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Review

The DRD4 exon 3 VNTR polymorphism and addiction-related phenotypes: A review ☆

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ABSTRACT

In addition to the large literatures on associations of the DRD4 VNTR polymorphism with ADHD and personality traits, there is an emerging literature linking this variant to addiction and addiction-related phenotypes. When only diagnosis-based studies are considered, an inconsistent picture emerges raising doubts as to the relevance of this polymorphism to addiction. However the use of multiple levels of analysis in examining the importance of this polymorphism has raised the possibility of an urge-related "intermediate phenotype" that puts one at risk for developing addiction but may not be found in all persons with an addiction diagnosis. From cellular assays through neuroimaging and behavioral phenotypes, these studies highlight the power of the "intermediate phenotype" approach and suggest a possible explanation of the mixed findings when diagnosis is used as the phenotype. Strengths and weaknesses of alternative DRD4 VNTR genotype grouping strategies are discussed. In sum, converging evidence across multiple methodologies supports the possibility of a robust relationship between the DRD4 exon 3 VNTR polymorphism and urge for addictive substances.

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1. DRD4 and addiction-related phenotypes

The D4 dopamine receptor gene, located on the short arm of chromosome 11, encodes a 7 transmembrane G-protein coupled receptor that responds to endogenous dopamine. A variable number of tandem repeats (VNTR) polymorphism in exon 3 impacts the length of the protein in the receptor's third cytoplasmic loop, altering receptor sensitivity (Van Tol et al., 1992). This 48 basepair sequence is repeated between 2 and 11 times with the most common versions being 2, 4 and 7 repeats. Most consistently in the literature, individuals have been grouped as either "short" carriers or "long" carriers with the category of "short" being defined as 6 or fewer repeats and "long" as 7 or more repeats. More recently, a newer classification system has arisen that compares the putative ancestral allele (i.e., the allele of the last common ancestor from which the other alleles are derived) of 4 repeats to the 2 and 7-repeat variants (Ding et al., 2002). However, this analytical scheme has not been universally adopted in newer literature, making direct comparisons across studies more difficult.

There is difficulty in reaching consensus as to the distribution of D4 receptors in human brain as a specific ligand has yet to be identified. The consequence of this is that only indirect methods have been used to infer D4 distribution. For example, D4 expression levels were characterized using RT-PCR in a single brain with results showing relatively increased expression in the occipital lobe, cerebellum, hippocampus, temporal lobe, middle frontal gyrus, frontal lobe, cingulated gyrus and amygdale. Relatively decreased expression was seen in the substantia nigra, caudate, globus pallidus and parietal lobe (Mulcrone and Kerwin,

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Table 1
Selected examples from the literature.

Authors and publication date	DRD4 allele grouping strategy	Population and size	Phenotype(s)	Brief results
Neuroimaging phenotypes				
Filbey et al. (2008)	S<7 repeats L≥7 repeats	73 heavy drinkers	BOLD response in orbitofrontal cortex, anterior cingulate and striatum	DRD4L individuals showed greater response to cues in examined regions than DRD4S individuals
McClernon et al. (2007)	S<7 repeats L≥7 repeats	15 smokers	Differential responses in superior frontal gyrus, anterior cingulated, insula and cuneus by DRD4 genotype	DRD4L individuals showed greater cue reactivity in examined regions than DRD4S individuals
Lab-based phenotypes				
Hutchison et al. (2002a)	S<7 repeats L≥7 repeats	68 smokers	Urge to smoke, arousal, positive affect and attention after being exposed to smoking cues	DRD4L individuals reported greater urges, more arousal, less positive affect and more attention when compared to DRD4S individuals
Hutchison et al. (2002b)	S<7 repeats L≥7 repeats	74 heavy drinkers	Urge to drink, subjective high, stimulation and arousal	DRD4L individuals reported greater urges, less stimulation and arousal when compared to DRD4S individuals
Hutchison et al. (2003)	S<7 repeats L≥7 repeats	67 heavy drinkers	Urge to drink, subjective high, stimulation and sedation	Olanzapine reduced urge to drink at baseline, after alcohol cues, and after alcohol drinks for DRD4L individuals and for DRD4S individuals at baseline only. DRD4L individuals reported greater increases in high across trials than DRD4S individuals
MacKillop et al. (2007)	S<7 repeats L≥7 repeats	35 heavy drinkers	Urge to drink, positive and negative affect, relative value of alcohol	Continuous analyses of data suggest that urge to drink was associated with the relative value of alcohol and DRD4L status amplified this relationship
McGeary et al. (2006)	S<7 repeats L≥7 repeats	93 non-treatment seeking heavy drinkers	Urge to drink, blood pressure and heart rate	Non-significant trend for DRD4L carriers to report greater urge after cues compared with carriers of 2 DRD4S alleles when dependence was included in the model
Shao et al. (2006)	S=2–4 repeats L=5–7 repeats	420 Chinese heroin abusers	Urge reactivity to heroin-related cues	Significantly greater increases in subjective urge reported by DRD4L carriers compared with carriers of 2 DRD4S alleles
Sobik et al. (2005)	S<7 repeats L≥7 repeats	48 healthy college students (study 1) and 31 adults with subclinical binge eating disorder (study 2)	Urge to consume preferred foods, attention to cues, and mood	DRD4L status associated with increased urge after priming doses of preferred food in study 1 only
Van den Wildenberg et al. (2007)	S<7 repeats L≥7 repeats	88 male drinkers	Urge, arousal, saliva reactivity	DRD4L individuals reported less urge, more arousal, and showed greater salivary responses by beverage when compared with carriers of 2 DRD4S alleles
Behavioral phenotypes				
Hopfer et al. (2005)	S<7 repeats L≥7 repeats	4432 youth assessed during adolescence	Average quantity of alcohol consumed per drinking episode over the past year	No association of DRD4 exon 3 VNTR with quantity of alcohol consumed
Laucht et al. (2005)	Presence vs. absence of 7-repeat allele	384 children from the Mannheim Study of Risk Children	ADHD and smoking in adolescence	Association of DRD4 exon 3 VNTR 7 repeat allele with smoking in ADHD diagnosed males but not females
Laucht et al. (2008)	Presence vs. absence of 7-repeat allele	220 children from the Mannheim Study of Risk Children	Smoking inventory developed by World Health Organization	DRD4 exon 3 VNTR 7-repeat carriers had higher rates of lifetime smoking and poorer quit rates for smoking
Ray et al. (2008)	S<7 repeats L≥7 repeats	101 heavy drinking college students	Rutgers Alcohol Problem Index	DRD4 exon 3 VNTR associated with greater alcohol problems (an effect partially mediated by novelty seeking)
Ray et al. (in press)	S<7 repeats L≥7 repeats	112 heavy drinkers	Real time collection of urge, drinking data, and subjective effects of alcohol using palmtop computers	DRD4L carriers reported greater urge following alcohol consumption compared to carriers of 2 DRD4S alleles
Rodríguez et al. (2006)	Did not group by DRD4 VNTR status (i.e., all variants treated individually)	3637 participants form three studies of the age of first smoking	Age of smoking onset	No significant association of DRD4 exon 3 VNTR status and age of smoking onset
Shields et al. (1998)	S<6 repeats L≥6 repeats	283 smokers and 192 controls (72 African Americans and 403 Caucasians)	Smoking status, time to first cigarette, age of smoking initiation	African Americans with DRD4L had a higher risk of smoking, shorter interval to first cigarette, and earlier age of smoking initiation and poorer smoking cessation outcomes. Similar findings not seen in Caucasians
Skowronek et al. (2006)	Presence vs. absence of 7-repeat allele	305 children from the Mannheim Study of Risk Children	Substance use questionnaire developed by World Health Organization	Male DRD4 exon 3 VNTR 7-repeat carriers had higher rates of substance use involvement, female carriers of 2 DRD4S alleles who also were homozygous for the LL genotype at the 5HTTLPR genotype had the highest substance use

(continued on next page)

Table 1 (*continued*)

Authors and publication date	DRD4 allele grouping strategy	Population and size	Phenotype(s)	Brief results
Behavioral phenotypes				
Tidey et al. (2008)	S<7 repeats L≥7 repeats	115 heavy drinkers	Real time collection of urge, drinking data, and subjective effects of alcohol using palmtop computers	No main effects of DRD4 exon 3 VNTR on measured variables, but an interaction with medication where DRD4L carriers on naltrexone had reduced drinking days but no effect was seen of naltrexone on carriers of 2 DRD4S alleles
Vandenbergh et al. (2007)	S≤5 repeats L>5 repeats	416 participants originally ascertained by random digit dialing	Smoking status, cigarettes per day, time to first cigarette, and withdrawal	DRD4 exon 3 VNTR associated with withdrawal symptoms. Desire/craving, anger irritability, and trouble sleeping were reported as less in DRD4L carriers
Vandenbergh et al. (2000)	S≤5 repeats L>5 repeats	184 substance abusers and 122 controls	Drug Use Survey (DUS)	DRD4L alleles more commonly found in individuals with high quantity/frequency of drug use compared with controls
Diagnostic phenotypes				
Ballon et al. (2007)	Did not group by DRD4 VNTR status (i.e., all variants treated individually)	97 cocaine-dependent patients and 88 controls	DSM-IV smoked cocaine dependence	Associations of DRD4 exon 3 VNTR with patients with childhood ADHD and those with high impulsivity
Cevoli et al. (2006)	Unclear if any grouping other than binning rare genotypes (e.g., 2/2, 3/7, etc.) was used	101 migraine sufferers, 97 chronic daily headache sufferers with drug abuse and 102 controls	Presence of headache, drug abuse (unclear how assessed)	No findings of DRD4 related to drug abuse status
Chen et al. (2004)	Presence vs. absence of 7-repeat allele	416 methamphetamine users and 435 controls	DSM-IV methamphetamine disorders	7-repeat allele more commonly found in methamphetamine abusers than controls
Chang et al. (1997)	Did not group by DRD4 VNTR status, also used haplotypes with other DRD4 polymorphisms	61 alcoholics and 66 non-alcoholics across three Taiwanese populations	DSM-III-R alcohol dependence	No associations of DRD4 with alcohol dependence status
Comings et al. (2001)	S = 2–4 repeats L = 5–7 repeats	139 pathological gamblers and 139 controls	DSM-IV diagnosis of pathological gambling	Association of DRD4L status with pathological gambling
Comings et al. (1999)	7 repeat carriers vs. all others, and other genotype groupings	707 index subjects and 737 controls	Sum score from the Addiction Severity Index for substance abuse and additional measures for Tourette's ADHD and pathological gambling	No findings for 7 repeat carriers vs. non-carriers, ASI sum scores were lowest in 4/4 individuals followed by all heterozygotes, 7/7 individuals, with 2/2 individuals having the highest scores
Franke et al. (2000a)	Did not group by DRD4 VNTR status for the case control study tested TDT using individual alleles and grouping 6–8 repeats as "long"	Case control design — 285 cases and 197 controls, TDT — 111 heroin dependent patients and their parents	DSM-III-R opioid dependence	No associations of DRD4 with opioid dependence status, no preferential transmission of DRD4 exon 3 VNTR alleles in TDT
Franke et al. (2000b)	Did not group by DRD4 VNTR status for the case control study tested TDT using individual alleles and grouping 5–7 repeats as "long"	Case control design — 218 cases and 197 controls, TDT — 76 alcoholics and their parents	DSM-III-R alcohol dependence	Association of 7-repeat allele and alcohol dependence in case control design but not supported by TDT results
Geijer et al. (1997)	Did not group by DRD4 VNTR status (i.e., all variants treated individually)	74 alcoholics and 108 controls	DSM-III-R alcohol dependence	No association of DRD4 exon 3 VNTR and alcohol dependence
George et al. (1993)	Did not group by DRD4 VNTR status (i.e., all variants treated individually)	72 alcohol-dependent individuals	Alcohol intake, other drug use, family history of alcohol dependence	Increased frequency of DRD4 3 and 6 repeat alleles in alcoholics compared to published rates in controls, 3/3 and 4/7 individuals reported more other drug use and family history status was associated with the 2/4 group
Ishiguro et al. (2000)	Did not group by DRD4 VNTR status (i.e., all variants treated individually)	185 Japanese alcoholics and 286 controls	DSM-IV alcohol dependence	No association of DRD4 exon 3 VNTR and alcohol dependence
Kotler et al. (1997)	Did not group by DRD4 VNTR status (i.e., all variants treated individually)	141 opioid dependent patients and 110 controls	DSM-IV opioid dependence	Association of 7-repeat allele and opioid dependence
Li et al. (2004)	Unclear	228 methamphetamine abusers and 181 controls	DSM-IV methamphetamine abuse	Association of DRD4 haplotype (including exon 3 VNTR) with methamphetamine abuse and interaction of exon 3 VNTR with COMT 158 Val/Met polymorphism
Li et al. (1997)	S = 2–4 repeats L = 5–7 repeats	121 Han Chinese opiate abusing patients and 154 controls	DSM-IV opiate abuse	Excess of 'long' repeat individuals in the patient group
Li et al. (2000)	S = 1–4 repeats L = 5–7 repeats	405 Han Chinese opiate abusing patients and 304 controls	DSM-IV opiate abuse	No association of DRD4 VNTR, −521 genotype or haplotypes and opiate abuse. DRD4 exon 3 VNTR associated with route of administration of heroin
Muramatsu et al. (1996)	Did not group by DRD4 VNTR status (i.e., all variants treated individually)	655 Japanese alcoholics and 144 unrelated controls	DSM-III-R alcohol dependence	Increased frequency of DRD4 5 repeat allele in alcoholics with protective ALDH2 allele compared with controls on alcoholics without this protective factor

Table 1 (*continued*)

Authors and publication date	DRD4 allele grouping strategy	Population and size	Phenotype(s)	Brief results
Diagnostic phenotypes				
Namkoong et al. (2008)	4 repeat homozygotes compared with all others	18 children of alcoholics and 23 children of nonalcoholic parents	DSM-IV alcohol dependence in parents	4-repeat homozygotes less common in children of alcoholics
Parsian and Zhang (1999)	Did not group by DRD4 VNTR status (i.e., all variants treated individually)	133 alcoholics and 89 unrelated controls	DSM-III-R alcohol dependence, Type II alcoholism	No association of DRD4 exon 3 VNTR with alcoholism or Type II alcoholism
Roman et al. (1999)	Did not group by DRD4 VNTR status (i.e., all variants treated individually)	136 alcoholics and a sample of Caucasians and Afro-Brazilians of 100 each	DSM-III-R alcohol depedence	No association of DRD4 exon 3 VNTR with alcoholism
Szilagyi et al. (2005)	Individual allele comparison and presence vs. absence of the 7-repeat allele	73 substance dependent patients and 362 controls	DSM-IV substance dependence	No association of DRD4 exon 3 VNTR variants with substance dependence
Tsai et al. (2002)	Did not group by DRD4 VNTR status (i.e., all variants treated individually)	116 methamphetamine dependent patients and 112 controls	DSM-IV methamphetamine dependence	No association of DRD4 exon 3 VNTR variants with methamphetamine dependence
Vandenbergh et al. (2000)	S<5 repeats L≥6 repeats	184 substance abusers and 122 controls	Scores on the Drug Use Survey of 3 were considered abusers and compared to those with scores of 0, 1 and no DSM-III-R diagnoses of abuse or dependence	Higher frequency of DRD4L alleles in the abusers compared with controls

1997). More recently using subtraction methods, Lahti et al. report evidence suggesting D4 receptors are more frequent in the insula, hippocampus, cingulated cortex, entorhinal cortex, and temporal cortex. They further report moderate density in substantia nigra relative to the caudate, putamen, and nucleus accumbens where no binding was detected (Lahti et al., 2005).

This VNTR polymorphism in the *DRD4* gene associates with ADHD across numerous studies (reviewed by Kuntsi et al., 2006), but the focus of this review will be on how the DRD4 relates to addiction diagnoses and related phenotypes. Studies reviewed have been divided into categories based upon the phenotype examined in order to highlight the advantages of using intermediate phenotypes that are more proximal to the level of action of the gene product than diagnosis. This review will not address the literature associating the DRD4 VNTR to personality traits except as those studies relate to behavior phenotypes (see Munafò et al., 2008a,b for a meta-analysis and review of DRD4 variants and personality traits). Similarly this review will focus on research examining the VNTR polymorphism and studies that incorporate this polymorphism in haplotypes (i.e., studies focused on the DRD4 −521 genotype and other individual variants will not be included).

The concept of an endophenotype (i.e., a narrowly defined phenotype that is more likely to be influenced by genetic variation than a heterogeneous category like diagnosis) has gained popularity in psychiatric genetics and may provide a method for dissecting genetic influences for subtypes of a disorder. Gottesman and Gould defined criteria for endophenotypes that included knowledge of heritability and co-segregation in families (2003). Since many putative endophenotypes lack information in these areas, the use of the term "intermediate phenotype" has been widely adopted for phenotypes more proximal to the action expected of genetic variation but for which information on heritability and co-segregation are not yet available. To demonstrate the relative strength of this approach, the following sections will summarize research findings in the broadly-based categories of cellular findings, neuroimaging findings, lab-based phenotypes, and behavioral phenotypes (see Table 1). These findings will then be contrasted with a section summarizing genetic association studies using diagnostic phenotypes. An overall summary and suggestions for future directions will also be presented.

1.1. Cellular findings

One of the most proximal phenotypes used to suggest functional relevance of a particular polymorphism is cellular assays (i.e., one is much more likely to find effects of altered gene products or expression differences at the level of a cell than at the level of an organism). A comprehensive review of this literature was completed by Oak et al. (2000). Research findings since then have largely come from the Moyzis group (e.g., Ding et al., 2002; Grady et al., 2003; Reist et al., 2007; Wang et al., 2004). This group has haplotyped and resequenced the *DRD4* gene (including the repeats themselves) to identify variation and inform the evolution of this gene. Their findings suggest two possible reinterpretations of the existing DRD4 literature: that the 4-repeat allele is the progenitor and should be compared to the 2-repeat and 7-repeat alleles that each show decreased cAMP activity (4>2>7) and that previous DRD4 findings may in fact be driven by rare variants in the 7-repeat allele rather than by the length polymorphism itself.

1.2. Neuroimaging findings

An important approach to understanding the relationship of genetic variation to differences in brain structure and function is the so-called imaging genetics approach. In addition to providing objective evidence of differences by genotype (i.e., the phenotype is not reliant on self-report), this approach can identify neurocircuits that underlie the phenotype of interest. Numerous studies across multiple substances of abuse have examined the neuroanatomy underlying urge. Brain regions consistently implicated by differential activation include the prefrontal cortex, anterior and posterior cingulated, fusiform gyrus, parietal lobe, temporal gyrus, amygdala, insula, hippocampus, precuneus and cuneus (e.g., Braus et al., 2001; Breiter et al., 1997; Garavan et al., 2000; McClernon et al., 2007; Myrick et al., 2004).

In spite of this potential utility, there appear to be only two fMRI studies examining DRD4 and addiction-related phenotypes. McClernon et al. (2007) report on differential brain activation in smokers undergoing cue reactivity trials for DRD4L (L≥7 repeats) carriers compared with carriers of 2 DRD4S alleles. Differential activation of right frontal gyrus and right insula by DRD4 genotype (i.e., greater activation in these regions for DRD4L carriers) may reflect the evidence that these areas are both involved in urge and are thought to be locations where D4 receptors are expressed in high numbers.

A study using alcohol cues and primes found consistent evidence for the importance of the DRD4 VNTR in cue reactivity (Filbey et al., 2008). These investigators found differential activation of the orbitofrontal cortex, anterior cingulate and striatum in DRD4L carriers compared with carriers of 2 DRD4S alleles prior to a priming dose but not after the administration of a priming dose. It is noteworthy that the brain regions implicated in this study have been seen as regions related to urge and

reward but not necessarily areas with high density D4 receptor expression providing support for the notion that a systems approach is needed in imaging genetics (e.g., Green et al., 2008). These two studies mark the beginning of a research area with much promise to parse the importance of this polymorphism with regard to addiction, as they are suggestive of a differential urge reactivity by DRD4 genotype. Numerous opportunities exist to examine additional fMRI tasks related to addiction, other drugs of abuse, and use of other neuroimaging techniques such as positron emission tomography and diffusion tensor imaging.

