Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 1033–1040

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

The role of dopamine transporter (*SLC6A3*) and dopamine D2 receptor/ankyrin repeat and kinase domain containing 1 (*DRD2/ANKK1*) gene polymorphisms in personality traits

A. Kazantseva [a,*], D. Gaysina [a,b,1], S. Malykh [c,2], E. Khusnutdinova [a]

[a] Institute of Biochemistry and Genetics, Ufa Scientific Centre, Russian Academy of Sciences, 71, Prospekt Oktyabrya, Ufa 450054, Russia
[b] MRC Unit for Lifelong Health and Ageing, University College London, 33 Bedford Place, London, WC1B 5JU, UK
[c] Psychological Institute, Russian Academy of Education, 9/4, Mohovaya Street, Moscow 125009, Russia

ARTICLE INFO

Article history:
Received 27 August 2010
Received in revised form 21 February 2011
Accepted 21 February 2011
Available online 24 February 2011

Keywords:
Association
Dopamine
Personality
Psychobiological model
Sex

ABSTRACT

Variations in personality traits are caused by interactions between multiple genes of small effect and environmental factors. To date, gender- and ethnicity-specific variations in personality have been established. In the present study, we aimed to test: 1) the effects of four polymorphisms of dopamine system genes: *ANKK1/DRD2 Taq1A, DRD2 rs6275, SLC6A3 40-bp VNTR* and *rs27072*, on personality traits; 2) whether these effects differ between men and women and between Russians and Tatars. A sample of 652 healthy individuals (222 men and 430 women) of Caucasian origin (233 Russians and 419 Tatars) from Russia was subjected to personality traits assessment with Eysenck Personality Inventory (EPI) and Temperament and Character Inventory-125 (TCI-125). The associations between each personality trait and polymorphisms were assessed with regression models adjusted for gender and ethnicity. There were significant effects of *ANKK1/DRD2 Taq1A* on Neuroticism ($p = 0.016$) and of *SLC6A3 rs27072* on Persistence ($p = 0.021$) in both genders. The association between *ANKK1/DRD2 Taq1A* A2/A2-genotype and higher Novelty Seeking and lower Reward Dependence was shown in men only (p for gender interaction = 0.018). In women only, there was a significant association between *SLC6A3* 10R*G-haplotype and higher Persistence ($p = 0.002$). Our findings provide evidence for a modifying effect of gender on the associations between dopamine system genes and approach-related traits (in men) and Persistence (in women).

1. Introduction

Personality traits are complex phenotypes affected by interactions of multiple genes of small effect with environmental factors. According to the psychobiological model, dopaminergic system represents the neurobiological basis for approach-related traits in general, and for Novelty Seeking (NS) in particular (Cloninger et al., 1993).

Dopamine D2 receptor gene (*DRD2*) (11q22-23) is a candidate for reward-related psychiatric disorders and personality traits. The most frequently examined single nucleotide polymorphism (SNP) is the *Taq1A* (*rs1800497*, or *32806C>T*) (Grandy et al., 1989) located in the 3′-untranslated region of *DRD2* (10 kB downstream of the last exon), and actually residing in a neighbouring ankyrin repeat and kinase domain containing 1 gene (*ANKK1*) and causing an amino acid substitution within the 11th ankyrin repeat of the *ANKK1* (Glu713Lys), which might affect substrate-binding specificity of the gene product (Neville et al., 2004). *Taq1A* is a marker of functional differences of both *DRD2* (Zhang et al., 2007) and *ANKK1* (Hoenicka et al., 2010). For instance, diminished D2 receptor binding has been reported for *Taq1A* minor A1-allele in the majority of studies (Jönsson et al., 1999; Noble et al., 1991; Pohjalainen et al., 1998a; Ritchie and Noble, 2003; Thompson et al., 1997). Recently, the group of authors suggested a potential relationship of *ANKK1* gene with the dopaminergic system based on the upregulation of ANKK1 mRNA level in mouse astrocyte cultures by apomorphine (Hoenicka et al., 2010). In addition, it has been hypothesized that the *ANKK1* gene can be probably involved in the dopaminergic reward pathway through signal transduction (or other cellular response) (Neville et al., 2004), since genes of related function are sometimes found clustered together.

According to molecular-genetic studies, *Taq1A* A1-allele carriers have more tendencies for "reward-related psychiatric disorders", including alcohol, opioid and nicotine addiction (Hietala et al., 1997;

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; *ANKK1*, Ankyrin repeat and kinase domain containing 1 gene; ANOVA, One-way analysis of variance; DRD2, Dopamine D2 receptor gene; EPI, Eysenck Personality Inventory; FDR, False discovery rate; HA, Harm Avoidance; NS, Novelty Seeking; PAAG, Polyacrylamide gel; PCR, Polymerase chain reaction; RD, Reward Dependence; *SLC6A3*, Dopamine transporter gene; SNP, Single nucleotide polymorphism; TCI, Temperament and Character Inventory; *VNTR*, Variable number of tandem repeats.

* Corresponding author. Tel./fax: +7 347 2356088.
E-mail address: Kazantsa@mail.ru (A. Kazantseva).
[1] Tel.: +44 20 7670 5719.
[2] Tel./fax: +7 495 202 81 28.

0278-5846/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2011.02.013

Ishiguro et al., 1998; Noble, 2003), pathologic gambling (Comings et al., 1996), hyperactive and impulsive symptoms (Rowe et al., 1999) and compulsive smoking habits (Hamajima et al., 2002). Moreover, the associations between A1-allele and higher NS (or sensation seeking) (Berman et al., 2002; Lin et al., 2007), higher Dependence (RD4 subscale of RD) (Lee et al., 2003), and increased reward responsiveness (Lee et al., 2007) have been reported. Synonymous substitution *939C>T* (*His313His*) (rs6275) in exon 6 of *DRD2* gene could be functional: for instance, the presence of G or C nucleotides in the last nucleotide in the codon could result in an increased gene expression (Sarkar et al., 1991). Molecular-genetic studies involving *DRD2 rs6275* demonstrated an association of N1-allele (C-allele) or N1/N1-genotype (C/C) with alcoholism (Chen et al., 1997), migraine with aura, depression, anxiety (Peroutka et al., 1998), and schizophrenia (Monakhov et al., 2008).

