (2005) DAT1, DRD4, and DRD5 polymorphisms are not associated with ADHD in Dutch families. Am J Med Genet B Neuropsychiatr Genet 132B(1):50–52
84. Barr CL, Wigg KG, Feng Y, Zai G, Malone M, Roberts W, Schachar R, Tannock R, Kennedy JL et al (2000) Attention-deficit hyperactivity disorder and the gene for the dopamine D5 receptor. Mol Psychiatry 5(5):548
85. Hawi Z, Lowe N, Kirley A, Gruenhage F, Nothen M, Greenwood T, Kelsoe J, Fitzgerald M, Gill M (2003) Linkage disequilibrium mapping at DAT1, DRD5 and DBH narrows the search for ADHD susceptibility alleles at these loci. Mol Psychiatry 8 (3):299–308
86. Hawi Z, Segurado R, Conroy J, Sheehan K, Lowe N, Kirley A, Shields D, Fitzgerald M, Gallagher L, Gill M (2005) Preferential transmission of paternal alleles at risk genes in attention-deficit/hyperactivity disorder. Am J Hum Genet 77(6):958–965
87. Manor I, Corbex M, Eisenberg J, Gritsenkso I, Bachner-Melman R, Tyano S, Ebstein RP (2004) Association of the dopamine D5 receptor with attention deficit hyperactivity disorder (ADHD) and scores on a continuous performance test (TOVA). Am J Med Genet B Neuropsychiatr Genet 127B(1):73–77
88. Mill J, Curran S, Richards S, Taylor E, Asherson P (2004) Polymorphisms in the dopamine D5 receptor (*DRD5*) gene and ADHD. Am J Med Genet B Neuropsychiatr Genet 125B(1):38–42
89. Payton A, Holmes J, Barrett JH, Hever T, Fitzpatrick H, Trumper AL, Harrington R, McGuffin P, O'Donovan M, Owen M, Ollier W, Worthington J, Thapar A (2001) Examining for association between candidate gene polymorphisms in the dopamine pathway and attention-deficit hyperactivity disorder: a family-based study. Am J Med Genet 105(5):464–470
90. Langley K, Fowler TA, Grady DL, Moyzis RK, Holmans PA, van den Bree MB, Owen MJ, O'Donovan MC, Thapar A (2009) Molecular genetic contribution to the developmental course of attention-deficit hyperactivity disorder. Eur Child Adolesc Psychiatry 18(1):26–32
91. Kim BN, Kang D, Cho SC, Park TW, Lim MH, Chung YC, Kim JW, Hwang JW, Yoo HJ, Chung US, Son JW, Yang JC, Chung SK, Lee JY, Jung YW (2009) Shorter dinucleotide repeat length in the *DRD5* gene is associated with attention deficit hyperactivity disorder. Psychiatr Genet 19(1):57
92. Tahir E, Yazgan Y, Cirakoglu B, Ozbay F, Waldman I, Asherson PJ (2000) Association and linkage of DRD4 and DRD5 with attention deficit hyperactivity disorder (ADHD) in a sample of Turkish children. Mol Psychiatry 5(4):396–404
93. Maher BS, Marazita ML, Ferrell RE, Vanyukov MM (2002) Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. Psychiatr Genet 12(4):207–215
94. Kustanovich V, Ishii J, Crawford L, Yang M, McGough JJ, McCracken JT, Smalley SL, Nelson SF (2004) Transmission disequilibrium testing of dopamine-related candidate gene polymorphisms in ADHD: confirmation of association of ADHD with DRD4 and DRD5. Mol Psychiatry 9(7):711–717
95. Vanyukov MM, Moss HB, Yu LM, Deka R (1995) A dinucleotide repeat polymorphism at the gene for monoamine oxidase A and measures of aggressiveness. Psychiatry Res 59(1–2):35–41
96. Eubanks JH, Djabali M, Selleri L, Grandy DK, Civelli O, McElligott DL, Evans GA (1992) Structure and linkage of the D2 dopamine receptor and neural cell adhesion molecule genes on human chromosome 11q23. Genomics 14(4):1010–1018
97. Beaulieu JM, Gainetdinov RR (2011) The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev 63 (1):182–217
98. Kamiya T, Saitoh O, Yoshioka K, Nakata H (2003) Oligomerization of adenosine A2A and dopamine D2 receptors in living cells. Biochem Biophys Res Commun 306(2):544–549
99. Binda AV, Kabbani N, Lin R, Levenson R (2002) D2 and D3 dopamine receptor cell surface localization mediated by interaction with protein 4.1 N. Mol Pharmacol 62(3):507–513
100. Smith FD, Oxford GS, Milgram SL (1999) Association of the D2 dopamine receptor third cytoplasmic loop with spinophilin, a protein phosphatase-1-interacting protein. J Biol Chem 274 (28):19894–19900
101. Kabbani N, Negyessy L, Lin R, Goldman-Rakic P, Levenson R (2002) Interaction with neuronal calcium sensor NCS-1 mediates desensitization of the D2 dopamine receptor. J Neurosci 22 (19):8476–8486
102. Boyson SJ, McGonigle P, Molinoff PB (1986) Quantitative autoradiographic localization of the D1 and D2 subtypes of dopamine receptors in rat brain. J Neurosci 6(11):3177–3188
103. Meador-Woodruff JH, Mansour A, Bunzow JR, Van Tol HH, Watson SJ, Civelli O (1989) Distribution of D2 dopamine receptor mRNA in rat brain. Proc Natl Acad Sci USA 86(19):7625–7628
104. Weiner DM, Brann MR (1989) The distribution of a dopamine D2 receptor mRNA in rat brain. FEBS Lett 253(1–2):207–213
105. Negyessy L, Goldman-Rakic PS (2005) Subcellular localization of the dopamine D2 receptor and coexistence with the calcium-binding protein neuronal calcium sensor-1 in the primate prefrontal cortex. J Comp Neurol 488(4):464–475
106. Doi M, Yujnovsky I, Hirayama J, Malerba M, Tirotta E, Sassone-Corsi P, Borrelli E (2006) Impaired light masking in dopamine D2 receptor-null mice. Nat Neurosci 9(6):732–734
107. Usiello A, Baik JH, Rouge-Pont F, Picetti R, Dierich A, LeMeur M, Piazza PV, Borrelli E (2000) Distinct functions of the two isoforms of dopamine D2 receptors. Nature 408(6809):199–203
108. Heber D, Carpenter CL (2011) Addictive genes and the relationship to obesity and inflammation. Mol Neurobiol 44(2):160–165
109. Tinsley RB, Bye CR, Parish CL, Tziotis-Vais A, George S, Culvenor JG, Li QX, Masters CL, Finkelstein DI, Horne MK (2009) Dopamine D2 receptor knockout mice develop features of Parkinson disease. Ann Neurol 66(4):472–484
110. Glickstein SB, Schmauss C (2001) Dopamine receptor functions: lessons from knockout mice [corrected]. Pharmacol Ther 91 (1):63–83
111. Maldonado R, Saiardi A, Valverde O, Samad TA, Roques BP, Borrelli E (1997) Absence of opiate rewarding effects in mice lacking dopamine D2 receptors. Nature 388(6642):586–589
112. Comings DE (1997) IBC's international conference on dopaminergic disorders novel approaches for drug discovery and development. The Ritz-Carlton, Boston
113. Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Comings DE (1995) Dopamine D2 receptor gene variants: association and linkage studies in impulsive–addictive–compulsive behaviour. Pharmacogenetics 5(3):121–141
114. Ponce G, Hoenicka J, Rodriguez-Jimenez R, Gozalo A, Jimenez M, Monasor R, Aragues M, Rubio G, Jimenez-Arriero MA, Ramos JA, Palomo T (2004) IDRD2 TaqIA polymorphism is associated with urinary homovanillic acid levels in a sample of Spanish male alcoholic patients. Neurotox Res 6(5):373–377

115. Laakso A, Pohjalainen T, Bergman J, Kajander J, Haaparanta M, Solin O, Syvalahti E, Hietala J (2005) The A1 allele of the human D2 dopamine receptor gene is associated with increased activity of striatal L-amino acid decarboxylase in healthy subjects. Pharmacogenet Genomics 15(6):387–391
116. Thompson J, Thomas N, Singleton A, Piggott M, Lloyd S, Perry EK, Morris CM, Perry RH, Ferrier IN, Court JA (1997) D2 dopamine receptor gene (*DRD2*) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. Pharmacogenetics 7(6):479–484
117. Park PS, Kim DK, Jung CH (2008) Dopamine transporter gene and dopamine D2, D3, D4 receptor gene polymorphisms in attention deficit hyperactivity disorder. J Kor Acad Child Adolesc Psychiatry 19(1):19–27
118. Paclt I, Drtilkova I, Kopeckova M, Theiner P, Sery O, Cermakova N (2010) The association between TaqI A polymorphism of ANKK1 (*DRD2*) gene and ADHD in the Czech boys aged between 6 and 13 years. Neuro Endocrinol Lett 31(1):131–136
119. Kopeckova M, Paclt I, Petrasek J, Pacltova D, Malikova M, Zagatova V (2008) Some ADHD polymorphisms (in genes *DAT1*, *DRD2*, *DRD3*, *DBH*, *5-HTT*) in case–control study of 100 subjects 6–10 age. Neuro Endocrinol Lett 29(2):246–251
120. Qian Q, Wang Y, Li J, Yang L, Wang B, Zhou R, Glatt SJ, Faraone SV (2007) Evaluation of potential gene–gene interactions for attention deficit hyperactivity disorder in the Han Chinese population. Am J Med Genet B Neuropsychiatr Genet 144B(2):200–206
121. Sery O, Drt I, Lkov AI, Theiner P, Pitelov AR, Staif R, Znojil V, Lochman J, Didden W (2006) Polymorphism of *DRD2* gene and ADHD. Neuro Endocrinol Lett 27(1–2):236–240
122. Huang YS, Lin SK, Wu YY, Chao CC, Chen CK (2003) A family-based association study of attention-deficit hyperactivity disorder and dopamine D2 receptor TaqI A alleles. Chang Gung Med J 26(12):897–903
123. Rowe DC, Van den Oord EJ, Stever C, Giedinghagen LN, Gard JM, Cleveland HH, Gilson M, Terris ST, Mohr JH, Sherman S, Abramowitz A, Waldman ID (1999) The DRD2 TaqI polymorphism and symptoms of attention deficit hyperactivity disorder. Mol Psychiatry 4(6):580–586
124. Le Coniat M, Sokoloff P, Hillion J, Martres MP, Giros B, Pilon C, Schwartz JC, Berger R (1991) Chromosomal localization of the human D3 dopamine receptor gene. Hum Genet 87(5):618–620
125. Ricci A, Vega JA, Mammola CL, Amenta F (1995) Localisation of dopamine D3 receptor in the rat cerebellar cortex: a light microscope autoradiographic study. Neurosci Lett 190(3):163–166
126. Meador-Woodruff JH, Damask SP, Wang J, Haroutunian V, Davis KL, Watson SJ (1996) Dopamine receptor mRNA expression in human striatum and neocortex. Neuropsychopharmacology 15 (1):17–29
127. Shafer RA, Levant B (1998) The D3 dopamine receptor in cellular and organismal function. Psychopharmacology (Berl) 135(1):1–16
128. Kuzhikandathil EV, Oxford GS (1999) Activation of human D3 dopamine receptor inhibits P/Q-type calcium channels and secretory activity in AtT-20 cells. J Neurosci 19(5):1698–1707
129. Cussac D, Newman-Tancredi A, Pasteau V, Millan MJ (1999) Human dopamine D(3) receptors mediate mitogen-activated protein kinase activation via a phosphatidylinositol 3-kinase and an atypical protein kinase C-dependent mechanism. Mol Pharmacol 56(5):1025–1030
130. Fields RD, Eshete F, Stevens B, Itoh K (1997) Action potential-dependent regulation of gene expression: temporal specificity in ca2+, cAMP-responsive element binding proteins, and mitogen-activated protein kinase signaling. J Neurosci 17(19):7252–7266
131. Cho DI, Oak MH, Yang HJ, Choi HK, Janssen GM, Kim KM (2003) Direct and biochemical interaction between dopamine D3 receptor and elongation factor-1Bbetagamma. Life Sci 73 (23):2991–3004
132. Black KJ, Hershey T, Koller JM, Videen TO, Mintun MA, Price JL, Perlmutter JS (2002) A possible substrate for dopamine-related changes in mood and behavior: prefrontal and limbic effects of a D3-preferring dopamine agonist. Proc Natl Acad Sci USA 99(26):17113–17118
133. Beninger RJ, Banasikowski TJ (2008) Dopaminergic mechanism of reward-related incentive learning: focus on the dopamine D(3) receptor. Neurotox Res 14(1):57–70
134. Lane HY, Liu YC, Huang CL, Hsieh CL, Chang YL, Chang L, Chang YC, Chang WH (2008) Prefrontal executive function and D1, D3, 5-HT2A and 5-HT6 receptor gene variations in healthy adults. J Psychiatry Neurosci 33(1):47–53
135. Limosin F, Romo L, Batel P, Ades J, Boni C, Gorwood P (2005) Association between dopamine receptor D3 gene BalI polymorphism and cognitive impulsiveness in alcohol-dependent men. Eur Psychiatry 20(3):304–306
136. Muglia P, Jain U, Kennedy JL (2002) A transmission disequilibrium test of the Ser9/Gly dopamine D3 receptor gene polymorphism in adult attention-deficit hyperactivity disorder. Behav Brain Res 130(1–2):91–95
137. Barr CL, Wigg KG, Wu J, Zai C, Bloom S, Tannock R, Roberts W, Malone M, Schachar R, Kennedy JL (2000) Linkage study of two polymorphisms at the dopamine D3 receptor gene and attention-deficit hyperactivity disorder. Am J Med Genet 96 (1):114–117
138. Guan L, Wang B, Chen Y, Yang L, Li J, Qian Q, Wang Z, Faraone SV, Wang Y (2009) A high-density single-nucleotide polymorphism screen of 23 candidate genes in attention deficit hyperactivity disorder: suggesting multiple susceptibility genes among Chinese Han population. Mol Psychiatry 14(5):546–554
139. Davis C, Patte K, Levitan RD, Carter J, Kaplan AS, Zai C, Reid C, Curtis C, Kennedy JL (2009) A psycho-genetic study of associations between the symptoms of binge eating disorder and those of attention deficit (hyperactivity) disorder. J Psychiatr Res 43(7):687–696