1.3. Lab-based behavioral findings

Laboratory studies provide the most consistent evidence that the DRD4 exon 3 VNTR is associated with addiction-related phenomena. A study of cue reactivity in smokers found that DRD4L individuals reported greater urge to smoke and greater arousal after smoking cues relative to non-smoking cues, more of a decrease in positive affect in the presence of cues and greater to attention to cues (Hutchison et al., 2002a). A similar study of alcohol cue reactivity and alcohol administration in heavy drinkers provided some support for the idea that this DRD4 association might extend to other drugs of abuse. This study found that DRD4L carriers reported greater urges to drink in the alcohol condition as compared to the placebo condition. In contrast to the smoking study however, DRD4L participants reported less stimulation and arousal across beverage trials (Hutchison et al., 2002b). Further evidence that the DRD4 effects on urge may be related to addictive urge as a whole was provided by a study of opiate abusers (Shao et al., 2006). In this study DRD4L participants reported more subjective urge than carriers of 2 DRD4S alleles when exposed to heroin-related cues. Of note however was a different classification of DRD4L and DRD4S in this study (DRD4L = 5–7 repeats, DRD4S = 2–4 repeats). Another report suggested DRD4L individuals experience greater urges to food cues, (Sobik et al., 2005) suggesting DRD4 effects on urge might represent an etiological pathway that is common to eating and addiction.

A further methodological refinement was used in a follow-up study by the Hutchison group (Hutchison et al., 2003). In order to help substantiate the role of the DRD4 VNTR, the alcohol cue reactivity and administration protocol was conducted with concurrent administration of either olanzapine, a pharmacological probe with DRD4 activity or cyproheptadine, an active placebo medication which does not act on DRD4. The study found that DRD4L carriers on active placebo reported greater urges to drink after being exposed to alcohol cues whereas DRD4L carriers on olanzapine did not. Olanzapine did not reduce cue-induced urge to drink in carriers of 2 DRD4S alleles. This approach provided important evidence that the DRD4 VNTR associations were not spuriously driven by an unmeasured third variable such as population stratification or an unmeasured genetic variation in another neurotransmitter system. That is, olanzapine should not attenuate urges to drink if the associations are being driven by an unmeasured variable unrelated to olanzapine's pharmacology.

The application of behavioral economic methods to laboratory studies of urge is also a promising new direction. When participants completed an alcohol/money choice task following a cue exposure the relationship between DRD4 VNTR status and relative value of alcohol was strengthened (Mackillop et al., 2007). Such behavioral economic approaches may provide a common metric by which to gauge the value of the addictive substance in comparison to alternative reinforcers in a fashion that may highlight competing reinforcers that may be useful in treatment.

Not all research supports the relationship between the VNTR and urge to use an addictive substance. For example, in McGeary et al. (2006) when the role of the DRD4 VNTR was examined in an alcohol cue reactivity study of mixed alcohol-dependent and non-dependent participants, there was no significant effect of DRD4 across the sample. Partitioning out variance associated with alcohol dependence clarified the relationship: DRD4L carriers appeared to experienced greater urge than carriers of 2 DRD4S alleles following cue exposure, but due to limited power, the effect was marginal ($p = 0.09$). Another alcohol cue reactivity study resulted in findings in the opposite direction of those expected based upon the above studies. DRD4L carriers in this study reported less urge and more subjective arousal following exposure to alcohol-related cues (van den Wildenberg et al., 2007). It is possible that the subjective reporting of urge as a phenotype may be impacted by several factors such as variability in awareness of one's own internal state, differences in attention and the context in which the lab study is performed (e.g., if a participant knows they have to study after completing their research participation that day, they may override any desire to drink for practical reasons and may not report a desire to consume more alcohol).

In summary, the use of lab-elicited intermediate phenotypes appears to have advantages over more heterogeneous diagnostic phenotypes (see below for detailed discussion). Although not without negative findings, there appears to be a fairly consistent pattern of findings across studies suggesting the relevance of the exon 3 VNTR polymorphism to urges relating to substance use. This area of research has been strengthened through the use of innovative techniques (e.g. pharmacological probes and behavioral economics) to substantiate and clarify earlier findings. Further directions might include expanding the drugs of abuse studied using these methods and more comprehensive analyses of DRD4 variability.

1.4. Behavioral findings

Diagnosis of a substance related disorder requires the endorsement of symptoms that are biologically and culturally based (cf tolerance vs. fulfillment of role obligations). Therefore, when attempting to elucidate etiological pathways that are moderated by genetic variation, intermediate phenotypes that are primarily biological in nature are required. For example, the use of quantity–frequency phenotypes may have utility whereas other social, occupational or legal consequences, like drunk driving, may be more environmental and less genetic in origin. Thus, these phenotypes may provide an opportunity to understand the role of genetically moderated factors such as pharmacokinetic and pharmacodynamic differences that may or may not lead to a formal dependence diagnosis. This approach has been used when examining substance use (broadly defined) by Vandenbergh et al., who found DRD4L carriers reported greater quantity and frequency of substance use when compared with controls (2000). Skowronek et al., examined participants in the Mannheim Study of Risk and found sex differences in DRD4 exon 3 VNTR effects wherein males who carry the 7-repeat allele had higher rates of substance use, but only female non-7-repeat carriers who were homozygous for the long version of the serotonin transporter 5HTTLPR polymorphism had higher substance use (2006).

Smoking researchers have provided numerous examples of behaviorally defined phenotypes in association analyses of the DRD4 exon 3 VNTR. Examples include the presence of the 7 repeat allele being associated with rates of smoking when compared with non-carriers of the7-repeat allele (Laucht et al., 2005, 2008) and African American (but not "Caucasian") carriers of >6 repeat alleles being at increased risk for smoking (Shields et al., 1998). The phenotype of smoking quit rates has also been examined with DRD4 exon VNTR status. Laucht et al., found that participants who carry the 7-repeat allele have lower quit rates than non-carriers of the 7-repeat allele (2008). This confirms and clarifies the earlier report that DRD4 long status (>6 repeats) associates with decreased success in quitting smoking in African Americans but not Caucasians (Shields et al., 1998). This group also examined the interval to the first cigarette of the day in this population and found that African Americans who carried a 6-repeat or longer allele had shorter intervals than those with shorter alleles. There was no difference by DRD4 genotype in Caucasians. Despite an emerging picture of consistency for longer DRD4 exon 3 VNTR alleles being associated with more severe smoking phenotypes, Vandenbergh et al., found that long carriers

(defined here as greater than 5 repeats) had fewer withdrawal symptoms, less desire/craving, less anger/irritability and less trouble sleeping than participants with shorter alleles (2007). Differences in allele grouping across these studies make comparisons difficult.