Dopamine transporter gene (*SLC6A3*) (5p15.3) plays a critical role in the regulation of dopaminergic transmission by mediating active reuptake of dopamine from the synapse into the presynaptic terminal (Giros and Caron, 1993). It has been shown that the putamen dopamine transporter density correlated with detached personality and social desirability scores (Laakso et al., 2000). The 40 bp (base pairs) variable number of tandem repeats (*VNTR*) in the 3′ untranslated region of *SLC6A3* gene (*SLC6A3 VNTR*) was shown to be functional, however increased gene expression was controversially associated either with 10-repeat allele (Fuke et al., 2001; VanNess et al., 2005) or 9-repeat allele (Miller and Madras, 2002). Several studies related dopamine transporter gene 9-repeat allele to severe alcohol withdrawal and alcohol dependence (Köhnke et al., 2005; Samochowiec et al., 2006). The *rs27072* (*2319G>A*), located in 3′-UTR of *SLC6A3,* has been associated with ADHD (Feng et al., 2005; Galili-Weisstub et al., 2005; Laurin et al., 2007), bipolar disorder (Greenwood et al., 2006) and smoking (Ling et al., 2004). To date there have been no studies of this polymorphism in personality traits. Despite of the absence of data indicating the functional significance of rs27072 polymorphism located in 3′-UTR of *SLC6A3* gene, there is some evidence pointing to the fact that sequence variation in the 3′-UTR of the gene could influence transcription, sub-cellular localization of mRNA, translation regulation, and/or maintenance of mRNA stability (Mignone et al., 2002).

Multiple studies indicated that gender could affect dopaminergic neurotransmission caused by hormonal and social influences on the individual during various phases of development (Costa et al., 2000). Thus, females were shown to have lower D2 receptor affinity for dopamine in human studies (Pohjalainen et al., 1998b) and dopamine D2 autoreceptor downregulation caused by estrogens was demonstrated in animal studies (Becker, 1999). Differences in traditions, social norms, and religion, as well as differences in allele frequencies in populations might also affect the personality. Since, very little is known about the role of gender and ethnicity as modifiers of association between dopamine system genes and personality, we aim to test: 1) the effects of four polymorphisms of dopamine system genes: *ANKK1/DRD2 TAq1A, DRD2 rs6275, SLC6A3 40-bp VNTR* and *rs27072*, on personality traits in different models; and 2) whether these effects differ between men and women. Since both of the studied subpopulations (Russians and Tatars) belong to Caucasians and possess, for instance, the small percent of East Eurasian mtDNA lineages (Khusnutdinova et al., 2007), the analysis was conducted in the total sample with ethnicity included as a covariate.

2. Method

2.1. Subjects

In total, 652 healthy individuals, college students from Bashkortostan Republic of Russia without any individual or family (a first degree relative) history of psychopathologies based on self-reports, were enrolled. This sample consists of 222 men (mean age ± SD: 19.86 ± 2.44 years and age range: 17–25 years) and 430 women (mean age ± SD: 19.84 ± 2.41 years and age range: 16–25 years) of Caucasian origin (Russians (N = 214) or Tatars (N = 388)). Ethnicity was assessed based on self-reports of involved individuals and those who were homogenous for the third generation in subpopulation (Russians or Tatars) were included into the research. The study was approved by the Biological Ethics Committee of Bashkortostan Republic and written inform consent was obtained from all the participants after they were acquainted with all the procedures.

2.2. Psychometric evaluation

Personality traits were assessed using the Russian version of psychological inventories EPI (Eysenck Personality Inventory) and TCI-125 (Temperament and Character Inventory) (Raygorodskiy, 2003). The EPI measures two global personality domains: Extraversion (the tendency to perform high social activity and dominance) and Neuroticism (the tendency to show emotional lability and anxiety). The TCI-125 evaluates 4 temperament traits: Novelty Seeking, Harm Avoidance, Reward Dependence, Persistence, and 3 character traits: Self-directedness, Cooperation and Self-transcendence. Since temperament traits are assumed to be highly heritable and manifest early in development, whereas character traits are thought to be influenced by different socio-cultural factors and change during the lifespan (Cloninger et al., 1993), we evaluated the influence of dopamine system gene polymorphisms on four temperament traits.

2.3. Genotyping

Genomic DNA was isolated from the whole blood using a standard phenol-chlorophorm technique. PCR primers for *DRD2/ANKK1 Taq1A*, *DRD2 rs6275*, *SLC6A3 VNTR* and *rs27072* were designed as described previously (Vandenbergh et al., 1992; Chen et al., 1997; Ueno et al., 1999). PCR was performed in total volume of 15 μl with 20–50 ng of genomic DNA, Taq polymerase (Silex, Russia).

The conditions for *DRD2/ANKK1 Taq1A* were the following: initial denaturation 94 °C 5 min, 35 cycles consisting of 94 °C 1 min, 50 °C 1 min, 72 °C 1 min, and final extension step on 72 °C 10 min. Subsequently, for allele detection PCR products were accomplished by overnight incubation with 3 U of TaqI restriction endonuclease (Fermentas, Canada) according to manufacturer's recommendations, resolved in 7% PAAG and visualized by staining with ethidium bromide. After incubation with TaqI, the A1-allele remains intact (310 bp) while the A2-allele is cleaved (130 bp and 180 bp).

The conditions for *DRD2 rs6275* were the following: initial denaturation 94 °C 5 min, 35 cycles consisting of 94 °C 30 s, 59 °C 30 s, 72 °C 1 min, and final extension step on 72 °C 10 min. PCR products were digested by 3 U of Bsp19I restriction endonuclease (Sibenzyme, Russia) according to manufacturer's recommendations resulting in N1-allele (454 bp) and N2-allele (274 and 180 bp).

Thermal PCR conditions for *SLC6A3 rs27072* were the following: initial denaturation 95 °C 5 min, 35 cycles consisting of 95 °C 30 s, 62 °C 30 s, 72 °C 30 s, and final extension step on 72 °C 10 min. Digestion of PCR products was performed by overnight incubation with 3 U of MspI restriction endonuclease (Fermentas, Canada) according to manufacturer's recommendations. Product sizes for cleaved products were: A-allele = 217 bp and G-allele = 135 bp + 82 bp.

The conditions for *SLC6A3 VNTR* were the following: initial denaturation 94 °C 5 min, 35 cycles consisting of 94 °C 30 s, 68 °C 30 s, 72 °C 1 min 30 s, and final extension step on 72 °C 10 min. PCR products from 7-repeats (363 bp) till 11-repeats (523 bp) differing in 40 bp were observed. Since the frequency of 9-repeats (443 bp) and 10-repeats (483 bp) was the highest, individuals possessing other repeats (<3%) were excluded from the analysis.

2.4. Statistical analysis

Genotype frequencies of *DRD2/ANKK1 Taq1A, DRD2 rs6275, SLC6A3 rs27072* and *SLC6A3 VNTR* polymorphisms were calculated in the total sample and in gender- and ethnicity-specific groups. One-way analysis of variance (ANOVA) was conducted in order to compare scores of personality measures in each genotype group.

As a next step, the regression models were fitted with independent variables of genotype (recoded as binary variables according to the "dominant" models due to non-additive effect of the studied polymorphisms). The reference groups were: A1-allele for *ANKK1/DRD2 Taq1A,* N2-allele for *DRD2 rs6275,* A-allele for *SLC6A3 rs27072*, and 9R-allele for *SLC6A3 VNTR*; women for gender and Russians for ethnicity.

First, we investigated the main effects of independent variables (gender and ethnicity) on personality traits using univariate regression models (Supplementary material, Table 1S, Model 1), then we included both variables as covariates to test for the main effect of gene polymorphisms (Models 2–5). If the main effect of gene polymorphisms was significant or marginally significant after FDR correction, the further analysis was performed using multivariate regression models to test the interaction effect (polymorphism-by-gender) with inclusion of gender, ethnicity, gene polymorphism as covariates (Models 6–9) (hierarchical regression model). If the interaction terms were marginally significant ($p<0.10$), the models were tested separately for each gender. The statistical package STATA 9 was used for ANOVA and regression analyses.

We have also performed a gene-based haplotype analysis for two polymorphisms of *ANKK1/DRD2* (*Taq1A* and *rs6275*) and two polymorphisms of *SLC6A3* (*rs27072* and *VNTR*). Haplotype blocks were delineated using the confidence interval method (Gabriel et al., 2002) and a measure of pairwise linkage disequilibrium was obtained with Haploview 4.1 (http://www.broad.mit.edu/mpg/haploview/). Haplotypes with a frequency lower than 1% were excluded from the analysis. The PLINK v.1.07 program (Purcell et al., 2007) was then used to examine the association of specific haplotype with personality traits.

As multiple positive findings were expected and found, false discovery rate (FDR) procedure (Simes procedure) (Benjamini and Hochberg, 1995) was carried out and p-value thresholds were calculated to quantify the joint probability of multiple findings reflecting true associations as opposed to false positives, taking into account all comparisons performed to test our hypotheses. This procedure provides an effective control of type I error rate in the context of multiple correlated tests and has good agreement with the permutation test (Uher et al., 2009). In ANOVA 12 independent tests (due to the number of personality traits equal to 6 and since *ANKK1/DRD2 Taq1A* is in linkage disequilibrium (LD) with *DRD2 rs6275*, as well as *SLC6A3 rs27072* is in LD with *SLC6A3 VNTR*) were made (Tables 1 and 2), while in the regression analysis 180 tests were performed (Table 1S). The haplotype analysis conducted in the total sample comprised 18 tests for *ANKK1/DRD2* haplotype testing and 24 tests for *SLC6A3* haplotype testing, since haplotypes with frequencies less than 1% were excluded from the analysis. The multiple comparison-corrected significance thresholds were then calculated as (k*0.05)/m, where m — is the number of statistical tests and k — is the order of the tested hypothesis.

3. Results

The distributions of genotype frequencies for all SNPs were consistent with Hardy–Weinberg equilibrium ($P=0.39$ for *DRD2/ANKK1 Taq1A,* $P=0.96$ for *DRD2 rs6275,* $P=0.71$ for *SLC6A3 rs27072*, and $P=0.051$ for *SLC6A3 VNTR*).

Personality scores for each genotype of the investigated polymorphisms (*DRD2/ANKK1 Taq1A*, *DRD2 rs6275*, *SLC6A3 rs27072* and *SLC6A3 VNTR* polymorphisms) in the total sample, and in men and women separately are presented in Table 1. ANOVA conducted in the total sample and in gender-specific groups revealed the trend for differences (after FDR correction) in Neuroticism scores between *ANKK1/DRD2 Taq1A* genotypes in total group and in women ($P=0.06$ and $P_{FDR}=0.12$), in NS scores between *ANKK1/DRD2 Taq1A* genotypes in men ($P=0.05$ and $P_{FDR}=0.11$), and in PS between *SLC6A3 rs27072* genotypes in women ($P=0.04$ and $P_{FDR}=0.11$).

According to post-hoc comparisons (Bonferroni-corrected), *ANKK1/DRD2 Taq1A* A2/A2-genotype carriers demonstrated the tendency for scoring lower on Neuroticism ($P=0.054$ in the total sample and $P=0.11$ in women) compared to A1/A2-genotype carriers; while males with A2/A2-genotype tended to score higher on NS ($P=0.11$) compared to those with A1/A1-genotype, however these results were not statistically significant.

No differences in personality scores between genotypes of the investigated SNPs were observed in either Tatars or Russians (Table 2).

3.1. Regression analysis

The subsequent regression analysis demonstrated that gender had statistically significant effects on Neuroticism ($P<0.001$ and $P_{FDR}=0.005$), NS ($P<0.001$ and $P_{FDR}=0.005$), and RD ($P<0.001$ and $P_{FDR}=0.005$) (Model 1). Ethnicity had statistically significant effects on Extraversion ($P<0.001$ and $P_{FDR}=0.005$), Neuroticism ($P=0.011$ and $P_{FDR}=0.041$), NS ($P=0.010$ and $P_{FDR}=0.041$), and HA ($P=0.013$ and $P_{FDR}=0.041$) (Model 1, Table 1S).

The regression analysis conducted with gender and ethnicity inclusion as covariates under the dominant models of gene polymorphisms revealed a statistically significant (after FDR correction) effect of *DRD2/ANKK1 Taq1A* on Neuroticism ($P=0.016$, Coef. $=0.826$; 95% CI: 0.15 and 1.49; and $P_{FDR}=0.045$) (Table 1S, Model 2), with the A1-allele having the highest score (Table 1S). R-square estimates point to the proportions of variance of independent variables contributing to personality trait. We revealed that the model considering simultaneous influence of gender, ethnicity and *ANKK1/DRD2 Taq1A* polymorphism accounted for 7.3% of variance in Neuroticism with *ANKK1/DRD2 Taq1A* polymorphism main effect equal to 4.2%.

The model adjusted for gender and ethnicity with Persistence as an outcome demonstrated that the effect of *SLC6A3 rs27072* genotype remained significant ($P=0.021$; Coef. $=-0.236$; 95% CI: -0.43 and -0.03; and $P_{FDR}=0.049$), with the G/G-genotype having the highest score (Table 1S, Model 4). The main effect of *SLC6A3 rs27072* polymorphism contributed to 0.5% of variance in Persistence.

There was a significant *ANKK1/DRD2 Taq1A* polymorphism-by-gender interaction effect on NS ($P=0.018$, Coef. $=-1.219$; and 95% CI: 0.21 and 2.22) that remained significant after FDR correction ($P_{FDR}=0.047$). In men, but not in women, A2/A2-carriers had higher NS score as compared to A1-allele carriers. The model estimating interaction effect of "*ANKK1/DRD2 Taq1A* polymorphism-by-gender" revealed 5.7% of variance in NS. Since polymorphism-by-gender interaction for *ANKK1/DRD2 Taq1A* on NS ($P=0.018$ and $P_{FDR}=0.047$) was significant and the trend for this interaction on RD ($P=0.043$ and $P_{FDR}=0.111$) was observed (Table 1S), the models were tested separately for each gender.

In men, but not in women, a statistically significant effect of *ANKK1/DRD2 Taq1A* A1-allele on NS and RD was demonstrated: higher NS and lower RD scores ($P_{FDR}=0.03$ for both) were shown in A2/A2-homozygotes compared with those in A1-allele carriers (Table 3). Among men, scores of NS were estimated to increase by 0.93 in the group of those with *ANKK1* A2/A2-genotype compared to A1-allele carriers, while men bearing A1-allele scored 0.65 higher on RD compared to A2/A2-genotype carriers.

No other significant polymorphism-by-gender interaction effects were shown for EPI- or TCI-measured personality traits.

3.2. LD structure and haplotype analysis

Maximum likelihood analysis of haplotype distributions demonstrated the presence of linkage disequilibrium between *ANKK1/DRD2*

Table 1
Sample description by genotype of *ANKK1/DRD2* and *SLC6A3* gene polymorphisms in the total sample and in gender-specific groups.

Polymorphism	Parameter	Total sample			Females			Males		
		A1/A1	*A1/A2*	*A2/A2*	*A1/A1*	*A1/A2*	*A2/A2*	*A1/A1*	*A1/A2*	*A2/A2*
		N = 30	*N* = 237	*N* = 385	*N* = 17	*N* = 158	*N* = 255	*N* = 13	*N* = 79	*N* = 130
ANKK1/DRD2 Taq1A	EX	13.80 ± 4.18	13.90 ± 3.66	14.03 ± 3.77	13.70 ± 4.66	14.15 ± 3.48	14.12 ± 3.86	13.92 ± 3.63	13.40 ± 3.98	13.86 ± 3.63
	NEU	13.60 ± 4.30[a]	13.86 ± 4.39	13.00 ± 4.47	15.23 ± 3.68[a]	14.62 ± 4.30	13.75 ± 4.16	11.46 ± 4.23	12.35 ± 4.21	11.53 ± 4.71
	NS	10.30 ± 3.36	11.14 ± 3.19	11.21 ± 3.10	11.53 ± 3.31	11.80 ± 3.84	11.52 ± 3.09	8.69 ± 2.78[b]	9.83 ± 3.48	10.61 ± 3.04
	HA	9.43 ± 3.44	8.93 ± 3.77	9.00 ± 3.83	9.47 ± 2.35	9.24 ± 3.71	9.19 ± 3.80	9.38 ± 4.61	8.33 ± 3.85	8.63 ± 3.89
	RD	7.56 ± 2.02	7.99 ± 2.32	7.82 ± 2.44	7.76 ± 1.78	8.11 ± 2.33	8.22 ± 2.50	7.31 ± 2.35	7.74 ± 2.29	7.03 ± 2.14
	PS	2.53 ± 1.54	2.72 ± 1.27	2.63 ± 1.23	2.41 ± 1.80	2.68 ± 1.30	2.65 ± 1.24	2.69 ± 1.18	2.82 ± 1.21	2.59 ± 1.23
		N1/N1	*N1/N2*	*N2/N2*	*N1/N1*	*N1/N2*	*N2/N2*	*N1/N1*	*N1/N2*	*N2/N2*
		N = 247	*N* = 309	*N* = 96	*N* = 155	*N* = 219	*N* = 56	*N* = 92	*N* = 90	*N* = 40
DRD2 rs6275	EX	14.20 ± 3.65	13.98 ± 3.84	13.38 ± 3.67	14.23 ± 3.65	14.22 ± 3.81	13.41 ± 3.77	14.15 ± 3.67	13.40 ± 3.89	13.35 ± 3.57
	NEU	13.12 ± 4.63	13.61 ± 4.37	13.04 ± 4.23	14.25 ± 4.31	14.11 ± 4.25	13.91 ± 3.82	11.22 ± 4.55	12.42 ± 4.43	11.82 ± 4.51
	NS	11.25 ± 3.21	11.26 ± 3.03	10.52 ± 3.30	11.83 ± 2.94	11.68 ± 2.97	10.85 ± 3.21	10.28 ± 3.41	10.24 ± 2.96	10.05 ± 3.41
	HA	8.85 ± 3.71	8.99 ± 3.78	9.44 ± 3.97	9.14 ± 3.53	9.27 ± 3.72	9.30 ± 4.13	8.36 ± 3.97	8.28 ± 3.86	9.65 ± 3.77
	RD	7.87 ± 2.40	7.83 ± 2.31	8.01 ± 2.55	8.14 ± 2.39	8.10 ± 2.36	8.51 ± 2.64	7.41 ± 2.36	7.20 ± 2.07	7.30 ± 2.25
	PS	2.73 ± 1.24	2.61 ± 1.30	2.64 ± 1.17	2.80 ± 1.31	2.53 ± 1.30	2.71 ± 1.11	2.61 ± 1.12	2.80 ± 1.29	2.55 ± 1.28
		A/A	*A/G*	*G/G*	*A/A*	*A/G*	*G/G*	*A/A*	*A/G*	*G/G*
		N = 27	*N* = 219	*N* = 406	*N* = 20	*N* = 144	*N* = 266	*N* = 7	*N* = 75	*N* = 140
SLC6A3 rs27072	EX	13.33 ± 3.30	14.35 ± 3.74	13.81 ± 3.77	13.75 ± 3.32	14.70 ± 3.67	13.83 ± 3.79	12.14 ± 3.18	13.68 ± 3.79	13.79 ± 3.75
	NEU	13.81 ± 4.35	13.33 ± 4.60	13.31 ± 4.37	14.30 ± 4.18	14.17 ± 4.32	14.09 ± 4.17	12.42 ± 4.85	11.73 ± 4.74	11.83 ± 4.40
	NS	11.11 ± 2.65	11.45 ± 3.20	10.98 ± 3.14	11.35 ± 2.94	11.97 ± 3.10	11.44 ± 2.95	10.43 ± 1.51	10.45 ± 3.18	10.09 ± 3.31
	HA	8.88 ± 4.01	9.04 ± 3.58	8.98 ± 3.89	8.90 ± 3.86	9.10 ± 3.66	9.31 ± 3.73	8.85 ± 4.74	8.93 ± 3.45	8.35 ± 4.10
	RD	8.03 ± 2.48	7.80 ± 2.34	7.89 ± 2.40	8.05 ± 2.35	8.15 ± 2.31	8.17 ± 2.47	8.00 ± 3.05	7.12 ± 2.25	7.37 ± 2.17
	PS	2.51 ± 1.28	2.52 ± 1.27	2.75 ± 1.25	2.25 ± 1.21[c]	2.50 ± 1.30	2.77 ± 1.27	3.28 ± 1.25	2.56 ± 1.22	2.71 ± 1.22
		9R/9R	*9R/10R*	*10R/10R*	*9R/9R*	*9R/10R*	*10R/10R*	*9R/9R*	*9R/10R*	*10R/10R*
		N = 38	*N* = 202	*N* = 412	*N* = 25	*N* = 133	*N* = 272	*N* = 13	*N* = 69	*N* = 140
SLC6A3 VNTR	EX	14.07 ± 3.40	13.78 ± 3.86	14.06 ± 3.73	13.88 ± 3.61	13.79 ± 3.94	14.29 ± 3.68	14.46 ± 3.04	13.75 ± 3.75	13.60 ± 3.81
	NEU	13.97 ± 4.85	13.23 ± 4.08	13.33 ± 4.58	14.14 ± 4.17	13.88 ± 4.11	14.25 ± 4.27	13.61 ± 6.22	12.04 ± 3.76	11.54 ± 4.66
	NS	10.70 ± 3.44	11.03 ± 3.10	11.25 ± 3.14	10.77 ± 3.59	11.35 ± 2.99	11.84 ± 2.93	10.53 ± 3.23	10.43 ± 3.22	10.09 ± 3.23
	HA	9.32 ± 3.83	8.78 ± 3.77	9.03 ± 3.79	9.37 ± 4.17	8.77 ± 3.53	9.43 ± 3.73	9.23 ± 3.16	9.07 ± 4.21	8.25 ± 3.81
	RD	8.10 ± 2.58	7.97 ± 2.38	7.81 ± 2.36	8.22 ± 2.75	8.21 ± 2.44	8.14 ± 2.36	7.84 ± 2.30	7.52 ± 2.22	7.15 ± 2.21
	PS	2.35 ± 1.23	2.63 ± 1.24	2.71 ± 1.27	2.22 ± 1.05	2.66 ± 1.25	2.69 ± 1.32	2.61 ± 1.55	2.57 ± 1.22	2.73 ± 1.19

EX — Extraversion, NEU — Neuroticism, NS — Novelty Seeking, HA — Harm Avoidance, RD — Reward Dependence, and PS — Persistence. The trend for an association between the genotypes and personality trait was indicated (uncorrected P-value).
[a] $P = 0.06$ ($P_{FDR} = 0.12$).
[b] $P = 0.05$ ($P_{FDR} = 0.11$).
[c] $P = 0.04$ ($P_{FDR} = 0.11$).

Taq1A and *DRD2 rs6275* ($D' = 0.90$) and *SLC6A3 rs27072* and *VNTR* ($D' = 0.72$).

Haplotype frequencies for *ANKK1/DRD2* (*Taq1A* and rs*6275* loci) were 0.396 (*A2*N1*), 0.375 (*A2*N2*), and 0.220 (*A1*N1*), while the frequency of *A1*N2* haplotype was less than 1%. With respect to *SLC6A3* haplotypes constructed based on *SLC6A3 VNTR* and *rs27072* the following frequencies were demonstrated: 0.596 (*10R*G*), 0.197 (*10R*A*), 0.194 (*9R*G*) and 0.012 (*9R*A*).

Haplotype analysis revealed an association between *SLC6A3 10R*G*-haplotype and higher Persistence in the total sample ($P = 0.002$, Coef. = 2.98, $R^2 = 1.4\%$; and $P_{FDR} = 0.048$), as well as in female group ($P = 0.002$, Coef. = 3.077, $R^2 = 2.2\%$; and $P_{FDR} = 0.040$) that remained significant after FDR correction. No significant haplotypic effect was observed for the investigated gene polymorphisms and EPI-measured traits.

4. Discussion

The present study of *ANKK1/DRD2* and *SLC6A3* genes in personality traits in healthy individuals was based on the results of personality traits measurement with two different inventories: Eysenck Personality Inventory (EPI) and Temperament and Character Inventory (TCI-125). The rationale for the inclusion of both inventories in the study was to test if not only the traits defined by TCI-125 (proposed to be influenced by neurotransmitter systems functioning (Cloninger et al., 1993)), but also EPI-assessed traits could have the neurobiological basis. However, despite the correlation between the EPI and TCI-defined traits: for instance, both inventories measure approach-related (Extraversion (EPI) and Novelty Seeking (TCI-125)) and anxiety-related (Neuroticism (EPI) and Harm Avoidance (TCI-125)) traits, our findings demonstrated inventory-specific pattern of association. For instance, we observed the association of *ANKK1/ DRD2 Taq1A* with Neuroticism (EPI), but not with Harm Avoidance (TCI), while *SLC6A3 rs27072* was associated with Persistence (TCI) only. We also showed *ANKK1/DRD2 Taq1A* polymorphism-by-gender interaction effects on Novelty Seeking (NS) and Reward Dependence (RD): an association of *ANKK1* A1-allele with lower NS and higher RD was indicated in men, but not in women. Moreover, we demonstrated an association between *SLC6A3 10R*G*-haplotype and higher Persistence in women, but not in men.

To the best of our knowledge, this is the first study to investigate association between *SLC6A3 rs27072* polymorphism and personality traits in a healthy population. Previously published findings have demonstrated an association between *SLC6A3 rs27072* A-allele with smoking (Ling et al., 2004) and alcoholism (Ueno et al., 1999). Since smoking (Manchia et al., 2010) and alcoholism (Müller et al., 2008) are both characterized by lower Persistence, these findings seem to be in agreement with our results showing the association of *SLC6A3 rs27072* G/G-genotype and *10R*G*-haplotype and higher Persistence. However, one study showed that *SLC6A3 rs27072* G-allele was over-transmitted to children with ADHD (Galili-Weisstub et al., 2005; Laurin et al., 2007) characterized by lower goal achievement,

Table 2
Sample description by genotype of *ANKK1/DRD2* and *SLC6A3* gene polymorphisms in ethnicity-specific groups.

Polymorphism	Parameter	Tatars			Russians		
		A1/A1	*A1/A2*	*A2/A2*	*A1/A1*	*A1/A2*	*A2/A2*
		N = 18	*N = 159*	*N = 242*	*N = 12*	*N = 78*	*N = 143*
ANKK1/DRD2 Taq1A	EX	13.83 ± 4.51	13.40 ± 3.54	13.69 ± 3.71	13.75 ± 3.81	14.92 ± 3.72	14.61 ± 3.83
	NEU	13.61 ± 4.13	14.03 ± 4.44	13.27 ± 4.36	13.58 ± 4.73	13.53 ± 4.31	12.53 ± 4.63
	NS	10.38 ± 3.69	10.96 ± 3.39	10.83 ± 3.06	10.16 ± 2.94	11.50 ± 2.73	11.86 ± 3.06
	HA	9.77 ± 3.55	9.05 ± 3.87	9.33 ± 3.91	8.91 ± 3.34	8.71 ± 3.57	8.43 ± 3.63
	RD	7.44 ± 2.25	8.02 ± 2.41	7.90 ± 2.48	7.75 ± 1.71	7.92 ± 2.14	7.68 ± 2.38
	PS	2.38 ± 1.54	2.71 ± 1.24	2.71 ± 1.21	2.75 ± 1.60	2.77 ± 1.33	2.48 ± 1.27
		N1/N1	*N1/N2*	*N2/N2*	*N1/N1*	*N1/N2*	*N2/N2*
		N = 147	*N = 202*	*N = 70*	*N = 100*	*N = 107*	*N = 26*
DRD2 rs6275	EX	13.87 ± 3.65	13.49 ± 3.73	13.25 ± 3.61	14.68 ± 3.62	14.89 ± 3.91	13.73 ± 3.89
	NEU	13.43 ± 4.53	13.89 ± 4.34	13.01 ± 4.19	12.68 ± 4.76	13.10 ± 4.38	13.11 ± 4.42
	NS	11.02 ± 3.31	10.97 ± 3.08	10.25 ± 3.36	11.59 ± 3.04	11.81 ± 2.88	11.23 ± 3.10
	HA	9.08 ± 3.98	9.24 ± 3.84	9.67 ± 3.76	8.52 ± 3.27	8.50 ± 3.65	8.84 ± 4.51
	RD	7.78 ± 2.57	8.02 ± 2.35	8.01 ± 2.44	8.00 ± 2.15	7.49 ± 2.21	8.00 ± 2.87
	PS	2.74 ± 1.21	2.69 ± 1.29	2.63 ± 1.17	2.71 ± 1.31	2.47 ± 1.33	2.69 ± 1.22
		A/A	*A/G*	*G/G*	*A/A*	*A/G*	*G/G*
		N = 20	*N = 145*	*N = 254*	*N = 7*	*N = 74*	*N = 152*
SLC6A3 rs27072	EX	13.15 ± 3.33	13.90 ± 3.66	13.44 ± 3.71	13.85 ± 3.44	15.23 ± 3.76	14.44 ± 3.81
	NEU	13.95 ± 4.51	13.54 ± 4.43	13.56 ± 4.36	13.43 ± 4.16	12.93 ± 4.94	12.89 ± 4.38
	NS	11.05 ± 2.68	11.04 ± 3.41	10.74 ± 3.14	11.28 ± 2.75	12.25 ± 2.62	11.37 ± 3.11
	HA	9.45 ± 4.27	9.43 ± 3.72	9.12 ± 3.94	7.28 ± 2.81	8.29 ± 3.21	8.73 ± 3.79
	RD	8.15 ± 2.39	7.74 ± 2.35	8.02 ± 2.50	7.71 ± 2.93	7.91 ± 2.33	7.69 ± 2.22
	PS	2.65 ± 1.31	2.52 ± 1.25	2.81 ± 1.22	2.14 ± 1.21	2.53 ± 1.33	2.65 ± 1.31
		9R/9R	*9R/10R*	*10R/10R*	*9R/9R*	*9R/10R*	*10R/10R*
		N = 25	*N = 122*	*N = 272*	*N = 15*	*N = 75*	*N = 143*
SLC6A3 VNTR	EX	13.36 ± 3.34	13.27 ± 3.88	13.75 ± 3.63	15.27 ± 3.28	14.61 ± 3.72	14.64 ± 3.89
	NEU	14.60 ± 5.14	13.07 ± 4.08	13.71 ± 4.44	12.93 ± 4.31	13.50 ± 4.09	12.61 ± 4.78
	NS	10.48 ± 3.61	10.71 ± 3.05	10.98 ± 3.26	11.06 ± 3.24	11.54 ± 3.14	11.77 ± 2.86
	HA	10.20 ± 3.66	8.90 ± 3.90	9.33 ± 3.88	7.87 ± 3.77	8.84 ± 3.59	8.47 ± 3.58
	RD	8.64 ± 2.74	7.88 ± 2.46	7.89 ± 2.41	7.20 ± 2.11	8.12 ± 2.27	7.64 ± 2.27
	PS	2.36 ± 1.31	2.68 ± 1.29	2.74 ± 1.21	2.33 ± 1.11	2.56 ± 1.16	2.64 ± 1.41

EX — Extraversion, NEU — Neuroticism, NS — Novelty Seeking, HA — Harm Avoidance, RD — Reward Dependence, and PS — Persistence.

persistence and attention (Yoo et al., 2006), thus is not in line with our finding, although we cannot make a direct comparison between ADHD sample and the sample of healthy individuals. On the other hand, this inconsistence could result from the involvement of another polymorphic marker linked to *rs27072* in personality traits and disorders, for instance *SLC6A3* 3′-*VNTR*. Since the presence of the nine repeat allele of the *SLC6A3* 3′-*VNTR* (in linkage with *SLC6A3 rs27072* G-allele (Ueno et al., 1999)) has generally been associated with reduced dopamine transporter binding potential (van Dyck et al., 2005) or reduced levels of SLC6A3 transcripts (Brookes et al., 2007), we can suggest that increased dopamine in synapse could be the biological predisposition to enhanced Persistence formation. However, we observed an association of *SLC6A3* 10R*G-haplotype and higher Persistence that seems to be in agreement with findings demonstrated by Samochowiec et al. (2001), since Persistence primarily comprised RD scale: *SLC6A3* 9R/9R-genotype was shown to be associated with decreased scores on one of RD subscales.

Table 3
Gender-specific associations between *ANKK1/DRD2 Taq1A* (dominant model) and personality traits: the mean and SD for each personality trait are presented.

Personality trait	Group, mean ± SD	*ANKK1/DRD2 Taq1A* group		*P*-value
		A2/A2 homozygotes	A1-allele carriers	
Novelty Seeking	Men	10.61 ± 3.04	9.67 ± 3.40	**0.03**
	Women	11.51 ± 3.09	11.77 ± 2.87	0.36
Reward Dependence	Men	7.03 ± 2.14	7.68 ± 2.29	**0.03**
	Women	8.22 ± 2.50	8.08 ± 2.28	0.48

Significant p-values are in bold.

Our study supports the role of *ANKK1* gene in Neuroticism, in both men and women, with *ANKK1/DRD2 Taq1A* A1-allele being associated with higher Neuroticism scores. Associations between *ANKK1 Taq1A* polymorphism and anxiety-related traits have been previously demonstrated in healthy subjects (Eisenberg et al., 2007; Hayden et al., 2010; Wacker et al., 2005), as well as in psychiatric patients (Ponce et al., 2003; Joe et al., 2008).

Our findings revealed that men, but not women, carriers of *ANKK1* A1-allele scored higher in Reward Dependence (RD). This observation could be explained by the tendency to compensate their decreased dopaminergic neurotransmission by increasing reward-related behavior. It has been suggested that decreased Dopamine D2 receptor availability in the striatum predisposes to reward-related traits and disorders (e.g., substance dependence) (Conner et al., 2010; Dalley et al., 2007) associated with *ANKK1/DRD2 Taq1A* A1-allele (Berggren et al., 2006; Connor et al., 2008; Noble, 2003). Consistent with our findings, the rewarding value of emotional eating has been observed in *ANKK1/DRD2 Taq1A* A1-allele carriers (Nisoli et al., 2007; van Strien et al., 2010), as well as *ANKK1/DRD2 Taq1A* A1-allele gender-specific association with smoking (Zuo et al., 2009), heroin dependence (Hou and Li, 2009), and reward responsiveness (Lee et al., 2007). However, there have been some opposite findings indicating that women carrying one or more copies of the in *DRD2 C957T* T-allele (associated with higher striatal DRD2 availability in healthy volunteers as in *ANKK1/DRD2 Taq1A* A2/A2-genotype carriers (Hirvonen et al., 2006)) had higher liability to alcoholism due to lower probability of being

abstinent (Munafò et al., 2009). These inconsistencies might result from influence of sex steroids on dopamine neurotransmission. Despite the multiple findings indicating the role of dopamine neurotransmission in reward-related traits and disorders, no main effect of rs6275 residing directly in *DRD2* gene compared to *Taq1A* polymorphism located in *ANKK1* gene on personality was observed thus confirming recent suggestion of a potential relationship of *ANKK1* gene with the dopaminergic system (Hoenicka et al., 2010).

Initially, we hypothesized that individuals with *ANKK1/DRD2 Taq1A* A1-allele would have more liability for increased Novelty Seeking (NS), the trait often accompanying addictive behavior. A few published studies reported association between *ANKK1/DRD2 Taq1A* A1-allele and higher NS scores in men (Noble et al., 1998; Berman et al., 2002; Lin et al., 2007), Extraversion in female-prevalent sample (Smillie et al., 2010), ADHD (characterized by higher NS) (Serý et al., 2006; Drtilkova et al., 2008), and alcohol dependence (Munafò et al., 2007). However, our data revealed the opposite association in men which may be attributed to sex hormone influence: men had markedly greater dopamine release than women in the striatal regions (Munro et al., 2006). One means by which testosterone may increase dopamine release and diminish dopamine transporter density is by upregulating nitric oxide synthase, which produces nitric oxide responsible for the enhanced dopamine release (Hull et al., 1999). Interestingly, our findings indicating lower NS in men with *ANKK1/DRD2 Taq1A* A1-allele seem to be in agreement with those revealed for male patients with type I alcohol addiction (Ponce et al., 2003; Huang et al., 2007) characterized by low NS, with *ANKK1/DRD2 Taq1A* A2-allele association with ADHD and compulsive smoking habits (Rowe et al., 1999; Hamajima et al., 2002) both characterized by high NS.

Our findings of the association between *ANKK1/DRD2 Taq1A* A1/A1-genotype with lower Novelty Seeking and higher Reward Dependence have a plausible biological explanation. The differences in dopamine release and metabolism have been reported between mesolimbic and cortical versus nigrostriatal dopaminergic systems (Hirvonen et al., 2009): dopamine transporter and D2-like autoreceptor functioning is less efficient in the cortex than in the striatum (Mazei et al., 2002). Thus, the presence of *ANKK1/DRD2 Taq1A* A1-allele resulted in the decreased dopamine D2-receptor density in striatum (Jönsson et al., 1999; Noble et al., 1991; Pohjalainen et al., 1998a; Ritchie and Noble, 2003; Thompson et al., 1997) and the trend for increased D2 density in extrastriatal regions was shown (Hirvonen et al., 2009). It has been suggested that the nucleus accumbens, an area within the ventral striatum, is principally important in the rewarding effects (for a review, see Di Chiara et al., 2004), while dopaminergic activity in the cortical areas can be expected to be increased in subjects with a higher Novelty Seeking score (Zhu et al., 2007), based on the hypothesis that Novelty Seeking uses an activated dopamine system (Cloninger et al., 1993). Moreover, sex differences in the striatal (Pohjalainen et al., 1998b), as well as in mesocorticolimbic (Kaasinen et al., 2001) dopamine system have been observed that probably explains the gender-specific association observed in the present study.

A sex-specific effect of dopamine receptor polymorphisms on temperament is not surprising due to the evidence of putatively estrogen- and testosterone-dependent gender differences in dopaminergic function (Sawada and Shimohama, 2000). For instance, it has been reported that women had higher tendency to major depression (Epperson, 1999), while men demonstrated higher incidence in developing Parkinsonian symptoms (Thompson et al., 1997), in smoking (Lee et al., 2002), in aggressive and impulsive behavior (Strous et al., 2003), ADHD (Biederman et al., 2008), and obsessive–compulsive disorder (Pooley et al., 2007). Moreover, stronger associations of *ANKK1/DRD2 Taq1A* with psychological phenotypes are often seen in men (Berman et al., 2002; Huang et al., 2007; Lin et al., 2007; Noble et al., 1998; Ponce et al., 2003;) due to the statistical noise generated by the women's cyclic variation in hormonal levels. Our data indicating the involvement of *ANKK1* gene in NS and RD in males rather than in females could be also explained by the testosterone secretion impact on reinforcing social behaviors, including mating and aggression observed in animals (Forger, 2009).

The present study has a number of methodological strengths including homogeneity of the sample in respect to age and education and occupation levels. Since the present study tested multiple independent hypotheses, we performed correction for multiple testing to decrease the possibility of false positive results under the false discovery rate (FDR) procedure (Simes procedure) (Benjamini and Hochberg, 1995). This procedure provides an effective control of type I error rate in the context of multiple correlated tests and has good agreement with the permutation test (Uher et al., 2009). However, the study has some limitations that should be mentioned. First, association studies of unrelated individuals warrant cautious interpretation as unknown sources of population stratification may affect the results (Hutchison et al., 2004). However, the risk for population stratification in our study is limited since our sample comprised two Caucasian subpopulations and we have adjusted for ethnicity in our regression models that demonstrated no significant effect. Second, the use of self-reports for the assessment of personality may result in over- or under-reporting some behavior due to social desirability. To minimize these biases, in the present study, individuals were not allowed to discuss questions or answers with anyone. On the other hand, TCI self-report measures were shown to be the strong predictors of self-reported personality by both peer-report measures and ratings by non-acquainted judges (Grucza and Goldberg, 2007). Finally, the present study involved only four polymorphisms of dopaminergic system genes; however, interaction of genes from different neurotransmitter systems is known to affect variation in personality (Comings et al., 2000).

5. Conclusions

The present results provide useful information for the interpretation of genetic studies exploring the role of *ANKK1/DRD2* and *SLC6A3* gene polymorphisms in personality traits in healthy individuals. Future psychogenetic investigations of personality should seek to replicate and extend the present research, perhaps by examining more thoroughly the role of demographic and also environmental variables on gene–personality relationships.

Supplementary materials related to this article can be found online at doi:10.1016/j.pnpbp.2011.02.013.

Acknowledgements

This work was supported by the grant of Russian Foundation for Humanities (09-06-95601a/E and 08-06-591a) and by 7th Framework Programme ADAMS HEALTH-2009-4.3.3-1 grant no. 02.527.11.0006/3.

References

Becker JB. Gender differences in dopaminergic function in striatum and nucleus accumbens. Pharmacol Biochem Behav 1999;64(4):803–12.
Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B Methodol 1995;57(1):289–300.
Berggren U, Fahlke C, Aronsson E, Karanti A, Eriksson M, Blennow K, et al. The taqI DRD2 A1 allele is associated with alcohol-dependence although its effect size is small. Alcohol Alcohol 2006;41(5):479–85.
Berman S, Ozkaragoz TZ, Young RM, Noble E. D2 dopamine receptor gene polymorphism discriminates two kinds of novelty seeking. Pers Individ Diff 2002;33:867–82.
Biederman J, Kim JW, Doyle AE, Mick E, Fagerness J, Smoller JW, et al. Sexually dimorphic effects of four genes (COMT, SLC6A2, MAOA, SLC6A4) in genetic associations of ADHD: a preliminary study. Am J Med Genet B Neuropsychiatr Genet 2008;147B(8):1511–8.
Brookes KJ, Neale BM, Sugden K, Khan N, Asherson P, D'Souza UM. Relationship between VNTR polymorphisms of the human dopamine transporter gene and expression in post-mortem midbrain tissue. Am J Med Genet B Neuropsychiatr Genet 2007;144B(8):1070–8.
Chen WJ, Lu ML, Hsu YP, Chen CC, Yu JM, Cheng AT. Dopamine D2 receptor gene and alcoholism among four aboriginal groups and Han in Taiwan. Am J Med Genet 1997;74(2):129–36.

Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993;50:975–90.
Comings DE, Rosenthal RJ, Lesieur HR, Rugle LJ, Muhleman D, Chiu C, et al. A study of the dopamine D2 receptor gene in pathological gambling. Pharmacogenetics 1996;6 (3):223–334.
Comings DE, Gade-Andavolu R, Gonzalez N, Wu S, Muhleman D, Blake H, et al. A multivariate analysis of 59 candidate genes in personality traits: the temperament and character inventory. Clin Genet 2000;58:375–85.
Conner BT, Hellemann GS, Ritchie TL, Noble EP. Genetic, personality, and environmental predictors of drug use in adolescents. J Subst Abuse Treat 2010;38(2):178–90.
Connor JP, Young RM, Saunders JB, Lawford BR, Ho R, Ritchie TL, et al. The A1 allele of the D2 dopamine receptor gene region, alcohol expectancies and drinking refusal self-efficacy are associated with alcohol dependence severity. Psychiatry Res 2008;160(1):94–105.
Costa Jr PT, Herbst JH, McCrae RR, Siegler IC. Personality at midlife: stability, intrinsic maturation, and response to life events. Assessment 2000;7:365–78.
Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Lääne K, et al. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 2007;315(5816):1267–70.
Di Chiara G, Bassareo V, Fenu S, De Luca MA, Spina L, Cadoni C, et al. Dopamine and drug addiction: the nucleus accumbens shell connection. Neuropharmacology 2004;47(Suppl 1):227–41.
Drtilkova I, Sery O, Theiner P, Uhrova A, Zackova M, Balastikova B, et al. Clinical and molecular-genetic markers of ADHD in children. Neuro Endocrinol Lett 2008;29(3): 320–7.
Eisenberg DT, Campbell B, Mackillop J, Lum JK, Wilson DS. Season of birth and dopamine receptor gene associations with impulsivity, sensation seeking and reproductive behaviors. PLoS ONE 2007;2(11):e1216.
Epperson CN. Postpartum major depression: detection and treatment. Am Fam Physician 1999;59(8):2247–54 2259–2260.
Feng Y, Wigg KG, Makkar R, Ickowicz A, Pathare T, Tannock R, et al. Sequence variation in the 3′-untranslated region of the dopamine transporter gene and attention-deficit hyperactivity disorder (ADHD). Am J Med Genet B Neuropsychiatr Genet 2005;139(1):1–6.
Forger NG. The organizational hypothesis and final common pathways: sexual differentiation of the spinal cord and peripheral nervous system. Horm Behav 2009;55(5):605–10.
Fuke S, Suo S, Takahashi N, Koike H, Sasagawa N, Ishiura S. The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. Pharmacogenomics J 2001;1(2):152–6.
Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, et al. The structure of haplotype blocks in the human genome. Science 2002;296(5576):2225–9.
Galili-Weisstub E, Levy S, Frisch A, Gross-Tsur V, Michaelovsky E, Kosov A, et al. Dopamine transporter haplotype and attention-deficit hyperactivity disorder. Mol Psychiatry 2005;10(7):617–8.
Giros B, Caron MG. Molecular characterization of the dopamine transporter. Trends Pharmacol Sci 1993;14(2):43–9.
Grandy DK, Litt M, Allen L, Bunzow JR, Marchionni M, Makam H, et al. The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a TaqI RFLP. Am J Hum Genet 1989;45(5):778–85.
Greenwood TA, Schork NJ, Eskin E, Kelsoe JR. Identification of additional variants within the human dopamine transporter gene provides further evidence for an association with bipolar disorder in two independent samples. Mol Psychiatry 2006;11(2):125–33.
Grucza RA, Goldberg LR. The comparative validity of 11 modern personality inventories: predictions of behavioral acts, informant reports, and clinical indicators. J Pers Assess 2007;89:167–87.
Hayden EP, Klein DN, Dougherty LR, Olino TM, Laptook RS, Dyson MW, et al. The dopamine D2 receptor gene and depressive and anxious symptoms in childhood: associations and evidence for gene–environment correlation and gene–environment interaction. Psychiatr. Genet. 2010;20(6):304–10.
Hamajima N, Ito H, Matsuo K, Saito T, Tajima K, Ando M, et al. Association between smoking habits and dopamine receptor D2 taqI A A2 allele in Japanese males: a confirmatory study. J Epidemiol 2002;12(4):297–304.
Hietala J, Pohjalainen T, Heikkilä-Kallio U, West C, Salaspuro M, Syvälahti E. Allelic association between D2 but not D1 dopamine receptor gene and alcoholism in Finland. Psychiatr Genet 1997;7(1):19–25.
Hirvonen MM, Lumme V, Hirvonen J, Pesonen U, Någren K, Vahlberg T, et al. C957T polymorphism of the human dopamine D2 receptor gene predicts extrastriatal dopamine receptor availability in vivo. Prog Neuropsychopharmacol Biol Psychiatry 2009;33(4):630–6.
Hoenicka J, Quiñones-Lombraña A, España-Serrano L, Alvira-Botero X, Kremer L, Pérez-González R, et al. The ANKK1 gene associated with addictions is expressed in astroglial cells and upregulated by apomorphine. Biol Psychiatry 2010;67(1):3–11.
Hou QF, Li SB. Potential association of DRD2 and DAT1 genetic variation with heroin dependence. Neurosci Lett 2009;464(2):127–30.
Hirvonen J, van Erp TG, Huttunen J, Någren K, Huttunen M, Aalto S, et al. Striatal dopamine D1 and D2 receptor balance in twins at increased genetic risk for schizophrenia. Psychiatry Res 2006;146(1):13–20.
Huang SY, Lin WW, Wan FJ, ang AJ, Ko HC, Wang TJ, et al. Monoamine oxidase-A polymorphisms might modify the association between the dopamine D2 receptor gene and alcohol dependence. J Psychiatry Neurosci 2007;32(3):185–92.
Hull EM, Lorrain DS, Du J, Matuszewich L, Lumley LA, Putnam SK, et al. Hormone–neurotransmitter interactions in the control of sexual behavior. Behav Brain Res 1999;105(1):105–16.
Hutchison KE, Stallings M, McGeary J, Bryan A. Population stratification in the candidate gene study: fatal threat or red herring? Psychol Bull 2004;130(1):66–79.
Ishiguro H, Arinami T, Saito T, Akazawa S, Enomoto M, