

## DRD4 receptor gene exon III polymorphism in inpatient suicidal adolescents

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**Summary.** Some studies have suggested possible association of the dopamine receptor subtype 4 (DRD4) gene exon III 48 bp repeat polymorphism with novelty seeking behavior. As suicidal behavior in adolescents is linked to risk taking behavior, we evaluated the association of suicidality with DRD4 polymorphism in Israeli inpatient suicidal adolescents. Sixty-nine inpatient adolescents who recently attempted suicide were assessed by structured interview and rating scales for detailed clinical history, diagnoses, suicide intent and risk, impulsivity, violence, and depression. The frequency of DRD4 alleles was compared between the suicidal inpatients and 167 healthy control subjects. No significant association between the DRD4 polymorphism and suicidal behavior was found. Analysis of the suicide-related measures demonstrated a significant difference in depression severity between suicidal inpatients homozygote and heterozygote for the DRD4 alleles ( $p = 0.003$ ). The relevance of this finding to increased depression severity in suicidal adolescents, if replicated, is as yet unclear.

**Keywords:** Suicide, adolescence, polymorphism, dopamine receptor D4 (DRD4), depression.

### Introduction

Suicidal behavior runs in families and seems to be partially genetically determined (Roy, 1983, 1997; Roy et al., 1997; Mann, 1998; Zalsman et al., 2002).

Inheritance of suicidal behavior may be higher if first seen in pre-puberty or adolescence (Brent et al., 2002). Dopamine (DA) has been implicated as an important factor in the regulation of the reward system (Ikemoto and Panksepp, 1999) and found to play a role in depression and some anxiety disorders (Willner, 1995). Drugs of abuse causing disinhibition, such as cocaine and amphetamines, are known to inhibit the dopamine transporter and to stimulate the DAergic system. Several studies indicated an association between risk taking behaviors and length of dopamine receptor type 4 (DRD4) alleles (for review see Kluger et al., 2002). There is scarce information on the association of suicidal behavior and depression with the DRD4 polymorphism.

Suicide is the second leading cause of death in the 15–24 year old age group, in Israel and other countries as well (Zalsman et al., 2002). Since adolescent suicidal behavior is unique and associated with risk taking behavior, impulsivity, depression and aggression (Apter et al., 1993, 1995), we assessed the possible association of the DRD4 polymorphisms with suicidal behavior and related traits in suicidal adolescent inpatients, from Ashkenazi and non-Ashkenazi origin.

#### *DRD4 and impulsive behavior*

Five major subtypes of DA receptors (D1–D5) were identified and characterized and cloned (Van Tol et al., 1992). The receptors are found at different areas throughout the DA tracts and have different affinities for the DA. The subtypes can be further classified into two groups: the D1 and D5 receptor subtypes which stimulate the production of cAMP, and the D2, D3 and D4 receptor subtypes which inhibit the formation of cAMP. The DA D4 receptor is abundant in the frontal brain, an area known to play an important role in human personality, in particular judgment, irritability and impulsivity (Benjamin et al., 1996; Ebstein et al., 1996, 1997). The D4 subtype is a candidate for novelty seeking behavior due to its abundance in areas of the brain involved in the regulation of cognitive and emotional functions. Initial investigations into the gene responsible for the D4 subtype supported the putative role of D4 in impulsive behavior (Van Tol et al., 1992).

The DRD4 gene was mapped by Gelernter et al. (1992) to the short arm of chromosome 11, and includes 48 base pair (bp) repeat polymorphism in exon III, with 2 to 10 repeat units (Van Tol et al., 1992). Allele frequencies of this polymorphism are known to vary between populations (Chang et al., 1996), but not between Ashkenazi and Non-Ashkenazi Jews (Frisch et al., 1999). The 7 repeat allele was found to be associated with novelty seeking (Benjamin et al., 1996; Ebstein et al., 1996; Malhotra et al., 1996) and opioid dependence (Kotler et al., 1997). Ebstein et al. (1996, 1997) were the first to look directly into the link between the DRD4 gene and the behavior classified as novelty seeking. Their work was performed on a group of Israeli subjects from a mixed ethnic background (Jewish Ashkenazi, Jewish Sephardi, Arab and Druze). They have demonstrated an association between the long allele, containing 7 repeats, and novelty seeking behavior as measured by the Cloninger Tridimensional Personality Questionnaire (TPQ) (Cloninger et al., 1993), which also includes harm avoidance, reward dependence and persistence. Malhotra et al. (1996), Ono

et al. (1997), and Noble et al. (1998) published further evidence to support this finding. However, Jonnson et al. (1997) and Gelernter et al. (1997) disputed this association. It is noteworthy that these studies were performed on a variety of different ethnic groups and that the methods for determining “novelty seeking” varied between groups.

