

The D₂ dopamine receptor gene as a determinant of reward deficiency syndrome

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SUMMARY

The dopaminergic system, and in particular the dopamine D₂ receptor, has been profoundly implicated in reward mechanisms in the brain. Dysfunction of the D₂ dopamine receptors leads to aberrant substance seeking behaviour (alcohol, drug, tobacco, and food) and other related behaviours (pathological gambling, Tourette's syndrome, and attention deficit hyperactivity disorder). We propose that variants of the D₂ dopamine receptor gene are important common genetic determinants of the 'reward deficiency syndrome'.

INTRODUCTION

After the finding by our laboratories of a strong association between the A₁ allele of the D₂ dopamine receptor gene and alcoholism¹, several groups were unable to replicate the observation²⁻⁹. We have suggested two possible reasons—first, inadequate screening of controls for alcohol, drug, and tobacco abuse; and, second, sampling errors in terms of characterization of alcoholics for chronicity and severity of the disease.

Here we review the evidence that the D₂ dopamine receptor gene (DRD₂) is associated not only with alcoholism but also with a group of impulsive-addictive-compulsive disorders including polysubstance abuse, smoking, attention deficit hyperactivity disorder, obesity, and Tourette's syndrome that we have termed 'reward deficiency syndrome'¹⁰.

The dopaminergic system plays a major role in the brain-reward mechanisms, in that deficits in dopamine function result in abnormal drug and alcohol seeking behaviour¹¹. DA receptors are profoundly involved¹². The D₂ dopamine receptor gene, localized in the q22-q23 segment of chromosome 11, has multiple allelic forms (Table 1)¹³⁻¹⁶.

A strong correlation between variants of the dopamine D₂ receptor gene and alcoholism and polysubstance abuse (including crack/cocaine) has been reported by several investigators^{1,9,17-29}.

In brain tissue obtained from patients carrying the A₁, B₁, and intron⁶-exon⁷ haplotypes of the DRD₂ gene dopamine D₂ receptor densities are low^{10,25,30}. Similarly, DRD₂ densities have been found lower in alcohol-preferring rodents than in alcohol-non-preferring animals³¹⁻³³. Moreover, D₂ receptor agonists reduce, and D₂ receptor agonists increase, alcohol intake in alcohol-preferring rats³⁴.

LINKAGE VERSUS ASSOCIATION

Although several studies excluded linkage of the DRD₂ gene with alcoholism^{9,10,23,26}, one group using affected sib-pair analyses found linkage with both heavy drinking and alcoholism²⁴. Further support for association comes from separate studies. In one, the A₁ allele was present in 69% of severe alcoholics¹ compared with 20% of controls. In another, the gene frequency of the A₁ allele of the DRD₂ gene in unclassified alcoholics was 0.27 compared with 0.07 in well-characterized non-alcoholic controls, a 3.85-fold risk in these probands²³. Moreover, a meta-analysis on all published exant studies related to alcoholism showed an odds ratio of 2.18 with a p-value of 10⁻⁷ indicating strong correlation of the DRD₂ gene with this disease^{35,36}. Variants of the DRD₂ gene have been correlated with increased risk of severe alcoholism^{1,17,20-22,24} crack/cocaine dependence^{28,29,38}, carbohydrate bingeing³⁹, obesity⁴⁰, attention deficit hyperactivity disorder⁴¹, Tourette's syndrome^{41,42}, pathological gambling⁴³, and smoking⁴⁴⁻⁴⁶.

Table 1 summarizes data for drug and alcohol seeking behaviour: in all reports chemical dependent subjects were

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Table 1 Summary of dopamine D₂ receptor gene variants and substance abuse/dependence

Substance abuse	Allele	% Prevalence		P value <	References
		Abusers	Controls		
Alcoholism	DRD ₂ A ₁	69	20	0.001	1
Alcoholism (less severe)	DRD ₂ A ₁	30	19	NS	12
Alcoholism (less severe)	DRD ₂ B ₁	17	13	NS	18
Alcoholism*	DRD ₂ C ₁	57	33	0.002	9
Severe alcoholism	DRD ₂ A ₁	47	17	0.001	17
Severe alcoholism	DRD ₂ B ₁	47	13	0.008	18
Severe alcoholism	DRD ₂ ^{In6-Ex7} haplotype I	39	16	0.02	66
Cocaine dependence	DRD ₂ A ₁	51	18	0.0001	28
Cocaine dependence	DRD ₂ B ₁	39	13	0.01	28
Polysubstance abuse	DRD ₂ A ₁	44	28	0.025	38
Polysubstance abuse	DRD ₂ B ₁	33	20	0.001	27