Alcohol-related behavioral phenotypes investigated in connection with the DRD4 exon 3 VNTR include quantity of alcohol consumed, alcohol-related problems, and naturalistic assessment of alcohol behaviors using ecological momentary assessment (EMA). A large study of adolescents using retrospective self-report found no relation of DRD4 exon 3 VNTR on the quantity of alcohol consumed (Hopfer et al., 2005). A recent study found that DRD4L carriers (>7 repeat alleles) reported more alcohol-related problems on the Rutgers Alcohol Problem Index (RAPI) and that this relationship may be mediated by novelty seeking (Ray et al., 2008). This relationship between DRD4 status and RAPI scores was also reported in a lab study of alcohol urge (Hutchison et al., 2002b) but personality traits were not tested as potential mediators. Two studies utilizing palmtop computers to collect alcohol-related data in real time while participants are in the natural environment (EMA) find evidence for the importance of the DRD4 exon 3 polymorphism. Tidey et al., found that this polymorphism moderated the effects of naltrexone on drinking days; those with 7 or more repeats on naltrexone had fewer drinking days compared to other groups (2008). An analysis that focused on the EMA data collected before participants were randomized to medication condition found that participants with 7 or more repeats reported greater urges to drink after alcohol consumption compared with those with fewer repeats (Ray et al., in press). These results suggest that the urge-related findings from laboratory studies may be generalized to urges experienced when drinking in the natural environment. Taken together studies of DRD4 associations with behavioral phenotypes present a mixed picture. In many cases it is possible that the more severe addiction-related behaviors could be influenced by differential urge (e.g., those who experience greater urge may have less success in quitting smoking), but many of these studies do not report on urge. It is of course likely that differential urge may be only one of several influences on complex behavioral phenotypes. Accordingly when other determinants of behavior predominate, the role of urge (and potentially DRD4 variation) may be ameliorated in a fashion that may result in the mixed findings reported in the literature.

1.5. Diagnostic findings

The use of diagnostic categories as a phenotype has a rich history. As might be expected for proponents of the intermediate phenotype approach, the results are mixed across multiple substances studied. In genetic association studies of substance abuse (broadly defined) and DRD4 exon 3 VNTR status, there are mixed findings with one study finding an association of >6 repeats with substance abuse (Vandenbergh et al., 2000) while two additional studies fail to find a relationship (Comings et al., 1999; Cevoli et al., 2006).

Within the alcohol field, there is one positive finding in unique study designed to investigate genetic risk factors that may override the protective effects of the aldehyde dehydrogenase ALDH2 polymorphism (the inactive gene product results in high blood high acetaldehyde levels and flushing, nausea, and headache). Muramatsu et al. found an increased presence of the 5-repeat allele in alcoholics with the protective ALDH2 allele compared with controls and alcoholics without the protective factor (Muramatsu et al., 1996). Another study found that the exon 3 VNTR 4-repeat homozygotes were less common in children of alcoholics (Namkoong et al., 2008). These findings contrast numerous studies that fail to find a relationship between DRD4 exon 3 VNTR status and alcohol dependence. Negative studies include those that examined genotype and allele frequencies without grouping (e.g., Parsian and Zhang, 1999; Ishiguro et al., 2000; Roman et al., 1999; Geijer et al., 1997), a study that examined the exon 3 VNTR with five other DRD4 polymorphisms using haplotype analyses (Chang et al., 1997), and combined case control and family-based association studies that could not confirm findings across both methodologies (Franke et al., 2000b).

Studies of heroin use disorders have similarly mixed findings with reports that the 7 repeat allele is over-represented in opioid dependent participants (Kotler et al., 1997) and those carrying 5–7-repeat alleles being associated with heroin abuse (Li et al., 1997). However when the authors expanded their sample of heroin abusers, they failed to replicate their original finding (Li et al., 2000). Interestingly, a phenotype related to route of administration was found to be associated with exon 3 VNTR genotype in this larger sample, leading the authors to speculate that administration route may vary with novelty seeking. Other negative findings for exon 3 VNTR status and heroin use disorders include a case control study examining the presence or absence of the 7-repeat allele (Szilagyi et al., 2005) and a mixed case control/family-based association methods (Franke et al., 2000a).

Investigations of stimulant drug misuse disorders show similarly mixed findings. Tsai et al., find no association of DRD4 alleles or genotypes with methamphetamine dependence. In contrast to these findings, Chen et al., report an over-representation of 7-repeat alleles in participants with methamphetamine abuse (2004) and a follow-up investigation by the same group finds epistatic interactions of DRD4 status with the COMT 158 Val/Met polymorphism (Li et al., 2004). In what appears to be the only published study examining the *DRD4* gene and cocaine dependence, Ballon et al., find in an African-Caribbean sample an excess of the 7-repeat allele and long grouping (5–10 repeat alleles) in those participants who were both cocaine dependent and had a childhood diagnosis of ADHD compare with controls and cocaine-dependent cases that did not have childhood ADHD, or low impulsivity (2007). Interestingly, studies of impulsive control disorders such as pathological gambling (sometimes referred to as a pseudo-addiction) find associations with DRD4 status (Comings et al., 1999, 2001).

In the absence of the intermediate phenotype data previously presented above, one might be tempted to take a dim view of the role of DRD4 VNTR genotype and addiction given the equivocal results linking DRD4 and distal outcomes like diagnosis of a substance use disorder. Despite thorough analyses of allelic and genotype variation across diagnostic categories, the negative studies appear to outweigh the affirmative findings. The endophenotype (or intermediate phenotype) approach to psychiatric genetics suggests this summary should not be surprising as the premise of the endophenotype approach is that diagnostic phenotypes are heterogeneous and the individual contribution of a particular polymorphism would be lost without considering a much more narrowly defined proximal outcome. Another possibility is that DRD4 associated differential urge is a risk factor for the development of an addiction diagnosis but is less relevant when individuals arrive at the same diagnostic criteria through multiple etiological pathways. Additionally, the DRD4 exon 3 VNTR polymorphism may be impacting some more general factor such as personality or attention that puts one at increased risk for impulsive behavior that may or may not result in the development of a substance use disorder.

2. Summary

When taken together, the studies reviewed above suggest an example of the power of the intermediate phenotype approach to begin to clarify an inconsistent literature based upon psychiatric diagnoses. With evidence spanning cellular assays through neuroimaging and lab-based assays to behavioral phenotypes, the importance of this polymorphism is becoming more apparent. While these findings may be reflective of an overarching construct such as the personality trait of impulsivity or unmeasured comorbidity with ADHD, there is now sufficient evidence to suggest that allelic differences are associated with differential brain activity and subjective urge for substances of abuse in multiple contexts (i.e., lab-based assays and the natural environment). Substantiation of these findings with pharmacological probes and behavior economics even further strengthens this emerging story.

Although beyond the scope of this review, it is important to note that there are rich literatures examining DRD4 variation and other phenotypes. For example the strength of the literature linking DRD4 variation to ADHD diagnosis cannot be ignored. DRD4 influences on attention could manifest in alterations in self-reported urge simply because DRD4L participants focus more on cues than DRD4S individuals. A recent meta-analysis suggested the exon 3 DRD4 VNTR is not associated with approach-related personality traits (Munafò et al., 2008a,b), but newly emerging evidence suggests this hypothesis is still worthy of consideration (e.g., Ray et al., 2008). These literatures may be reflective of pleiotropic effect of DRD4 variation or may challenge the notion that differential urge is driving associations with addiction-related phenotypes (e.g., differences in self-reported urge might reflect altered attentional processes or novelty seeking personality traits more directly impacted by DRD4 variation). Additional research is needed to jointly model the possibilities to further clarify the role of the exon 3 VNTR and other DRD4 variation.

Although the intermediate phenotype approach in psychiatric genetics may hold great promise, caution is recommended. This approach has been used to justify smaller sample sizes as one may expect larger effect sizes by assessing a phenotype that is more related to gene variation. Green and colleagues suggest that this approach may increase the chance of Type 1 error rates (Box 1 in Green et al., 2008). A relatively simple, but often overlooked, concern with the use of this approach is that the endophenotype should necessarily have a higher heritability than the phenotype it is considered intermediate to. This may pose difficulties when the phenotype of interest has a very high heritability as candidate endophenotypes will have a particularly high standard to compete with. A recently published study demonstrates this point when brain activation during a working memory task was found to be less heritable than performance on neuropsychological task (Blokland et al., 2008).

A further concern in this approach is defining the limitations of what constitutes an intermediate phenotype. Although such approaches as cellular assays and neuroimaging seem relatively straightforward in this regard, the further a phenotype is from the mechanism of direct gene action the muddier this becomes. Thus when considering two phenotypes, it may be possible in some cases to argue for either phenotype to be intermediate to the other. For example, is impulsivity a constituent of addictive behavior that may involve fewer genes, or is addictive behavior a subset of an overarching phenotype of impulsivity?

The reviewed studies are clearly limited by the inconsistencies in grouping schemes used to bin DRD4 exon 3 VNTR alleles. Given the international nature of this work, these decisions may be based upon practical issues of power (driven by geographic differences in allele frequencies) in addition to the heterogeneous traditions in the existing literature. The classification system proposed by the Moyzis group may help clarify the literature and could be analyzed in the existing datasets without incurring additional genotyping costs. On the contrary, unless this proposed grouping scheme is universally adopted, it may actually further obscure an already muddy literature by presenting another set of analyses to be run in an already underpowered dataset or allowing the possibility of selective publication of results that have been tested using several grouping schemes without controlling for the multiple comparisons. Other limitations in the existing literature include the relative underutilization of promising intermediate phenotypes such as neuroimaging and the as yet unfulfilled promise of examining epigenetic influences found in the *DRD4* gene that may further clarify the role of this promising gene in addiction.

The ultimate goal of this research is the identification of genetic influences on behavior so that treatments may be developed on an individualized basis rather than treating based upon average response (the traditional foundation of medicine prior to the Human Genome Project). The work described above has led to pharmacogenetic trials to identify new medications for the treatment of addiction (e.g., use of olanzapine for alcohol dependence in a clinical trial by Hutchison et al., 2006) and the identification of genetic moderators of existing treatments (e.g., nicotine replacement therapy, David et al., 2008). Importantly, the identification of a behavioral trajectory influenced by genetic variation may point the way to behavioral as well as pharmacological interventions. For example, the evidence that the DRD4 exon 3 VNTR is related to urge for drugs of abuse may suggest a behavioral treatment that focuses on urge management such as cue exposure treatment may be differentially beneficial for DRD4L carriers.

Research with intermediate phenotypes in this area is some of the most comprehensive in addiction genetics and despite the limitations outlined above, there is great promise that these efforts will result in substantial public health benefit. Future directions in this area of research might include expanding the use of intermediate phenotypes to other drugs of abuse, more complete characterization of variation in the *DRD4* gene (with concurrent haplotype analysis to assist with issues of power). Additionally, a standardization of grouping rules for exon 3 VNTR alleles to facilitate cross-study comparisons, and further development of novel pharmacological and behavioral treatments will help capitalize on these new findings.

References

Ballon N, Leroy S, Roy C, Bourdel MC, Olie JP, Charles-Nicolas A, et al. Polymorphisms TaqI A of the DRD2, BalI of the DRD3, exon III repeat of the DRD4, and 3′ UTR VNTR of the DAT: association with childhood ADHD in male African-Caribbean cocaine dependents? Am J Med Genet B Neuropsychiatr Genet 2007;144B(8):1034–41 [Dec 5].

Blokland GA, McMahon KL, Hoffman J, Zhu G, Meredith M, Martin NG, et al. Quantifying the heritability of task-related brain activation and performance during the N-back working memory task: a twin fMRI study. Biol Psychol 2008;79(1):70–9 [Sep].

Braus DF, Wrase J, Grüsser S, Hermann D, Ruf M, Flor H, et al. Alcohol-associated stimuli activate the ventral striatum in abstinent alcoholics. J Neural Transm 2001;108(7):887–94.

Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, et al. Acute effects of cocaine on human brain activity and emotion. Neuron 1997;19(3):591–611 [Sep].

Cevoli S, Mochi M, Scapoli C, Marzocchi N, Pierangeli G, Pini LA, et al. A genetic association study of dopamine metabolism-related genes and chronic headache with drug abuse. Eur J Neurol 2006;13(9):1009–13 [Sep].

Chang FM, Ko HC, Lu RB, Pakstis AJ, Kidd KK. The dopamine D4 receptor gene (DRD4) is not associated with alcoholism in three Taiwanese populations: six polymorphisms tested separately and as haplotypes. Biol Psychiatry 1997;41(4):394–405 [Feb 15].

Chen CK, Hu X, Lin SK, Sham PC, Loh el-W, Li T, et al. Association analysis of dopamine D2-like receptor genes and methamphetamine abuse. Psychiatr Genet 2004;14(4):223–6 [Dec].

Comings DE, Gade-Andavolu R, Gonzalez N, Wu S, Muhleman D, Chen C, et al. The additive effect of neurotransmitter genes in pathological gambling. Clin Genet 2001;60(2):107–16 [Aug].

Comings DE, Gonzalez N, Wu S, Gade R, Muhleman D, Saucier G, et al. 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 1999;88(4):358–68 [Aug 20].

David SP, Munafò MR, Murphy MF, Proctor M, Walton RT, Johnstone EC. Genetic variation in the dopamine D4 receptor (DRD4) gene and smoking cessation: follow-up of a randomised clinical trial of transdermal nicotine patch. Pharmacogenomics J 2008;8(2):122–8 [Apr].

Ding YC, Chi HC, Grady DL, Morishima A, Kidd JR, Kidd KK, et al. Evidence of positive selection acting at the human dopamine receptor D4 gene locus. Proc Natl Acad Sci U S A 2002;99(1):309–14 [Jan 8].

Filbey FM, Ray L, Smolen A, Claus ED, Audette A, Hutchison KE. Differential neural response to alcohol priming and alcohol taste cues is associated with DRD4 VNTR and OPRM1 genotypes. Alcohol Clin Exp Res 2008;32(7):1113–23 [Jul].

Franke P, Nöthen MM, Wang T, Knapp M, Lichtermann D, Neidt H, et al. DRD4 exon III VNTR polymorphism-susceptibility factor for heroin dependence? Results of a case–control and a family-based association approach. Mol Psychiatry 2000a;5(1):101–4 [Jan].

Franke P, Wang T, Nöthen MM, Knapp M, Neith H, Lichtermann D, et al. DRD4 exon III VNTR polymorphism: a case–control and family-based association approach. Addiction Biology 2000b;5(1):289–95 [Jan].

Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, et al. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry 2000;157(11):1789–98 [Nov].

Geijer T, Jönsson E, Neiman J, Persson ML, Brené S, Gyllander A, et al. Tyrosine hydroxylase and dopamine D4 receptor allelic distribution in Scandinavian chronic alcoholics. Alcohol Clin Exp Res 1997;21(1):35–9 [Feb].

George SR, Cheng R, Nguyen T, Israel Y, O'Dowd BF. Polymorphisms of the D4 dopamine receptor alleles in chronic alcoholism. Biochem Biophys Res Commun 1993;196(1):107–14 [Oct 15].

Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;160(4):636–45 [Apr].

Grady DL, Chi HC, Ding YC, Smith M, Wang E, Schuck S, et al. High prevalence of rare dopamine receptor D4 alleles in children diagnosed with attention-deficit hyperactivity disorder. Mol Psychiatry 2003;8(5):536–45 [May].

Green AE, Munafò MR, DeYoung CG, Fossella JA, Fan J, Gray JR. Using genetic data in cognitive neuroscience: from growing pains to genuine insights. Nat Rev Neurosci 2008;9(9):710–20 [Sep].
Hopfer CJ, Timberlake D, Haberstick B, Lessem JM, Ehringer MA, Smolen A, et al. Genetic influences on quantity of alcohol consumed by adolescents and young adults. Drug Alcohol Depend 2005;78(2):187–93 [May 9].
Hutchison KE, LaChance H, Niaura R, Bryan A, Smolen A. The DRD4 VNTR polymorphism influences reactivity to smoking cues. J Abnorm Psychol 2002a;111(1):134–43 [Feb].
Hutchison KE, McGeary J, Smolen A, Bryan A, Swift RM. The DRD4 VNTR polymorphism moderates craving after alcohol consumption. Health Psychol 2002b;21(2):139–46 [Mar].
Hutchison KE, Ray L, Sandman E, Rutter MC, Peters A, Davidson D, et al. The effect of olanzapine on craving and alcohol consumption. Neuropsychopharmacology 2006;31(6):1310–7 [Jun].
Hutchison KE, Wooden A, Swift RM, Smolen A, McGeary J, Adler L, et al. Olanzapine reduces craving for alcohol: a DRD4 VNTR polymorphism by pharmacotherapy interaction. Neuropsychopharmacology 2003;28(10):1882–8 [Oct].
Ishiguro H, Saito T, Shibuya H, Arinami T. Association study between genetic polymorphisms in the 14-3-3 eta chain and dopamine D4 receptor genes and alcoholism. Alcohol Clin Exp Res 2000;24(3):343–7 [Mar].
Kotler M, Cohen H, Segman R, Gritsenko I, Nemanov L, Lerer B, et al. Excess dopamine D4 receptor (D4DR) exon III seven repeat allele in opioid-dependent subjects. Mol Psychiatry 1997;2(3):251–4 [May].
Kuntsi J, McLoughlin G, Asherson P. Attention deficit hyperactivity disorder. Neuromolecular Med 2006;8(4):461–84.
Lahti J, Räikkönen K, Ekelund J, Peltonen L, Raitakari OT, Keltikangas-Järvinen L. Novelty seeking: interaction between parental alcohol use and dopamine D4 receptor gene exon III polymorphism over 17 years. Psychiatr Genet 2005;15(2):133–9 [Jun].
Laucht M, Becker K, El-Faddagh M, Hohm E, Schmidt MH. Association of the DRD4 exon III polymorphism with smoking in fifteen-year-olds: a mediating role for novelty seeking? J Am Acad Child Adolesc Psychiatry 2005;44(5):477–84 [May].
Laucht M, Becker K, Frank J, Schmidt MH, Esser G, Treutlein J, et al. Genetic variation in dopamine pathways differentially associated with smoking progression in adolescence. J Am Acad Child Adolesc Psychiatry 2008;47(6):673–81 [Jun].
Li T, Chen CK, Hu X, Ball D, Lin SK, Chen W, et al. Association analysis of the DRD4 and COMT genes in methamphetamine abuse. Am J Med Genet B Neuropsychiatr Genet 2004;129(B(1)):120–4 [Aug 15].
Li T, Xu K, Deng H, Cai G, Liu J, Liu X, et al. Association analysis of the dopamine D4 gene exon III VNTR and heroin abuse in Chinese subjects. Mol Psychiatry 1997;2(5):413–6 [Sep].
Li T, Zhu ZH, Liu X, Hu X, Zhao J, Sham PC, et al. Association analysis of polymorphisms in the DRD4 gene and heroin abuse in Chinese subjects. Am J Med Genet 2000;96(5):616–21 [Oct 9].
Mackillop J, Menges DP, McGeary JE, Lisman SA. Effects of craving and DRD4 VNTR genotype on the relative value of alcohol: an initial human laboratory study. Behav Brain Funct 2007;3:11 [Feb 19].
McClernon FJ, Hutchison KE, Rose JE, Kozink RV. DRD4 VNTR polymorphism is associated with transient fMRI-BOLD responses to smoking cues. Psychopharmacology (Berl) 2007;194(4):433–41 [Nov].
McGeary JE, Monti PM, Rohsenow DJ, Tidey J, Swift R, Miranda Jr R. Genetic moderators of naltrexone's effects on alcohol cue reactivity. Alcohol Clin Exp Res 2006;30(8):1288–96 [Aug].
Mulcrone J, Kerwin RW. The regional pattern of D4 gene expression in human brain. Neurosci Lett 1997;234(2–3):147–50 [Oct 3].
Munafò MR, Johnstone EC. Smoking status moderates the association of the dopamine D4 receptor (DRD4) gene VNTR polymorphism with selective processing of smoking-related cues. Addict Biol 2008a [Mar 7].
Munafò MR, Yalcin B, Willis-Owen SA, Flint J. Association of the dopamine D4 receptor (DRD4) gene and approach-related personality traits: meta-analysis and new data. Biol Psychiatry 2008b;63(2):197–206 [Jan 15].
Muramatsu T, Higuchi S, Murayama M, Matsushita S, Hayashida M. Association between alcoholism and the dopamine D4 receptor gene. J Med Genet 1996;33(2):113–5 [Feb].
Myrick H, Anton RF, Li X, Henderson S, Drobes D, Voronin K, et al. Differential brain activity in alcoholics and social drinkers to alcohol cues: relationship to craving. Neuropsychopharmacology 2004;29(2):393–402 [Feb].
Namkoong K, Cheon KA, Kim JW, Jun JY, Lee JY. Association study of dopamine D2, D4 receptor gene, GABAA receptor beta subunit gene, serotonin transporter gene polymorphism with children of alcoholics in Korea: a preliminary study. Alcohol 2008;42(2):77–81 [Mar].
Oak JN, Oldenhof J, Van Tol HH. The dopamine D(4) receptor: one decade of research. Eur J Pharmacol 2000;405(1–3):303–27 [Sep 29].
Parsian A, Zhang ZH. Human chromosomes 11p15 and 4p12 and alcohol dependence: possible association with the GABRB1 gene. Am J Med Genet 1999;88(5):533–8 [Oct 15].
Ray L, Bryan A, Mackillop J, McGeary J, Hesterberg K, Hutchison KE. The dopamine D4 receptor (DRD4) gene exon III polymorphism, problematic alcohol use, and novelty seeking: direct and mediated genetic effects. Addict Biol 2008 [Aug 19., Electronic publication ahead of print].
Ray L, Miranda R, Tidey J, McGeary J, Mackillop J, Gwaltney C, et al. Polymorphisms of the μ-opioid receptor (OPRM1) and Dopamine D4 receptor (DRD4) genes and subjective responses to alcohol in the natural environment. J. Abnorm. Psychology in press.
Reist C, Ozdemir V, Wang E, Hashemzadeh M, Mee S, Moyzis R. Novelty seeking and the dopamine D4 receptor gene (DRD4) revisited in Asians: haplotype characterization and relevance of the 2-repeat allele. Am J Med Genet B Neuropsychiatr Genet 2007;144(B(4)):453–7 [Jun 5].
Rodríguez S, Huang S, Chen XH, Gaunt TR, Syddall HE, Gilg JA, et al. A study of TH01 and IGF2-INS-TH haplotypes in relation to smoking initiation in three independent surveys. Pharmacogenet Genomics 2006;16(1):15–23 [Jan].
Roman T, Bau CHD, Almeida S Hutz MH. Lack of association of the dopamine D4 receptor gene polymorphism with alcoholism in a Brazilian population. Addiction Biology 1999;4:203–7.
Shao C, Li Y, Jiang K, Zhang D, Xu Y, Lin L, et al. Dopamine D4 receptor polymorphism modulates cue-elicited heroin craving in Chinese. Psychopharmacology (Berl) 2006;186(2):185–90 [Jun].
Shields PG, Lerman C, Audrain J, Bowman ED, Main D, Boyd NR, et al. Dopamine D4 receptors and the risk of cigarette smoking in African-Americans and Caucasians. Cancer Epidemiol Biomarkers Prev 1998;7(6):453–8 [Jun].
Skowronek MH, Laucht M, Hohm E, Becker K, Schmidt MH. Interaction between the dopamine D4 receptor and the serotonin transporter promoter polymorphisms in alcohol and tobacco use among 15-year-olds. Neurogenetics 2006;7(4):239–46 [Nov].
Sobik L, Hutchison K, Craighead L. Cue-elicited craving for food: a fresh approach to the study of binge eating. Appetite 2005;44(3):253–61 [Jun].
Szilagyi A, Boór K, Székely A, Gaszner P, Kalász H, Sasvári-Székely M, et al. Combined effect of promoter polymorphisms in the dopamine D4 receptor and the serotonin transporter genes in heroin dependence. Neuropsychopharmacol Hung 2005;7(1):28–33 [Mar].
Tidey JW, Monti PM, Rohsenow DJ, Gwaltney CJ, Miranda Jr R, McGeary JE, et al. Moderators of naltrexone's effects on drinking, urge, and alcohol effects in non-treatment-seeking heavy drinkers in the natural environment. Alcohol Clin Exp Res 2008;32(1):58–66 [Jan].
Tsai SJ, Cheng CY, Shu LR, Yang CY, Pan CW, Liou YJ, et al. No association for D2 and D4 dopamine receptor polymorphisms and methamphetamine abuse in Chinese males. Psychiatr Genet 2002;12(1):29–33 [Mar].
van den Wildenberg E, Janssen RG, Hutchison KE, van Breukelen GJ, Wiers RW. Polymorphisms of the dopamine D4 receptor gene (DRD4 VNTR) and cannabinoid CB1 receptor gene (CNR1) are not strongly related to cue-reactivity after alcohol exposure. Addict Biol 2007;12(2):210–20 [Jun].
Van Tol HH, Wu CM, Guan HC, Ohara K, Bunzow JR, Civelli O, et al. Multiple dopamine D4 receptor variants in the human population. Nature 1992;358(6382):149–52 [Jul 9].
Vandenbergh DJ, O'Connor RJ, Grant MD, Jefferson AL, Vogler GP, Strasser AA, et al. Dopamine receptor genes (DRD2, DRD3 and DRD4) and gene–gene interactions associated with smoking-related behaviors. Addict Biol 2007;12(1):106–16 [Mar].
Vandenbergh DJ, Rodriguez LA, Hivert E, Schiller JH, Villareal G, Pugh EW, et al. Long forms of the dopamine receptor (DRD4) gene VNTR are more prevalent in substance abusers: no interaction with functional alleles of the catechol-o-methyltransferase (COMT) gene. Am J Med Genet 2000;96(5):678–83 [Oct 9].
Wang E, Ding YC, Flodman P, Kidd JR, Kidd KK, Grady DL, et al. The genetic architecture of selection at the human dopamine receptor D4 (DRD4) gene locus. Am J Hum Genet 2004;74(5):931–44 [May].