In the last few years, the association between DRD4 gene polymorphism and a variety of disorders associated with impulsivity including Tourette syndrome (Grice et al., 1996), pathological gambling and attention deficit hyperactivity disorder (ADHD) was studied. Comings et al. (1999) found a significant association between carriers of the longer alleles of DRD4 and pathological gambling, a compulsive-impulsive behavior, with the gamblers more frequently being heterozygous. ADHD has incurred interest because of the behavioral expression of the disorder in three domains: inattention, hyperactivity and impulsive behavior (LaHoste et al., 1996). Roman et al. (2001) found no link between the carriers of the long allele of DRD4 and ADHD as a diagnostic entity. However, when focusing specifically on the hyperactivity/impulsivity dimension of ADHD, a significant link with the DRD4 long seven-repeat allele was found. This further suggests a possible relationship between the DRD4 gene and impulsivity.

#### *DRD4 and suicidal behavior*

It was suggested that suicide and suicidal behavior might be an extension of novelty-seeking behavior with aggression and violence being possibly as important in the act of suicide as is depression (Apter et al., 1995). Twin and adoption studies have supported the view that suicide may not be exclusively linked to a specific psychiatric disorder and suggested a genetic component to suicidality. This suggestion is based on the observation of higher concordance rates for suicide (Roy et al., 1991) and suicide attempts (Roy et al., 1995) in monozygotic than in dizygotic twins regardless of psychiatric diagnosis.

Recent interest has turned towards the role of the DRD4 gene in the pathogenesis of depression, and suicide (Mann, 1998; Zalsman et al., 2002). Evidence that DA is involved in these disorders led Frisch et al. (1999) to look into a possible association between the DRD4 gene and unipolar major depressive disorder. Although no significant association was found the authors suggested a possible minor role for the DRD4 gene in this disorder. Another study has further looked at the association between suicide attempt and the DRD4 gene (Persson et al., 1999). In this initial study, performed in Swedish population, no association was found between the DRD4 gene polymorphism and suicidal behavior. No significant differences were found between the control subjects and the suicide attempters even when the suicide attempters were further classified into categories according to the underlying diagnosis – depression, anxiety, adjustment and cluster B personality disorders.

To the best of our knowledge, despite established relationship between adolescent suicidal behavior and impulsive traits, there has been no study examining the association between the DRD4 genotype and suicidal behavior in this age group. In the present study we assessed the association between DRD4

polymorphism and suicidal behavior in adolescent inpatients, using independent valid and reliable state and trait questionnaires for adolescents.

## Material and methods

### *Patient sample*

The study was conducted in the adolescent psychiatric department of a university affiliated psychiatric hospital (Geha Mental Health Center, Petach Tikva, Israel). The group of suicide attempters consisted of 69 patients, 40 (58%) girls and 29 (42%) boys. The age range of the participants was 15.2–24.0 years (Mean  $17.7 \pm 3.2$ ). Thirty-five of the group were of Ashkenazi Jewish origin. The other thirty-four were from non-Ashkenazi Jewish descent. The diagnosis of underlying disorders was made according to the DSM IV (APA, 1994) criteria using a semi-structured interview. Most patients were diagnosed with more than one psychiatric disorder during their admission to the department. However for the purpose of the research the most dominant diagnosis was recorded. The most common primary diagnoses in the sample were: borderline personality disorder ( $n = 20$ , 29%), schizophrenia ( $n = 17$ , 24.6%) and major depression ( $n = 12$ , 17.4%). Other diagnoses were: bipolar affective disorder I ( $n = 3$ , 4.3%); antisocial personality disorder ( $n = 5$ , 7.2%); anorexia nervosa ( $n = 2$ , 2.9%); adjustment disorder ( $n = 2$ , 2.9%); schizoaffective disorder, obsessive compulsive disorder, post-traumatic stress disorder, unspecified depression, and binge eating (for each diagnosis  $n = 1$ , 1.4%). For one patient, no formal diagnosis could be established. None of the patients had a current or lifetime diagnosis of ADHD. All patients were negative for drugs of abuse by urine toxicology screen. As a routine procedure, patients are washed out of medication when admitted to the unit after suicide attempt. The mean score on the Global Assessment of Functioning Scale was 56.1 (SD = 16.4; range 20–90).