*C₁ allele denoted only with regard to homozygote genotype. Alcoholics (47/82); controls (29/87): ($\chi^2=9.8$, $df=1$, $P=0.002$)

identified who did not have the DRD₂ allele or other variants, together with healthy non-drug-abusing individuals who had the A₁ allele^{1,9,10,17,18,25,28,38}. Uhl and co-workers⁴⁷ reported that the A₁ and B₁ alleles of the DRD₂ gene account for 27% of the variance of drug dependence, independent of the environment or other gene defects, and data from twin studies indicate that genes influence up to 60% of the vulnerability to severe substance abuse⁴⁸. If these two findings are taken together, the DRD₂ variants could represent one of the most important single-gene determinants of susceptibility to severe substance abuse. The consensus among researchers is that vulnerability to drug and alcohol seeking behaviour is polygenic in nature, the DRD₂ genotype being only one of the factors^{49-52,59-61}. We have used Bayes⁵³ theorem as a mathematical method to evaluate the predictive value of the A₁ allele of the DRD₂ gene in impulsive-addictive-compulsive disorders.

Bayes' theorem is widely used in medicine to predict the likelihood that a particular event (defect) will result in an another event (disease)—here, for example, that possession of the A₁ allele of DRD₂ will cause abnormal drug and alcohol seeking behaviour (Table 2).

When a screening test is evaluated, sensitivity is the probability that the test will be positive in a person with the disease in question; and specificity is the probability that the test will be negative in a person who does not have the disease. For Bayes' theorem we used the following formula:

$$\text{Predictive value} = \frac{(\text{prevalence})(\text{sensitivity})}{(\text{prevalence})(\text{sensitivity}) + (1 - \text{prevalence})(1 - \text{specificity})}$$

To calculate the specificity, we used well-characterized controls, screened for alcohol, drug, and tobacco use in some samples (Table 1). No previous study has used rigid

Table 2 The dopamine D₂ receptor gene as a predictor of compulsive disease

Risk behaviour	Predictive value (%)
Alcoholism (severe)	14.3
Cocaine dependence (severe)	12.3
Polysubstance abuse	12.8
Chemical dependency	28.3
Overeating (severe)	18.6
Ingestive behaviour	35.0
ADHD	16.0
Smoking	41.5
Pathological gambling	4.6
Tourette's syndrome	5.5
Total impulsive-addictive-compulsive behaviour	74.4

The assumptions supporting the data are explained in Blum *et al. Functional Neurol* 1995 10:37-44

exclusion criteria for controls³⁵, and such efforts are essential because alcoholism *per se* is not the true phenotype associated with DRD₂ gene polymorphisms^{10,23,41}. Moreover, to calculate the sensitivity of genotyping we took data from studies where the probands were characterized for chronicity or severity of disease (Table 2).

The positive predictive value (PV+) of a test is the percentage of positive results that are true positives when the test is applied to a population containing both healthy and diseased individuals⁵⁴. With the *Taq1* A₁ genotype, PV+ was 0.744 or 74%; in other words, positive predictive value was high; but PV- was only 0.548 or 54.8%. We would expect better negative predictive value in studies where individuals with related impulsive-addictive-compulsive

behaviours are excluded from the control groups. Pooled data on patients with these disorders point to a strong positive correlation with the DRD₂ gene variant (Yates $\chi^2=68.38$, $df=1$, $P<10^{-7}$).

DNA testing to predict high risk

Using logistic regression modelling, we found especially with cocaine dependent probands that the prevalence of the variants of the DRD₂ gene increases with three factors—parental alcoholism; intake of potent drugs; and early deviant behaviour²⁸. Of eight individuals with the three risk factors, seven had the A₁ allele. A similar pattern was seen in obesity, the risk factors for prevalence of the A₁ allele including parental obesity, adolescent or adult-onset of obesity, and carbohydrate bingeing: of 13 obese individuals with these three risk factors 11 had the A₁ allele³⁸. We also find that co-morbid substance abuse with obesity yielded a D₂A₁ allelic prevalence of 82%⁵⁵.

In summary, there is now convincing cumulative evidence that certain variants of the DRD₂ are associated with impulsive-addictive-compulsive disorders. Moreover, in the alcohol-naïve sons of alcoholic fathers, presence of the A₁ allele correlates with a neurophysiological feature—delayed latency of the P300 wave—that predicts drug and alcohol seeking behaviour^{56,57}. The association was also present in a neuropsychiatric population⁵⁸.

DRD₂ seems to be a major gene in these disorders, with the larger role played by a combination of other genes (DRD₄) and environmental factors⁴⁶.

Lately Crabbe *et al.*⁵⁹, working with animal models of alcohol and drug seeking behaviour, found evidence that several responses to alcohol (sensitivity to ataxia, tolerance to hypothermic and ataxia effects, preference drinking, and conditioned place preference) are influenced by loci in the middle portion of chromosome 9. In fact, four of the five traits showed their highest association with the same marker, Cyp1A₁, at 9:31. This strongly suggests that a single locus accounts for all these associations. Consumption of methamphetamine (in saccharin), methamphetamine-stimulated activity, and haloperidol-induced catalepsy also map to this region, and morphine-induced Straub tail maps nearby. Moreover, the ethanol-preference and haloperidol-catalepsy associations with markers near DRD₂ have been verified in F2 mice with PCR genotyping. The potential importance of this synthetic approach is a cluster of ethanol, morphine, and cocaine responses mapping to chromosome 9. Finally, Crabbe *et al.* point out that, in the mouse, the DRD₂ gene maps to chromosome 9. These findings in animals support our proposal that variants of the D₂ dopamine receptor gene are important common genetic determinants of addictive behaviours.

Although several studies strongly support a genetic aetiology for severe alcoholism⁶⁰, others point to the importance of environmental factors such as peer pressure, family, and socioeconomics⁶¹.

Since the DRD₂ gene was found to be associated with various 'reward deficiency syndrome' behaviours (Table 1), we agree with Neiswanger's²³ suggestion that alleles of the DRD₂ gene associate with aberrant behavioural phenotype. An example of polygenic inheritance has been observed with attention deficit hyperactivity disorder (ADHD). Comings and associates⁶² found three dopaminergic genes—DRD₂, dopamine β -hydroxylase, and the dopamine transporter—to associate individually with ADHD in patients originally diagnosed with Tourette's syndrome: those who inherited all three of the alleles in question had the highest ADHD scores, well into the clinical range, and those who inherited none of the three alleles had the lowest ADHD scores, well into the normal range. The results for conduct disorder and oppositional defiant disorder were particularly important because these conditions were so widely regarded as due entirely to environmental factors. There is further evidence of common genetic factors. Gittleman⁶³ found a correlation between ADD and adult drug abuse and Comings *et al.*^{62,64} showed an intimate relationship between Tourette's syndrome and ADD: 50–80% of persons with Tourette's syndrome had ADD.

REWARD DEFICIENCY SYNDROME

The concept of a 'reward deficiency syndrome' unites addictive, impulsive, and compulsive behaviours and may explain how simple genetic anomalies give rise to complex aberrant behaviour. What are the possible therapeutic implications? Nishimura⁶⁵ has reported that bromocriptine shortens the latency of the N200 wave in persons with long latency. Such N200 wave abnormalities occur in 'reward deficiency syndrome', and if bromocriptine or other D₂ agonists can stabilize or shorten wave latency, they could have clinical value. In a double-blind study bromocriptine or a placebo was administered to alcoholics with either the A₁ (A₁/A₁ and A₁/A₂ genotypes) or only the A₂ (A₂/A₂) genotype allele of the DRD₂ gene. The greatest improvement in craving and anxiety occurred in the bromocriptine-treated A₁ alcoholics and attrition was highest in the placebo group A₁ alcoholics. These findings raise the possibility of selection in treatment of alcoholics.

One important obstacle to treatment or rehabilitation in substance use disorders is denial, and we believe that a positive result of the 'reward deficiency syndrome' concept will be its aid in countering this reaction: as many as one out of every two individuals seeking treatment for a 'reward deficiency syndrome' disorder carry the A₁ allele. For

prevention and early identification the test has a predictive value of only 74%. A time will come, however, when we have identified all the gene variants and we shall have a stronger DNA test for reward deficiency syndrome.

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