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Article *in* Molecular Neurobiology · May 2012

DOI: 10.1007/s12035-012-8278-5 · Source: PubMed

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

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

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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.

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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

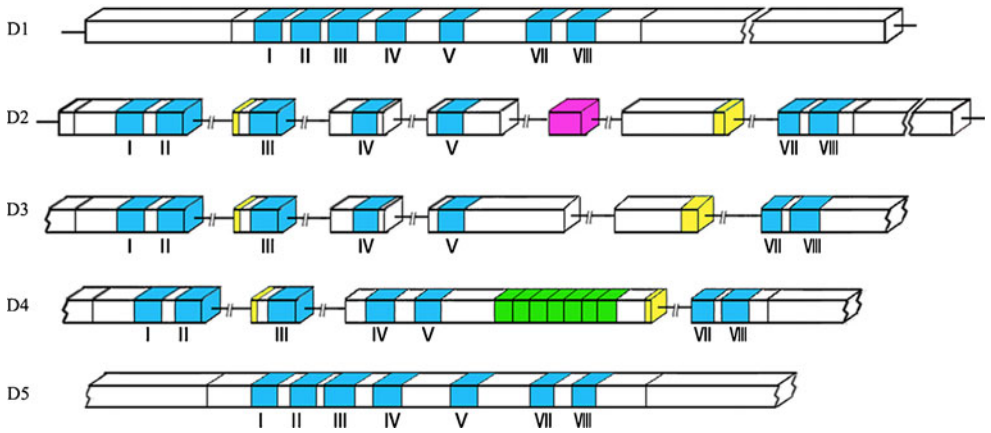

Fig. 1 Genetic schematic of human dopamine receptors. *Lines* introns, *boxes* exons, *blue boxes* the putative transmembrane domains, *yellow boxes* the untranslated region of the corresponding mRNA; the watery *red exon* of the D2 receptor gene indicates the alternatively spliced exon (D2S and D2L); 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

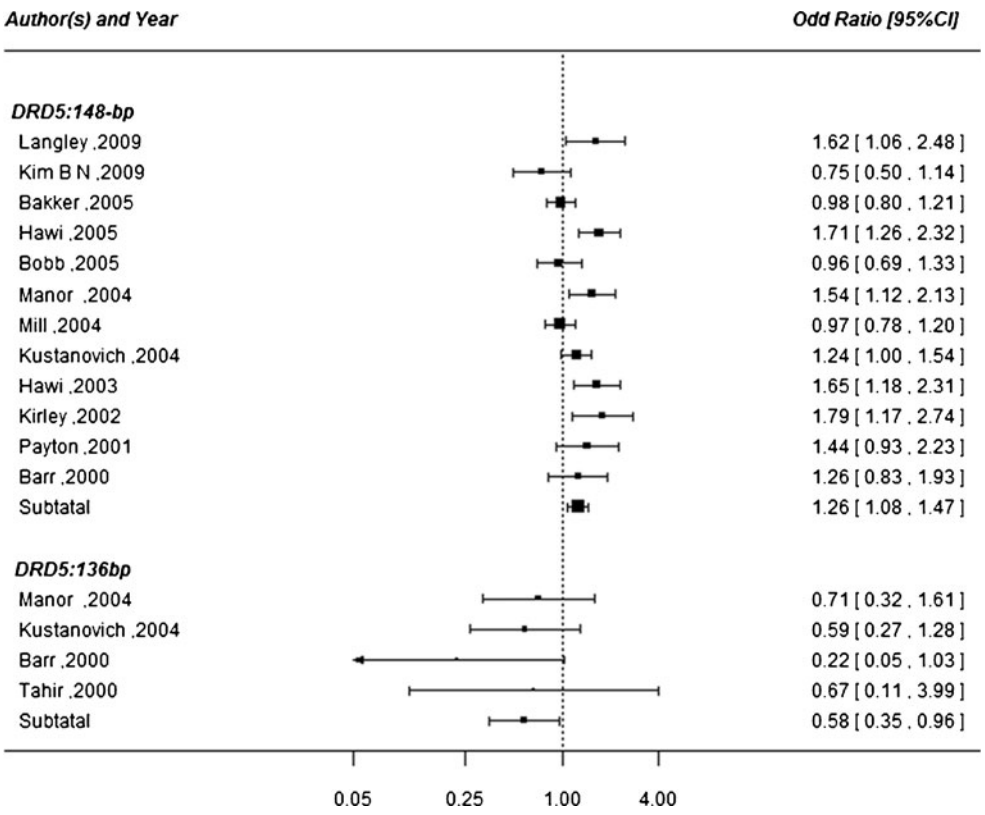

Fig. 2 Summary estimates for risk of ADHD associated with 148-bp and 136-bp of microsatellite flanking DRD5 from meta-analysis. Summary statistics: 148-bp (pooled OR=1.26, 95 % CI=1.08–1.47, P=0.0036; Q-statistic χ^2=.04, Pheterogeneity=0.0011, I^2=65.74); 136-bp (pooled OR=0.58, 95 % CI=0.35–0.96, P=0.0329;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

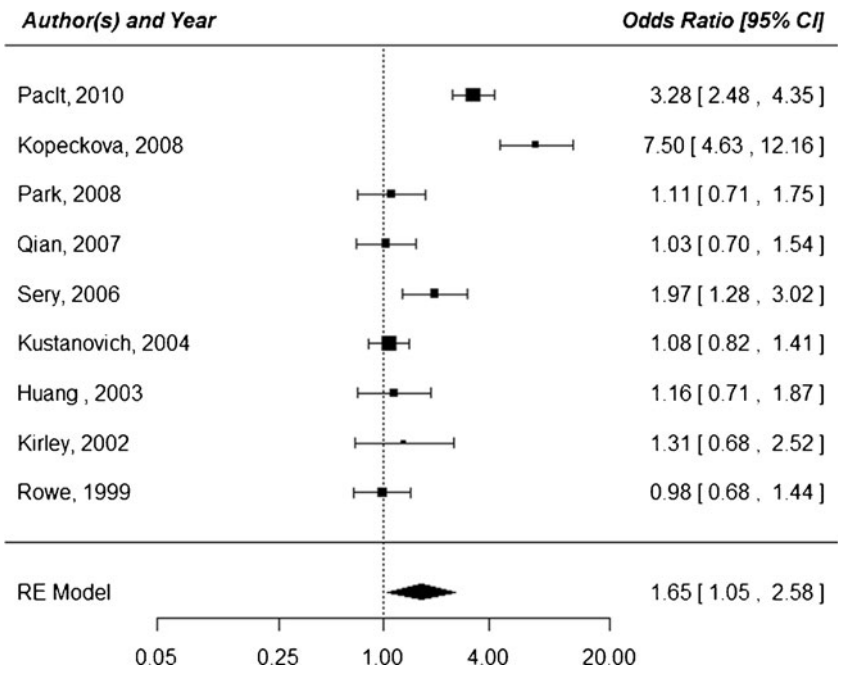

Fig. 3 Summary estimates for risk of ADHD associated with DRD2-TaqI (rs1800497) from meta-analysis (pooled OR= 1.65, 95 % CI=1.05–2.58, P= 0.0294; Q-statistic χ^2=89.12, Pheterogeneity<0.0001, I^2= 91.42). *CI* confidence interval, *RE Model* random effects model

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,

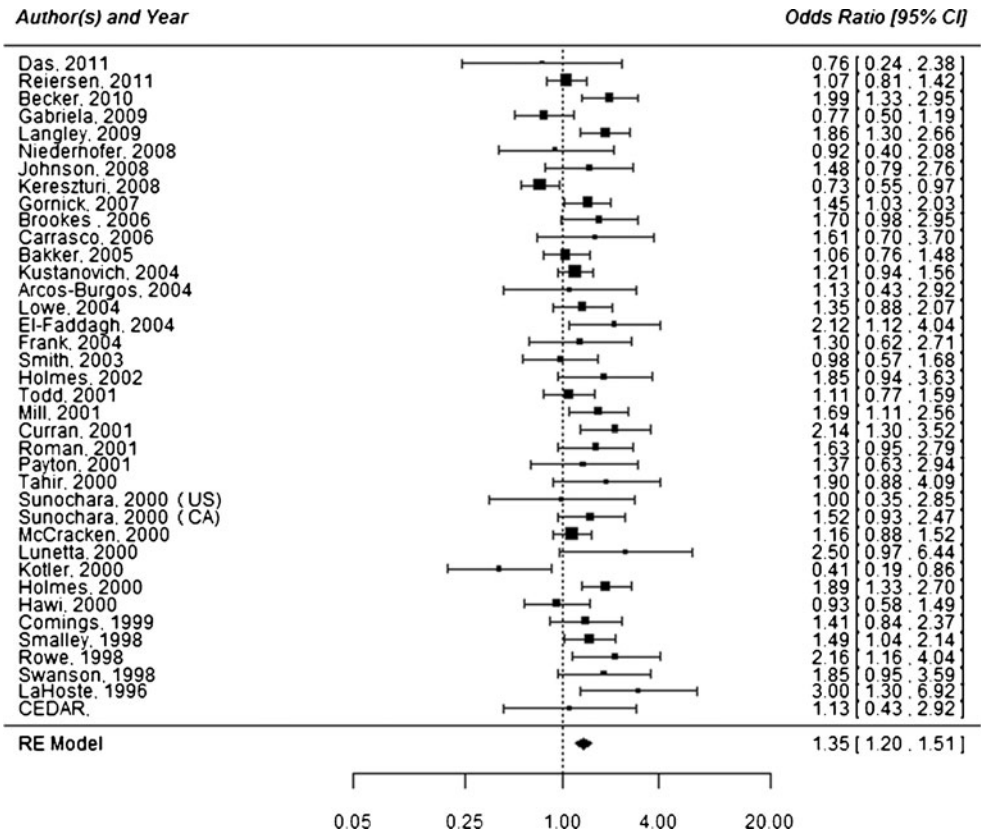

Fig. 4 Summary estimates for risk of ADHD associated with 7-repeat of DRD4 exon 3 VNTR from meta-analysis (pooled OR=1.35, 95 % CI=1.20–1.51, $P<0.0001$; Q-statistic $\chi^2=75.2$, Pheterogeneity=0.0002, $I^2=50.92$). *CI* confidence interval, *RE Model* random effects model

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.

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