140. Brookes K, Xu X, Chen W, Zhou K, Neale B, Lowe N, Anney R, Franke B, Gill M, Ebstein R, Buitelaar J, Sham P, Campbell D, Knight J, Andreou P, Altink M, Arnold R, Boer F, Buschgens C, Butler L, Christiansen H, Feldman L, Fleischman K, Fliers E, Howe-Forbes R, Goldfarb A, Heise A, Gabriels I, Korn-Lubetzki I, Johansson L, Marco R, Medad S, Minderaa R, Mulas F, Muller U, Mulligan A, Rabin K, Rommelse N, Sethna V, Sorohan J, Uebel H, Psychogiou L, Weeks A, Barrett R, Craig I, Banaschewski T, Sonuga-Barke E, Eisenberg J, Kuntsi J, Manor I, McGuffin P, Miranda A, Oades RD, Plomin R, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Taylor E, Thompson M, Faraone SV, Asherson P (2006) The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in *DRD4*, *DAT1* and 16 other genes. Mol Psychiatry 11(10):934–953
141. Petronis A, Van Tol HH, Lichter JB, Livak KJ, Kennedy JL (1993) The D4 dopamine receptor gene maps on 11p proximal to HRAS. Genomics 18(1):161–163
142. Gelernter J, Kennedy JL, van Tol HH, Civelli O, Kidd KK (1992) The D4 dopamine receptor (DRD4) maps to distal 11p close to HRAS. Genomics 13(1):208–210
143. Defagot MC, Malchiodi EL, Villar MJ, Antonelli MC (1997) Distribution of D4 dopamine receptor in rat brain with sequence-specific antibodies. Brain Res Mol Brain Res 45(1):1–12
144. Wedzony K, Chocyk A, Mackowiak M, Fijal K, Czyrak A (2000) Cortical localization of dopamine D4 receptors in the rat brain—immunocytochemical study. J Physiol Pharmacol 51(2):205–221
145. Rivera A, Cuellar B, Giron FJ, Grandy DK, de la Calle A, Moratalla R (2002) Dopamine D4 receptors are heterogeneously

distributed in the striosomes/matrix compartments of the striatum. J Neurochem 80(2):219–229
146. Deth R, Muratore C, Benzecry J, Power-Charnitsky VA, Waly M (2008) How environmental and genetic factors combine to cause autism: a redox/methylation hypothesis. Neurotoxicology 29 (1):190–201
147. Kuznetsova AY, Deth RC (2008) A model for modulation of neuronal synchronization by D4 dopamine receptor-mediated phospholipid methylation. J Comput Neurosci 24(3):314–329
148. Dulawa SC, Grandy DK, Low MJ, Paulus MP, Geyer MA (1999) Dopamine D4 receptor-knock-out mice exhibit reduced exploration of novel stimuli. J Neurosci 19(21):9550–9556
149. Rubinstein M, Phillips TJ, Bunzow JR, Falzone TL, Dziewczapolski G, Zhang G, Fang Y, Larson JL, McDougall JA, Chester JA, Saez C, Pugsley TA, Gershanik O, Low MJ, Grandy DK (1997) Mice lacking dopamine D4 receptors are supersensitive to ethanol, cocaine, and methamphetamine. Cell 90(6):991–1001
150. Das M, Das BA, Bhaduri N, Sarkar K, Ghosh P, Sinha S, Ray A, Chatterjee A, Mukhopadhyay K (2011) Role of gene–gene/gene–environment interaction in the etiology of eastern Indian ADHD probands. Prog Neuropsychopharmacol Biol Psychiatry 35 (2):577–587
151. Gabriela ML, John DG, Magdalena BV, Ariadna GS, Francisco DL, Liz SM, Lino PC, Josefina RG, Ernesto RZ, Carlos CF (2009) Genetic interaction analysis for *DRD4* and *DAT1* genes in a group of Mexican ADHD patients. Neurosci Lett 451 (3):257–260
152. Niederhofer H, Menzel F, Gobel K, Hackenberg B, Richter R, Walter MH, Gross C, Huber M, Pycha R, Menzel HJ (2008) A preliminary report of the dopamine receptor D(4) and the dopamine transporter 1 gene polymorphism and its association with attention deficit hyperactivity disorder. Neuropsychiatr Dis Treat 4(4):701–705
153. Johnson KA, Kelly SP, Robertson IH, Barry E, Mulligan A, Daly M, Lambert D, McDonnell C, Connor TJ, Hawi Z, Gill M, Bellgrove MA (2008) Absence of the 7-repeat variant of the DRD4 VNTR is associated with drifting sustained attention in children with ADHD but not in controls. Am J Med Genet B Neuropsychiatr Genet 147B(6):927–937
154. Gornick MC, Addington A, Shaw P, Bobb AJ, Sharp W, Greenstein D, Arepalli S, Castellanos FX, Rapoport JL (2007) Association of the dopamine receptor D4 (*DRD4*) gene 7-repeat allele with children with attention-deficit/hyperactivity disorder (ADHD): an update. Am J Med Genet B Neuropsychiatr Genet 144(3):379–382
155. Cheuk DK, Li SY, Wong V (2006) Exon 3 polymorphisms of dopamine D4 receptor (DRD4) gene and attention deficit hyperactivity disorder in Chinese children. Am J Med Genet B Neuropsychiatr Genet 141B(8):907–911
156. Leung PW, Lee CC, Hung SF, Ho TP, Tang CP, Kwong SL, Leung SY, Yuen ST, Lieh-Mak F, Oosterlaan J, Grady D, Harxhi A, Ding YC, Chi HC, Flodman P, Schuck S, Spence MA, Moyzis R, Swanson J (2005) Dopamine receptor D4 (*DRD4*) gene in Han Chinese children with attention-deficit/hyperactivity disorder (ADHD): increased prevalence of the 2-repeat allele. Am J Med Genet B Neuropsychiatr Genet 133B(1):54–56
157. Kim YS, Leventhal BL, Kim SJ, Kim BN, Cheon KA, Yoo HJ, Kim SJ, Badner J, Cook EH (2005) Family-based association study of DAT1 and DRD4 polymorphism in Korean children with ADHD. Neurosci Lett 390(3):176–181
158. Brookes KJ, Xu X, Chen CK, Huang YS, Wu YY, Asherson P (2005) No evidence for the association of DRD4 with ADHD in a Taiwanese population within-family study. BMC Med Genet 6:31
159. Qian Q, Wang Y, Zhou R, Yang L, Faraone SV (2004) Family-based and case–control association studies of DRD4 and DAT1 polymorphisms in Chinese attention deficit hyperactivity disorder patients suggest long repeats contribute to genetic risk for the disorder. Am J Med Genet B Neuropsychiatr Genet 128B(1):84–89
160. Arcos-Burgos M, Castellanos FX, Konecki D, Lopera F, Pineda D, Palacio JD, Rapoport JL, Berg K, Bailey-Wilson J, Muenke M (2004) Pedigree disequilibrium test (PDT) replicates association and linkage between DRD4 and ADHD in multigenerational and extended pedigrees from a genetic isolate. Mol Psychiatry 9 (3):252–259
161. Smith KM, Daly M, Fischer M, Yiannoutsos CT, Bauer L, Barkley R, Navia BA (2003) Association of the dopamine beta hydroxylase gene with attention deficit hyperactivity disorder: genetic analysis of the Milwaukee longitudinal study. Am J Med Genet B Neuropsychiatr Genet 119B(1):77–85
162. Holmes J, Payton A, Barrett J, Harrington R, McGuffin P, Owen M, Ollier W, Worthington J, Gill M, Kirley A, Hawi Z, Fitzgerald M, Asherson P, Curran S, Mill J, Gould A, Taylor E, Kent L, Craddock N, Thapar A (2002) Association of DRD4 in children with ADHD and comorbid conduct problems. Am J Med Genet 114(2):150–153
163. Mill J, Curran S, Kent L, Richards S, Gould A, Virdee V, Huckett L, Sharp J, Batten C, Fernando S, Simanoff E, Thompson M, Zhao J, Sham P, Taylor E, Asherson P (2001) Attention deficit hyperactivity disorder (ADHD) and the dopamine D4 receptor gene: evidence of association but no linkage in a UK sample. Mol Psychiatry 6(4):440–444
164. Todd RD, Neuman RJ, Lobos EA, Jong YJ, Reich W, Heath AC (2001) Lack of association of dopamine D4 receptor gene polymorphisms with ADHD subtypes in a population sample of twins. Am J Med Genet 105(5):432–438
165. Curran S, Mill J, Sham P, Rijsdijk F, Marusic K, Taylor E, Asherson P (2001) QTL association analysis of the DRD4 exon 3 VNTR polymorphism in a population sample of children screened with a parent rating scale for ADHD symptoms. Am J Med Genet 105(4):387–393
166. Roman T, Schmitz M, Polanczyk G, Eizirik M, Rohde LA, Hutz MH (2001) Attention-deficit hyperactivity disorder: a study of association with both the dopamine transporter gene and the dopamine D4 receptor gene. Am J Med Genet 105(5):471–478
167. Kotler M, Manor I, Sever Y, Eisenberg J, Cohen H, Ebstein RP, Tyano S (2000) Failure to replicate an excess of the long dopamine D4 exon III repeat polymorphism in ADHD in a family-based study. Am J Med Genet 96(3):278–281
168. Hawi Z, McCarron M, Kirley A, Daly G, Fitzgerald M, Gill M (2000) No association of the dopamine DRD4 receptor (*DRD4*) gene polymorphism with attention deficit hyperactivity disorder (ADHD) in the Irish population. Am J Med Genet 96 (3):268–272
169. Holmes J, Payton A, Barrett JH, Hever T, Fitzpatrick H, Trumper AL, Harrington R, McGuffin P, Owen M, Ollier W et al (2000) A family-based and case–control association study of the dopamine D4 receptor gene and dopamine transporter gene in attention deficit hyperactivity disorder. Mol Psychiatry 5(5):523
170. Comings DE, Gonzalez N, Wu S, Gade R, Muhleman D, Saucier G, Johnson P, Verde R, Rosenthal RJ, Lesieur HR, Rugle LJ, Miller WB, MacMurray JP (1999) Studies of the 48 bp repeat polymorphism of the *DRD4* gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. Am J Med Genet 88(4):358–368
171. Swanson JM, Sunohara GA, Kennedy JL, Regino R, Fineberg E, Wigal T, Lerner M, Williams L, LaHoste GJ, Wigal S (1998) Association of the dopamine receptor D4 (*DRD4*) gene with a refined phenotype of attention deficit hyperactivity disorder (ADHD): a family-based approach. Mol Psychiatry 3(1):38–41
172. Rowe DC, Stever C, Giedinghagen LN, Gard J, Cleveland HH, Terris ST, Mohr JH, Sherman S, Abramowitz A, Waldman ID

(1998) Dopamine DRD4 receptor polymorphism and attention deficit hyperactivity disorder. Mol Psychiatry 3(5):419–426
173. Sunohara GA, Roberts W, Malone M, Schachar RJ, Tannock R, Basile VS, Wigal T, Wigal SB, Schuck S, Moriarty J, Swanson JM, Kennedy JL, Barr CL (2000) Linkage of the dopamine D4 receptor gene and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 39(12):1537–1542
174. Reiersen AM, Todorov AA (2011) Association between DRD4 genotype and autistic symptoms in DSM-IV ADHD. J Can Acad Child Adolesc Psychiatry 20(1):15
175. Becker K, Blomeyer D, El-Faddagh M, Esser G, Schmidt MH, Banaschewski T, Laucht M (2010) From regulatory problems in infancy to attention-deficit/hyperactivity disorder in childhood: a moderating role for the dopamine D4 receptor gene? J Pediatr 156 (5):798–803
176. Kereszturi E, Tarnok Z, Bognar E, Lakatos K, Farkas L, Gadoros J, Sasvari-Szekely M, Nemoda Z (2008) Catechol-*O*-methyltransferase Val158Met polymorphism is associated with methylphenidate response in ADHD children. Am J Med Genet B Neuropsychiatr Genet 147B(8):1431–1435
177. Carrasco X, Rothhammer P, Moraga M, Henriquez H, Chakraborty R, Aboitiz F, Rothhammer F (2006) Genotypic interaction between DRD4 and DAT1 loci is a high risk factor for attention-deficit/hyperactivity disorder in Chilean families. Am J Med Genet B Neuropsychiatr Genet 141B(1):51–54
178. El-Faddagh M, Laucht M, Maras A, Vohringer L, Schmidt MH (2004) Association of dopamine D4 receptor (*DRD4*) gene with attention-deficit/hyperactivity disorder (ADHD) in a high-risk community sample: a longitudinal study from birth to 11 years of age. J Neural Transm 111(7):883–889
179. Lowe N, Kirley A, Mullins C, Fitzgerald M, Gill M, Hawi Z (2004) Multiple marker analysis at the promoter region of the *DRD4* gene and ADHD: evidence of linkage and association with the SNP -616. Am J Med Genet B Neuropsychiatr Genet 131B (1):33–37
180. Frank Y, Pergolizzi RG, Perilla MJ (2004) Dopamine D4 receptor gene and attention deficit hyperactivity disorder. Pediatr Neurol 31(5):345–348
181. Lunetta KL, Faraone SV, Biederman J, Laird NM (2000) Family-based tests of association and linkage that use unaffected sibs, covariates, and interactions. Am J Hum Genet 66(2):605–614
182. McCracken JT, Smalley SL, McGough JJ, Crawford L, Del Homme M, Cantor RM, Liu A, Nelson SF et al (2000) Evidence for linkage of a tandem duplication polymorphism upstream of the dopamine D4 receptor gene (*DRD4*) with attention deficit hyperactivity disorder (ADHD). Mol Psychiatry 5(5):531–536
183. Smalley SL, Bailey JN, Palmer CG, Cantwell DP, McGough JJ, Del'Homme MA, Asarnow JR, Woodward JA, Ramsey C, Nelson SF et al (1998) Evidence that the dopamine D4 receptor is a susceptibility gene in attention deficit hyperactivity disorder. Mol Psychiatry 3(5):427
184. LaHoste GJ, Swanson JM, Wigal SB, Glabe C, Wigal T, King N, Kennedy JL (1996) Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol Psychiatry 1(2):121–124
185. Payton A, Holmes J, Barrett JH, Sham P, Harrington R, McGuffin P, Owen M, Ollier W, Worthington J, Thapar A (2001) Susceptibility genes for a trait measure of attention deficit hyperactivity disorder: a pilot study in a non-clinical sample of twins. Psychiatry Res 105(3):273–278
186. Asghari V, Schoots O, van Kats S, Ohara K, Jovanovic V, Guan HC, Bunzow JR, Petronis A, Van Tol HH (1994) Dopamine D4 receptor repeat: analysis of different native and mutant forms of the human and rat genes. Mol Pharmacol 46(2):364–373
187. Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH (1995) Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J Neurochem 65 (3):1157–1165
188. Kotler M, Cohen H, Segman R, Gritsenko I, Nemanov L, Lerer B, Kramer I, Zer-Zion M, Kletz I, Ebstein RP (1997) Excess dopamine D4 receptor (D4DR) exon III seven repeat allele in opioid-dependent subjects. Mol Psychiatry 2(3):251–254
189. Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH (1996) Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. Nat Genet 12(1):81–84
190. Bhaduri N, Das M, Sinha S, Chattopadhyay A, Gangopadhyay PK, Chaudhuri K, Singh M, Mukhopadhyay K (2006) Association of dopamine D4 receptor (DRD4) polymorphisms with attention deficit hyperactivity disorder in Indian population. Am J Med Genet B Neuropsychiatr Genet 141B(1):61–66
191. Shaw P, Gornick M, Lerch J, Addington A, Seal J, Greenstein D, Sharp W, Evans A, Giedd JN, Castellanos FX, Rapoport JL (2007) Polymorphisms of the dopamine D4 receptor, clinical outcome, and cortical structure in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 64(8):921–931
192. Swanson J, Oosterlaan J, Murias M, Schuck S, Flodman P, Spence MA, Wasdell M, Ding Y, Chi HC, Smith M et al (2000) Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention. Proc Natl Acad Sci 97(9):4754
193. Yang JW, Jang WS, Hong SD, Ji YI, Kim DH, Park J, Kim SW, Joung YS (2008) A case–control association study of the polymorphism at the promoter region of the *DRD4* gene in Korean boys with attention deficit-hyperactivity disorder: evidence of association with the -521 C/T SNP. Prog Neuropsychopharmacol Biol Psychiatry 32(1):243–248
194. Kereszturi E, Kiraly O, Csapo Z, Tarnok Z, Gadoros J, Sasvari-Szekely M, Nemoda Z (2007) Association between the 120-bp duplication of the dopamine D4 receptor gene and attention deficit hyperactivity disorder: genetic and molecular analyses. Am J Med Genet B Neuropsychiatr Genet 144B(2):231–236
195. Seaman MI, Fisher JB, Chang F, Kidd KK (1999) Tandem duplication polymorphism upstream of the dopamine D4 receptor gene (*DRD4*). Am J Med Genet 88(6):705–709
196. Ronai Z, Guttman A, Keszler G, Sasvari-Szekely M (2004) Capillary electrophoresis study on DNA–protein complex formation in the polymorphic 5′ upstream region of the dopamine D4 receptor (*DRD4*) gene. Curr Med Chem 11(8):1023–1029
197. D'Souza UM, Russ C, Tahir E, Mill J, McGuffin P, Asherson PJ, Craig IW (2004) Functional effects of a tandem duplication polymorphism in the 5′ flanking region of the *DRD4* gene. Biol Psychiatry 56(9):691–697
198. Rogers G, Joyce P, Mulder R, Sellman D, Miller A, Allington M, Olds R, Wells E, Kennedy M (2004) Association of a duplicated repeat polymorphism in the 5′-untranslated region of the *DRD4* gene with novelty seeking. Am J Med Genet B Neuropsychiatr Genet 126B(1):95–98
199. Barr CL, Feng Y, Wigg KG, Schachar R, Tannock R, Roberts W, Malone M, Kennedy JL (2001) 5′-untranslated region of the dopamine D4 receptor gene and attention-deficit hyperactivity disorder. Am J Med Genet 105(1):84–90
200. Martel MM, Nikolas M, Jernigan K, Friderici K, Nigg JT (2010) Personality mediation of genetic effects on attention-deficit/hyperactivity disorder. J Abnorm Child Psychol 38 (5):633–643
201. Szilagyi A, Boor K, Szekely A, Gaszner P, Kalasz H, Sasvari-Szekely M, Barta C (2005) Combined effect of promoter polymorphisms in the dopamine D4 receptor and the serotonin transporter genes in heroin dependence. Neuropsychopharmacol Hung 7(1):28–33

202. Okuyama Y, Ishiguro H, Toru M, Arinami T (1999) A genetic polymorphism in the promoter region of DRD4 associated with expression and schizophrenia. Biochem Biophys Res Commun 258(2):292–295
203. Lakatos K, Nemoda Z, Toth I, Ronai Z, Ney K, Sasvari-Szekely M, Gervai J (2002) Further evidence for the role of the dopamine D4 receptor (*DRD4*) gene in attachment disorganization: interaction of the exon III 48-bp repeat and the −521 C/T promoter polymorphisms. Mol Psychiatry 7(1):27–31
204. Ronai Z, Szekely A, Nemoda Z, Lakatos K, Gervai J, Staub M, Sasvari-Szekely M (2001) Association between novelty seeking and the −521 C/T polymorphism in the promoter region of the *DRD4* gene. Mol Psychiatry 6(1):35–38
205. Guan LL, Wang YF, Li J, Wang B, Yang L, Qian QJ (2007) Association analysis of dopamine D4 receptor gene polymorphism and attention deficit hyperactivity disorder with/without disruptive behavior disorder]. Beijing da xue xue bao. Yi xue ban=. J Peking Univ Health Sci 39(3):233
206. Williams T, Tjian R (1991) Analysis of the DNA-binding and activation properties of the human transcription factor AP-2. Genes Dev 5(4):670–682
207. Imagawa M, Chiu R, Karin M (1987) Transcription factor AP-2 mediates induction by two different signal-transduction pathways: protein kinase C and cAMP. Cell 51(2):251–260
208. Wu F, Lee AS (1998) Identification of AP-2 as an interactive target of Rb and a regulator of the G1/S control element of the hamster histone H3.2 promoter. Nucleic Acids Res 26(21):4837–4845
209. Ronai Z, Szantai E, Szmola R, Nemoda Z, Szekely A, Gervai J, Guttman A, Sasvari-Szekely M (2004) A novel A/G SNP in the −615th position of the dopamine D4 receptor promoter region as a source of misgenotyping of the −616 C/G SNP. Am J Med Genet B Neuropsychiatr Genet 126B(1):74–78
210. Catalano M, Nobile M, Novelli E, Nothen MM, Smeraldi E (1993) Distribution of a novel mutation in the first exon of the human dopamine D4 receptor gene in psychotic patients. Biol Psychiatry 34(7):459–464
211. Barr CL, Wigg KG, Bloom S, Schachar R, Tannock R, Roberts W, Malone M, Kennedy JL (2000) Further evidence from haplotype analysis for linkage of the dopamine D4 receptor gene and attention-deficit hyperactivity disorder. Am J Med Genet 96 (3):262–267
212. Hong CJ, Chiu HJ, Chang YS, Sim CB (1998) Twelve-nucleotide repeat polymorphism of D4 dopamine receptor gene in Chinese familial schizophrenic patients. Biol Psychiatry 43(6):432–435
213. Uh M, White BH, Sidhu A (1998) Alteration of association of agonist-activated renal D1(A) dopamine receptors with G proteins in proximal tubules of the spontaneously hypertensive rat. J Hypertens 16(9):1307–1313
214. Kimura K, White BH, Sidhu A (1995) Coupling of human D-1 dopamine receptors to different guanine nucleotide binding proteins. Evidence that D-1 dopamine receptors can couple to both Gs and G(o). J Biol Chem 270(24):14672–14678
215. Sidhu A (1998) Coupling of D1 and D5 dopamine receptors to multiple G proteins: implications for understanding the diversity in receptor-G protein coupling. Mol Neurobiol 16(2):125–134
216. Sidhu A, Kimura K, Uh M, White BH, Patel S (1998) Multiple coupling of human D5 dopamine receptors to guanine nucleotide binding proteins Gs and Gz. J Neurochem 70(6):2459–2467
217. Obadiah J, Avidor-Reiss T, Fishburn CS, Carmon S, Bayewitch M, Vogel Z, Fuchs S, Levavi-Sivan B (1999) Adenylyl cyclase interaction with the D2 dopamine receptor family; differential coupling to Gi, Gz, and Gs. Cell Mol Neurobiol 19(5):653–664
218. Wolfe SE, Morris SJ (1999) Dopamine D2 receptor isoforms expressed in AtT20 cells differentially couple to G proteins to acutely inhibit high voltage-activated calcium channels. J Neurochem 73(6):2375–2382
219. Watts VJ, Wiens BL, Cumbay MG, Vu MN, Neve RL, Neve KA (1998) Selective activation of Galphao by D2L dopamine receptors in NS20Y neuroblastoma cells. J Neurosci 18(21):8692–8699
220. Grunewald S, Reilander H, Michel H (1996) In vivo reconstitution of dopamine D2S receptor-mediated G protein activation in baculovirus-infected insect cells: preferred coupling to Gi1 versus Gi2. Biochemistry 35(48):15162–15173
221. O'Hara CM, Tang L, Taussig R, Todd RD, O'Malley KL (1996) Dopamine D2L receptor couples to G alpha i2 and G alpha i3 but not G alpha i1, leading to the inhibition of adenylate cyclase in transfected cell lines. J Pharmacol Exp Ther 278(1):354–360
222. Newman-Tancredi A, Cussac D, Audinot V, Pasteau V, Gavaudan S, Millan MJ (1999) G protein activation by human dopamine D3 receptors in high-expressing Chinese hamster ovary cells: A guanosine-5′-O-(3-[35S]thio)-triphosphate binding and antibody study. Mol Pharmacol 55(3):564–574
223. Robinson SW, Caron MG (1997) Selective inhibition of adenylyl cyclase type V by the dopamine D3 receptor. Mol Pharmacol 52 (3):508–514
224. Levy F (1991) The dopamine theory of attention deficit hyperactivity disorder (ADHD). Aust N Z J Psychiatry 25(2):277–283
225. Yamaguchi I, Harmon SK, Todd RD, O'Malley KL (1997) The rat D4 dopamine receptor couples to cone transducin (Galphat2) to inhibit forskolin-stimulated cAMP accumulation. J Biol Chem 272(26):16599–16602
226. Oldenhof J, Vickery R, Anafi M, Oak J, Ray A, Schoots O, Pawson T, von Zastrow M, Van Tol HH (1998) SH3 binding domains in the dopamine D4 receptor. Biochemistry 37(45):15726–15736