

Received: 2011.06.11
Accepted: 2011.08.17
Published: 2011.09.01

Dopamine D4 receptor gene DRD4 and its association with psychiatric disorders

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Source of support: Self financing

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Summary

Dopamine receptors control neural signals that modulates behavior. Dopamine plays an important role in normal attention; that is the reason for studying the genes of the dopaminergic system, mainly in connection with disorders of attention. DRD4 influences the postsynaptic action of dopamine and is implicated in many neurological processes, exhibits polymorphism and is one of the most studied genes in connection with psychiatric disorders. Associations were found with ADHD (attention deficit hyperactivity disorder), substance dependences, several specific personality traits, and reaction to stress. These findings have implications for pharmacogenetics. This article reviews the principle published associations of DRD4 variants with psychiatric disorders.

key words:

DRD4 • dopamine receptor gene • psychiatric disorders • ADHD

Full-text PDF: <http://www.medscimonit.com/fulltxt.php?ICID=881925>

Word count: 1821

Tables: 1

Figures: –

References: 108

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BACKGROUND

Dopamine receptors are implicated in many biological (mainly neurological) processes [1–9], including cognition, memory, learning, and motor control, as well as modulation of neuroendocrine signaling [10], and thus are connected to many psychiatric and neurological disorders.

The human dopamine receptor D4 (*DRD4*) gene, located near the telomere of chromosome 11p, exhibits an unusual amount of expressed polymorphism. It contains a 48-bp Variable Number Tandem Repeat (VNTR) polymorphism in the third exon [11], repeated between 2 and 11 times, with the most common versions being 2 (2R), 4 (4R) and 7 (7R) repeats. The 48-bp repeat is thought to reside in the third cytoplasmic loop of the receptor protein; this variation has been shown to affect the function of the D4 receptor. In most geographic locations, the 4R allele is the most common, whereas 2R and 7R allele frequencies vary widely [12].

The frequency of allele variants varies among ethnic groups, which makes the study of their associations more difficult. The 7R allele has low prevalence in Asia (2%), but high prevalence in America (48%) [13].

The 7-repeat allele has been reported to encode a receptor with lower affinity for dopamine. *In vitro* studies indicate that the sensitivity of the 7R allele is half that of the 2R and 4R variants [12]. The 7R allele is associated with various psychiatric disorders including ADHD, dependences, pathological gambling, alcoholism, drug dependence and bulimia nervosa [14,15]. Several studies also described associations with autism and schizophrenia [16–18]. However, in these disorders other genes have received more attention (e. g. [19]). *DRD4* length polymorphism has been described in connection with specific behavioral phenotypes including externalizing behavior problems [20], the personality trait of novelty seeking, impulsive personality traits, anger, short temper and thrill seeking and aggressive and delinquent behavior, as compared to other genotypes (e. g. [21]). Kang et al. [22] found that the short allele was associated with significantly lower anger in tendency to anger and higher forgiveness traits. *DRD4* variants also play an important role in pharmacogenetics [23]. However, the functions of all the individual variants have not been confirmed [24] and the effects of the variants on transporter levels cannot be generalized to neuropsychiatric disorders. Despite the large number of empirical studies in this field, a review article on the dopamine D4 receptor gene *DRD4* and its association with psychiatric disorders is still lacking from the literature; hence, the present article reviews current scientific findings in this area.

DRD4 AND PERSONALITY TRAITS

Personality traits are suggested to play an important role in psychiatric disorders. Each individual behaves according to certain distinctive patterns throughout a variety of situations. Personality traits have both environmental and biological backgrounds (e.g. [25–27]). Evidence based on twin and adoption studies suggests that personality traits are partially heritable.

Several studies have described the association of *DRD4* and temperament or personality traits (e.g. [28]). Results suggest that the long allele (7 and more repetitions) is associated with high novelty seeking and risk taking, constricted emotional responses, but is also associated with preserved attention processing of emotional stimuli and efficient problem solving [28,29].

Kluger et al. [30], in a meta-analysis, stated that despite many authors having found the presence of longer alleles to be associated with higher novelty seeking scores, on average there is no association between *DRD4* polymorphism and novelty seeking. The heterogeneity among the studies is very high.

De Luca et al. [31], in a follow-up study, presented evidence indicating that there is a genetic influence of the *DRD4* gene on human temperament at birth, at 1 month of age and at 3 years of age [32]. The study showed, only in part, previous results of a link between the *DRD4* gene and human temperament. None of the extraversion or exploratory behavior measures were related to the 7R form of *DRD4*.

DRD4 AND ASSOCIATION WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

The role of polymorphisms of this gene on etiology of ADHD has been intensively researched (e.g. [33–36]). Dopamine dysfunction may be involved with ADHD symptoms. Along with other candidate genes (*DRD2*, *DAT1*, *DRD1*, *DRD5*, *DBH*), *DRD4* is one of the most studied genes [37,38]. VNTR polymorphism in the *DRD4* gene associates with ADHD across numerous studies. Association between ADHD and the 7-repeat allele has been widely documented (e.g. [39]). The 7-repeat allele was found in 41% of ADHD patients, but in only 21% of the control group. A meta-analysis of 21 studies revealed evidence of significant association [39]; however, negative results were also published. According to Faraone [40] there is an association between ADHD and *DRD4*, but it is small.

Independent studies showed an association between the presence of allele 7 and personality traits associated with impulsivity [39].

It was found that the presence of the 7-repeat allele of *DRD4* and the 10-repeat allele of *DAT* is connected with high perfusion in the right middle temporal gyrus associated with working memory and selective attention [40]. Lower attention was described in children carrying 7R [41]. Bellgrove [42] contradicted this finding and found 7R leads to better long-term memory.

However, the *DRD4* polymorphism itself does not cause ADHD. Many other factors were found to take part in ADHD (e.g. [35,36,43]). Further studies are needed to confirm these findings and explore the role of specific gene-gene and gene-environment interactions and other co-occurring psychopathology among individuals with ADHD [44].

DRD4 AND DEVELOPMENTAL DISORDERS

Autism is a widely studied disorder (e.g. [45–48]) and many candidate genes have been identified. Although a genetic component for autism has received much consideration, to

date genome scans have failed to identify genes of major effect. Authors suggest a genetic similarity to ADHD and focus on similar genes, such as DRD4.

Several studies found a positive association of the 7R allele of the DRD4 gene and autism (e.g. [49]), but the DRD4 exon 3 polymorphism is still unlikely to play a major role in the etiology of autism [50].

DRD4 AND DEPENDENCES

Dopaminergic abnormalities are implicated in the pathogenesis of substance abuse. Several genetic variants, especially DRD2 and DRD4, were previously reported in the literature as associated with substance abuse [51]. Carriers of the DRD4 7R allele showed greater susceptibility to alcohol dependence [52,53] and opioid dependence [14]. Among carriers of the 7R allele, a higher rate of cigarette smoking was observed [54]. Ellis et al. [55] described a connection between 7R and neuroticism and nicotine dependence, and Nederhof [56] describes a connection to pathological gambling.

McGeary [57] points to the inconsistency of studies investigating relations between DRD4 polymorphisms and dependences, and suggests focusing on addiction-related phenotypes more than diagnosis of dependence itself. Dependences can be associated with specific traits or disorders (e.g. [58]).

DRD4 AND REACTION TO STRESS

According to various studies DRD4 variants can affect individual responses to stress or trauma, similar to several other gene variants (e.g. [33,59]). Das et al. [54] described the effect of the DRD4 gene and childhood environment interaction on resilience to stressors. Armbruster et al. [60] found that carriers of the 7R allele together with the 5HTTLPR L allele exhibit lower cortisol stress responses.

The DRD4 genotype also moderates the association of experienced parental problems during childhood (e.g., parental depression, marital discord) with loss or trauma [61]. The 7R allele influences the development of personality in a way that provides protection against adverse outcomes [54].

Opposite results were published by Dragan et al. [62] in relation to post-traumatic stress disorder (PTSD). Participants with at least 1 copy of the DRD4 7 or 8 repetitions allele had more intense PTSD symptoms.

DRD4 AND ITS IMPORTANCE IN PHARMACOGENETICS

Individual differences in drug response are very important in medicine, including psychiatry (e.g. [63–65]). A specific drug can be highly beneficial for some patients but have little or no effect in others and, moreover, the same drug can have serious adverse effects for others (e.g. [66–68]).

DRD4 is mainly considered to affect treatment response by stimulants in ADHD. Effects vary as a function of DRD4 and DAT1 variants and these 2 genes are the main candidate genes for pharmacogenetic investigation [69]. Several studies suggested that DRD4 7R variant is associated with lower response to stimulants, and patients with 7R require

higher doses of methylphenidate (e.g. [70]). However, the currently available literature on the role of DRD4 in pharmacological response to methylphenidate still presents conflicting results [71].

The D4 receptor gene also affects response to neuroleptics in schizophrenia, where 4R/4R is considered to be predictor of better neuroleptic response [72]. Other studies pointed to the influence of DRD4 variants on effects of antipsychotic treatment in alcoholism [23]. However, effect of treatment is influenced by many other factors, thus reliable assessment of the importance of genetic factors is complicated [73–81].

CONCLUSIONS AND DISCUSSION

DRD4 is a widely studied gene in psychiatric disorders. However, it is very controversial and results of studies are ambivalent. Despite the dopamine D4 receptor gene (DRD4) showing promise for explaining significant variance in individual differences in both behavioral and neural measures of inhibitory control [87], the DRD4 gene is one of the most variable human genes and unlikely causes psychiatric disorders.

Generally, both genetic (e.g. [88–90]) and environmental factors play a role in the etiology of psychiatric disorders (e.g. [91–95]). Psychiatric disorders are not monogenic, and many interactions participate in the development of a disorder. The utility of candidate genes is limited. Many polymorphisms have been so widely studied that they have been associated with an implausibly large number of psychiatric and non-psychiatric phenotypes, many of which are likely to be false positives. The presence of many comorbidities in psychiatric disorders also complicates the investigation (e.g. [96–101]).

DRD4 is one of the most studied genes in attention deficit disorders. Although many studies found associations, the relationship between DRD4 and attention deficit is not simple. The limitation of most studies on DRD4 is studying only the DRD4 polymorphisms themselves without connections to and interactions with other genes of the dopaminergic system. A number of genes, each yielding a small effect size, contribute to the phenotype, and any polymorphism may neither be necessary nor sufficient to determine the trait.

Schizophrenia is one of the most studied disorders (e.g. [79,102]) and despite the fact that schizophrenia is considered to have a significant genetic component and that there are a number of genes that contribute to susceptibility to or pathology of schizophrenia, none exhibit full responsibility for the disease. In schizophrenia, as in many other psychiatric disorders, many gene variations that were identified as being linked to the disorder are common in general populations. This makes assessment of genetic relations in psychiatric disorders complicated [103–106].

DRD4 variants are therefore considered only to be associated with increased risk of developing the disorder, and are not thought to be a causative factor. Many studies mentioned that psychiatric disorders are caused by a number of genetic and environmental factors [107,108]; this fact has to be considered in interpretation of findings.

Table 1. Described influence of DRD4 polymorphism in psychiatric diagnoses.

Disorder according to DSM IV	Genetic association			References
	Strong	Mild/ Debatable	Not confirmed/ Not known	
Disorders usually first diagnosed in infancy, childhood, or adolescence				
<i>Pervasive developmental disorders – 299.00 Autistic disorder</i>		X		50
<i>Attention-deficit and disruptive behavior disorders – 314.01 314.00, 314.9 - Attention deficit hyperactive disorder</i>	X			39
Delirium, dementia, and amnesic and other cognitive disorders			X	
Substance-related disorders				
<i>305.00, 303.90, 291.1–9 Alcohol related disorders</i>	X			52, 53
<i>305.1 – Nicotine dependence</i>	X			82
Schizophrenia and other psychotic disorders				
<i>295.1–9 Schizophrenia</i>			X	83
Mood disorders				
<i>Depressive disorders, Bipolar disorders</i>		X		84
Anxiety disorders				
<i>300.3 – Obsessive-compulsive disorder</i>		X		85, 86
Somatiform disorders				
Factitious disorders				
Dissociative disorders				
Sexual and gender identity disorders				
Eating disorders		X		15
Sleep disorders			X	
Impulse-control disorders not elsewhere classified			X	

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