The mean number of previous suicide attempts in the study population was 1.6 (range 2–9). Methods of attempted suicide included overdose of tablets ( $n = 24$ , 34.8%), jumping from a high place ( $n = 18$ , 26%), cutting of veins ( $n = 8$ , 11.6%), hanging ( $n = 5$ , 7.2%), ingesting poisons ( $n = 3$ , 4.3%) and other unspecified methods ( $n = 11$ , 15.9%).

### *Study design*

This is a case-control retrospective study. The frequency of genotypes and alleles in the suicidal subjects ( $n = 69$ ) was compared to that of a historical control group which included healthy Ashkenazi ( $n = 109$ ) and non-Ashkenazi ( $n = 58$ ) Jewish population (total  $n = 167$ ), from a previous study performed in our laboratory (Frisch et al., 1999).

The study was approved by the Geha Mental Health Center Review Board. All the subjects and their parents gave written informed consent after the nature of the study was fully explained to them, prior to their inclusion in the study.

### *Procedure*

All patients were interviewed within a week after their most recent suicide attempt. One patient completed only the IS questionnaire and one patient did not complete any questionnaire. Blood samples were collected during the first week after the suicide attempt.

### *Clinical assessment*

The clinical phenotype of the suicidal subjects was determined, as described previously (Zalsman et al., 2001a, b), by five questionnaires and a diagnostic semi-structured interview:

1. *Past Feelings and Acts of Violence Scale (PFAVS)*, a 12-item questionnaire checking risk of violence, anger, and legal problems linked to violence. The scale is reliable in detecting history of violence and predicts violence as the reason for hospitalization. It is mainly a trait questionnaire. Answers are rated from never to always on a 4-point Likert scale, and the score ranges from 0 to 36. Internal validity is 0.77 (Plutchik and Van Praag, 1990).

2. *Impulsivity Scale (IS)*, a 15-item questionnaire for impulsivity. Answers are rated on a 4-point Likert scale, and scores range from 15 to 60. The internal validity is 0.77 (Plutchik and Van Praag, 1986; Apter et al., 1990).
3. *Suicide Risk Scale (SRS)*, a 26-item pencil-and-paper questionnaire, which checks for the actual risk for suicide. Answers are given as yes-no. Score ranges from 26 to 52 (lower scores means higher risk). The internal validity is 0.84 (Plutchik et al., 1989; Apter et al., 1990).
4. *Beck Depression Inventory (BDI)*, a well-known tool for measuring depression. The scores range from 0 to 63; scores above 9 are considered positive for depression. The internal validity is 0.73–0.92 (Beck and Steer, 1987; Beck et al., 1988).
5. *Beck Suicide Intent scale (BSIS)*, a 15-item questionnaire on seriousness of the suicide attempt. The scores range from 0 to 30. The questionnaire has been found to differentiate between suicide attempters and completers (Beck et al., 1974a, b).
6. *Schedule for Affective Disorders and Schizophrenia for children-Patient Version (K-SADS-P)*, a structured interview for Axis I diagnoses in children and adolescents. The K-SADS-P has been translated into Hebrew and showed good inter-rater reliability in our earlier studies (Apter et al., 1989; Shanee et al., 1997). In patients older than 18 years, we used the Hebrew version of the Structured Clinical Interview for DSM IV-patient version (SCID-P), version 2.0 (First et al., 1994).

### *Blood collection*

Ten milliliters of venous blood was collected from each patient. The blood was collected into EDTA-containing tubes. DNA isolation was performed using standard methods (Miller et al., 1998).

### *Genotyping*

DRD4 genotyping was performed using Polymerase Chain Reaction (PCR) techniques as described previously (Frisch et al., 1999). The alleles were classified as short (<7 repeats) and long (7 and longer), as suggested by others (Benjamin et al., 1996; Ebstein et al., 1997). The PCR primers used were D4-3 (5'-GCC ACT ACG TGG TCT ACT CG-3') and D4-42 (5'-AGG ACC CTC ATG GCC TTG-3'). Alleles sizes were determined by comparison with DNA markers.

### *Statistical analysis*

The distribution of the frequency of the DRD4 genotypes and alleles in the patients and the healthy controls was compared using the Fisher's exact test. The analyses were performed both using the patient group as a whole and dividing the patient and control groups into Ashkenazi and non-Ashkenazi subjects. Student's t-test was performed to assess the differences within the suicide patients in scores on the following scales: Past Feelings and Acts of Violence Scale, the Impulsivity Scale, the Suicide Risk Scale, the Beck Depression Inventory and the Beck Suicide Intent Scale. Patients were classified as carriers of the short (<7 repeats) or long (>7 repeats or longer) alleles, and being homozygote or heterozygote for these alleles. Bonferroni post-hoc test was employed to correct for multiple testing. All test were two tailed.

## **Results**

Table 1 describes the range, means and the standard deviations of the patients' scores in the various rating scales. PFAVS showed low to moderate violence rates. Impulsivity, using the Impulsivity Scale as a guide, was moderate to high. The risk for suicide was moderate to high, as assessed by both the Suicide Risk Scale and the Beck Suicide Intent Scale. The depression severity in the sample population was also moderate, as assessed by the Beck Depression Inventory.

Table 2 shows the differences between the two groups, including further sub-dividing into Ashkenazi and non – Ashkenazi subgroups. As shown in

**Table 1.** Psychometric clinical assessment of the suicidal adolescents

Scale	n	Sample range (scale range)	Mean	S.D.
PFAVS	67	1–26 (0–36)	9.27	6.70
IS	68	21–60 (15–60)	35.32	6.82
SRS	67	28–52 (26–52)	36.12	5.56
BDI	67	0–49 (0–63)	23.24	14.22
BSIS	67	2–20 (0–30)	13.40	6.77

*PFAVS* Past Feelings and Acts of Violence Scale, *IS* Impulsivity Scale, *SRS* Suicide Risk Scale, *BDI* Beck Depression Inventory, *BSIS* Beck Suicide Intent Scale

**Table 2.** Assessment for association of short and long alleles of DRD4 polymorphism and suicidality in adolescents and controls by ethnic groups

No. of repeats	Ethnicity	Suicidal adolescents	Healthy controls	P <sup>a</sup>
≥7	All sample	24	75	0.27
	Ashkenazi	14	48	0.87
	Non-Ashkenazi	10	27	0.19
<7	All sample	114	259	
	Ashkenazi	56	170	
	Non-Ashkenazi	58	89	

<sup>a</sup> Fisher's Exact Test: All sample:  $p = 0.27$ ;  $RR = 1.09$ ; 95% C.I. = 0.96–1.24. Ashkenazi:  $p = 0.87$ ;  $RR = 1.03$ ; 95% C.I. = 0.89–1. Non-ashkenazi:  $p = 0.19$ ;  $RR = 1.21$ ; 95% C.I. = 0.95–1.53

Table 2, no significant differences were found for the short (<7 repeats) and the long (≥7 repeats) DRD4 polymorphic alleles, for both the total sample and the divided ethnic groups. No age or gender effects were detected.

### Psychometric analyses

The Student's t-test was used to analyze the differences in clinical assessments in the carriers of the DRD4 alleles (<7 repeats and ≥7) (Table 3) as well as homozygotes (4,4 or 7,7 repeats) vs. heterozygotes (Table 4).

**Table 3.** Clinical assessment of carriers and non-carriers of the ≥7 repeats DRD4 allele in suicidal adolescents

Scale	Carriers of the ≥7 repeat			Non-carriers of the ≥7 repeat			t	df	p
	n	Mean	S.D.	n	Mean	S.D.			
PFAVS	21	9.05	7.01	46	9.37	6.63	0.18	65	0.86
IS	21	35	6.60	47	35.47	6.99	0.26	66	0.79
SRS	21	37.05	6.05	46	35.70	5.34	0.92	65	0.36
BDI	21	19.95	13.89	46	24.74	14.26	1.29	65	0.20
BSIS	21	11.48	5.78	46	14.28	7.06	1.58	65	0.12

*PFAVS* Past Feelings and Acts of Violence Scale, *IS* Impulsivity Scale, *SRS* Suicide Risk Scale, *BDI* Beck Depression Inventory, *BSIS* Beck Suicide Intent Scale

**Table 4.** Clinical assessments of the suicidal adolescents homozygotes and heterozygotes for DRD4

Scale	DRD4 homozygotes			DRD4 heterozygotes			t	df	p
	n	Mean	S.D.	n	Mean	S.D.			
PFAVS	36	9	6.69	31	9.58	6.81	0.35	65	0.72
IS	36	35.86	5.85	32	34.72	7.83	0.68	66	0.50
SRS	36	34.97	4.64	31	37.45	6.29	1.85	65	0.0685
BDI	36	27.86	14.13	31	17.87	12.49	3.04	65	0.0034*
BSIS	36	14.08	7.74	31	12.61	5.45	0.88	65	0.38

*PFAVS* Past Feelings and Acts of Violence Scale, *IS* Impulsivity Scale, *SRS* Suicide Risk Scale, *BDI* Beck Depression Inventory, *BSIS* Beck Suicide Intent Scale. \*Significant also following Bonferroni post-hoc test

Since the DRD4  $\geq 7$  repeat alleles were reported by some researchers (Kluger et al., 2002) to be associated with novelty-seeking behavior, we analyzed the relationship between these alleles and the psychometric properties of the suicide attempters. As shown in Table 3, no differences in the scores of the various rating scales were revealed between carriers and non-carriers of the  $\geq 7$  repeats alleles of the DRD4.

However, as shown in Table 4, homozygosity for the DRD4 gene polymorphism, including all allele lengths (4,7,>7), was associated in the suicidal adolescents with more severe depression as measured by the BDI scale ( $27.86 \pm 14.13$  vs.  $17.87 \pm 12.49$ , respectively  $t = 3.04$ ,  $df = 65$ ,  $p = 0.0034$ ). This finding was also significant following Bonferroni post-hoc test.

## Discussion

In this study the distribution of the polymorphic alleles of the DRD4 gene was assessed for its possible association with suicidal behavior in a group of suicidal adolescent inpatients. Current opinion holds that suicidal behavior is not simply an entity which is connected to depression in an individual but it is often a behavior linked to impulsivity, violence and aggression (Apter et al., 1993, 1995). Since novelty-seeking behaviour may be associated with risk-taking behaviour and impulsivity, and has been shown to be associated with the long ( $\geq 7$  repeats) DRD4 alleles (Benjamin et al., 1996; Ebstein et al., 1996), we hypothesized that these alleles may be overrepresented among the suicidal adolescent inpatients. However, no association was found in our study between the length of the DRD4 alleles ( $\geq 7$  and  $< 7$  repeats) and suicidal behavior when compared to an historical adult healthy control group. This negative finding is consistent with previous study in adult suicidal population (Persson et al., 1999). The results remained non-significant also when the populations were subdivided according to ethnic origin (Ashkenazi and a non-Ashkenazi).

The positive finding of this study was that homozygosity for the DRD4 polymorphism in suicidal adolescent inpatients showed significant association with severity of depression, as measured by the BDI. This is consistent with

multiple reports that dopaminergic system plays a role in the pathophysiology of depression (Mann, 1998). A recent meta-analysis suggested that homozygosity for the DRD4 long alleles may be associated with novelty-seeking (Kluger et al., 2002). Association of DRD4 gene homozygosity and depression was also found in smokers (Lerman et al., 1998). Moreover, the latter study demonstrated an association of homozygosity for the short DRD4 alleles and the beneficial effects of nicotine replacement therapy in depressed smokers, a phenomenon that may be related to genetic factors involved in dopamine transmission. Considering the role of the dopaminergic system in impulsive behavior, it is of note that homozygosity at the dopamine DRD3 gene was reported in cocaine dependence (Comings et al., 1999), a phenotype associated with novelty-seeking.

The association of the DRD4 polymorphism with depression was studied by Serretti et al. (1998) who have shown association of the 7 repeats allele with higher scores in Hamilton Depression Rating Scale with delusional symptomatology in mood disorder patients. Association of DRD4 polymorphism was not found with antidepressant activity of two selective serotonin reuptake inhibitors (Serretti et al., 2001).

The complex relationship between DRD4 genotype, suicidality, impulsivity, substance abuse and novelty-seeking behavior in adolescents merits further investigation.

#### *Study limitations*

The major limitation of this study is the small sample size. Recruitment of adolescent immediately after a suicide attempt with a parental consent for research is a difficult task (Brent et al., 2002). We are aware that the results in small samples are liable to both type I and II errors. Unfortunately, the sample size and the multiplicity of the genotypes do not allow a proper power analysis. Our findings should be considered as preliminary and need replication in an independent, larger sample. The positive finding of the association of homozygosity with depression severity may be a result of type I error because of multiple comparisons. We addressed this limitation, using the Bonferroni post-hoc test.

Because of the sample size, we could not assess association of this polymorphism with subtypes of subjects such as aggressive vs. non-aggressive, severe vs. non-severe suicide attempters or subtypes of depression.

Although psychiatric diagnoses in this sample are heterogeneous, suicidal behavior in this age group seemed to cross all diagnostic categories and may be related more to impulsive-aggression than to Axis I or II diagnoses (Brent et al., 2002; Apter et al., 1990, 1993, 1995).

This is the first study of this polymorphism that focused on a group of suicidal adolescent inpatients that represent a unique population. Although some of the patients in this sample are older, they are all under 24 years old and most of the literature on suicidality consider the 15–24 years old as one group (Brent et al., 2002; Apter et al., 1995). Adolescent inpatients as a group may have different personality traits and different neurobiology compared to

adult patients and therefore the results of this study can not be generalized to the population as a whole.

In conclusion, no association between suicidal, impulsive and aggressive behaviors and DRD4 alleles in adolescent inpatients was found. However, homozygosity for the DRD4 gene was associated with the severity of depression, as measured by the BDI, in adolescent suicidal inpatients. Although it was claimed in the past that homozygosity can affect the function of a protein, the functional significance of DRD4 homozygosity and its relevance to increased depression severity in suicidal adolescents, if replicated, is as yet unclear. Further large scale family-based studies with a more clinically homogenous population (including community-based population), with looking on single nucleotide polymorphisms and haplotypes, are required to clarify the relation between the DRD4 gene polymorphism, depression and suicidality in adolescents.

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### References

- American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn (DSM-IV). American Psychiatric Association Press, Washington DC
- Apter A, Orvaschel H, Laseg M, Moses T, Tyano S (1989) Psychometric properties of the K-SADS-P in an Israeli adolescent psychiatric population. *J Am Acad Child Adolesc Psychiatry* 28: 61–65
- Apter A, Van Praag HM, Plutchik R, Sevy S, Korn M, Brown SL (1990) Interrelationships among anxiety, aggression, impulsivity, and mood; a serotonergically linked cluster? *Psychiatry Res* 32: 191–199
- Apter A, Plutchik R, Van Praag HM (1993) Anxiety, impulsivity and depressed mood in relation to suicide and violent behavior. *Acta Psychiatr Scand* 87: 1–5
- Apter A, Gothelf D, Orbach I, Weizman R, Ratzoni G, Har-Even D, Tyano S (1995) Correlation of suicidal and violent behavior in different diagnostic categories in hospitalized adolescent patients. *J Am Acad Child Adolesc Psychiatry* 34: 912–918
- Beck AT, Schuyler D, Herman I (1974a) Development of suicidal intent scales. In: Beck AT, Lettieri DJ, Resnick HLP (eds) *The prediction of suicide*. Charles Press, Bowie MD, pp 45–56
- Beck RW, Morris JB, Beck AT (1974b) Cross-validation of the suicidal intent scale. *Psychol Rep* 34: 445–446
- Beck AT, Steer RA (1987) *Beck Depression Inventory – manual*. Psychological Corporation, New York, pp 1–25
- Beck AT, Steer RA, Garbin M (1988) Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. *Clin Psychol Rev* 8: 77–100
- Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH (1996) Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. *Nature Genet* 12: 81–84
- Brent DA, Oquendo M, Birmaher B, Greenhill L, Kolko D, Stanley B, Zelazny J, Brodsky B, Bridge J, Ellis S, Salazar JO, Mann JJ (2002) Familial pathways to early-onset suicide attempt: risk for suicidal behavior in offspring of mood-disordered suicide attempters. *Arch Gen Psychiatry* 59: 801–807
- Chang FM, Kidd JR, Livak KJ, Pakstis AJ, Kidd KK (1996) The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Hum Genet* 98: 91–101
- Cloninger CR, Svrakik DM, Przybeck TR (1993) A psychobiological model of temperament and character. *Arch Gen Psychiatry* 50: 975–990

- Comings DE, Gonzalez N, Wu S, Gade R, Muhleman D, Saucier G, Johnson P, Verde R, Rosenthal RJ, Lesieur HR, Rugle LJ, Miller WB, MacMurray JP (1999) Studies of the 48 bp repeat polymorphism of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. *Am J Med Genet* 88: 358–368
- Ebstein RP, Novick O, Umansky R, Pirlli B, Osher Y, Blaine D, Bennett ER, Nemanov L, Katz M, Belmaker RH (1996) Dopamine D4 receptor exon III polymorphism associated with the human personality trait of novelty seeking. *Nat Genet* 12: 78–80
- Ebstein RP, Nemanov L, Klotz I, Gritsenko I, Belmaker RH (1997) Additional evidence for an association between the dopamine D4 receptor exon III repeat polymorphism and the human personality trait of novelty seeking. *Mol Psychiatry* 2: 472–477
- First MB, Spitzer RL, Gibbon M, Williams BW (1994) Structured clinical interview for axis I DSM IV disorder, patient edition (SCID-I/P), version 2.0. Biometric Research Department, NY State Psychiatric Institute, New York
- Frisch A, Postilnick D, Rockah R, Michaelovsky E, Postilnick S, Birman E, Laor N, Rauchverger B, Kreinin A, Poyurovsky M, Schneidman M, Modai I, Weizman R (1999) Association of unipolar major depressive disorder with genes of the serotonergic and dopaminergic pathways. *Mol Psychiatry* 4: 389–392
- Gelernter J, Kennedy JL, Van Tol HH, Civelli O, Kidd KK (1992) The D4 dopamine receptor (DRD4) maps to distal 11p close to HRAS. *Genomics* 13: 208–210
- Gelernter J, Kranzler H, Coccaro E, Siever L, New A, Mulgrew CL (1997) D4 Dopamine-receptor (DRD4) alleles and novelty seeking in substance-dependent, personality disorder and control subjects. *Am J Hum Genet* 61: 1144–1152
- Grice DE, Leckman JF, Pauls DL, Kurlan R, Kidd KK, Pakstis AJ, Chang FM, Buxbaum JD, Cohen DJ, Gelernter J (1996) Linkage disequilibrium between an allele at the dopamine D4 receptor locus and Tourette syndrome, by the transmission disequilibrium test. *Am J Hum Genet* 59: 644–652
- Ikemoto S, Panksepp J (1999) The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. *Brain Res Rev* 31: 6–41
- Jonsson EG, Nothen MM, Gustavsson JP, Neidt H, Brene S, Tylec A, Propping P, Sedvall GC (1997) Lack of evidence for allelic association between personality traits and the dopamine D4 receptor gene polymorphisms. *Am J Psychiatry* 154: 697–699
- Kluger AN, Siegfried Z, Ebstein RP (2002) A meta-analysis of the association between DRD4 polymorphism and novelty seeking. *Mol Psychiatry* 7: 712–717
- Kotler M, Cohen H, Segman R, Gritsenko I, Nemanov L, Lerer B, Kramer I, Zer-Zion M, Kletz I, Ebstein RP (1997) Excess dopamine D4 receptor (D4DR) exon III seven repeat allele in opioid-dependent subjects. *Mol Psychiatry* 2: 251–254
- LaHoste GJ, Swanson JM, Wigal SB, Glabe C, Wigal T, King N, Kennedy JL (1996) Dopamine D4 receptor polymorphism is associated with attention deficit hyperactivity disorder. *Mol Psychiatry* 1: 121–124
- Lerman C, Caporaso N, Main D, Audrain J, Boyd NR, Bowman ED, Shields PG (1998) Depression and self-medication with nicotine: the modifying influence of the dopamine D4 receptor gene. *Health Psychol* 17: 56–62
- Malhotra AK, Virkkunen M, Rooney W, Eggert M, Linnoila M, Goldman D (1996) The association between the DRD4 16 amino acid repeat polymorphism and novelty seeking. *Mol Psychiatry* 1: 388–391
- Mann JJ (1998) The neurobiology of suicide. *Nature Med* 4: 25–30
- Miller SA, Dykes DD, Polesky HF (1998) A simple salting out procedure for extracting DNA from nucleated cells. *Nucl Acid Res* 16: 1215
- Noble EP, Ozkaragoz TZ, Ritchie TL, Zhang X, Belin TR, Sparkes RS (1998) D2 and D4 dopamine receptor polymorphisms and personality. *Am J Med Genet* 81: 257–267
- Ono Y, Manki H, Yoshimura K, Muramatsu T, Higuchi S, Yagi G, Kanba S, Asai M (1997) Association between dopamine D4 receptor exon III polymorphism and novelty seeking in Japanese subjects. *Am J Med Genet* 74: 501–503

- Persson ML, Geijer T, Wasserman D, Rockah R, Frisch A, Michaelovsky E, Jonsson EG, Apter A, Weizman A (1999) Lack of association between suicide attempt and a polymorphism at the dopamine receptor D4 locus. *Psychiatr Genet* 9: 97–100
- Plutchik R, Van Praag HM (1986) The measurement of suicidality, aggressivity and impulsivity. *Clin Neuropharmacol* 9 [Suppl]: 380–382
- Plutchik R, Van Praag HM (1990) A self-report measure of violence risk, II. *Compr Psychiatry* 31: 450–456
- Plutchik R, Van Praag HM, Conte HR, Picard S (1989) Correlates of suicide and violence risk 1: the suicide risk measure. *Compr Psychiatry* 30: 296–302
- Roman T, Schmitz M, Polanczyk G, Eizirik M, Rohde LA, Hutz MA (2001) Attention-deficit hyperactivity disorder: a study of association with both the dopamine transporter gene and the dopamine D4 receptor gene. *Am J Med Genet* 105: 471–478
- Roy A (1983) Family history of suicide. *Arch Gen Psychiatry* 40: 971–974
- Roy A (1997) Genetics of suicide. *Family studies and molecular genetics. Ann NY Acad Sci* 836: 135–157
- Roy A, Segal NL, Centerwall BS, Robinette CD (1991) Suicide in twins. *Arch Gen Psychiatry* 48: 29–32
- Roy A, Segal NL, Sarchiapone M (1995) Attempted suicide among living co-twins of twin suicide victims. *Am J Psychiatry* 152: 1075–1076
- Shanee N, Apter A, Weizman A (1997) Psychometric properties of the K-SADS-PL in an Israeli adolescent clinical population. *Isr J Psychiatry Relat Sci* 34: 179–186
- Serretti A, Macciardi F, Cusin C, Lattuada E, Lilli R, Smeraldi E (1998) Dopamine receptor D4 gene is associated with delusional symptomatology in mood disorders. *Psychiatry Res* 80: 129–136
- Serretti A, Zanardi R, Cusin C, Rossini D, Lilli R, Lorenzi C, Lattuada E, Smeraldi E (2001) No association between dopamine D(2) and D(4) receptor gene variants and antidepressant activity of two selective serotonin reuptake inhibitors. *Psychiatry Res* 104: 195–203
- Van Tol HMM, Caren MW, Guan HC, O'Hara K, Bunzow JR, Civelli O, Kennedy J, Seeman P, Niznik HB, Jovanovic V (1992) Multiple dopamine D4 receptor variants in the human population. *Nature* 358: 149–152
- Willner P (1995) Dopamine mechanisms in depression and mania. In: Bloom FE, Kupfer D (eds) *Psychopharmacology: the fourth generation of progress*. Raven Press, New York, pp 921–931
- Zalsman G, Frisch A, Bromberg M, Gelernter J, Michaelovsky E, Campino A, Erlich Z, Tyano S, Apter A, Weizman A (2001a) Family-based association study of serotonin transporter promoter in suicidal adolescents: possible role in violence traits. *Am J Med Genet (Neuropsychiatr Genet)* 105: 239–245
- Zalsman G, Frisch A, King RA, Pauls DL, Grice DE, Gelernter J, Alsobrook J, Michaelovsky E, Apter A, Tyano S, Weizman A, Leckman JF (2001b) Case-control and family-based association studies of tryptophan hydroxylase A218C polymorphism and suicidality in adolescents. *Am J Med Genet (Neuropsychiatr Genet)* 105: 451–457
- Zalsman G, Frisch A, Apter A, Weizman A (2002) Genetics of suicidal behavior: candidate association genetic approach. *Isr J Psychiatry Relat Sci* 39: 252–261

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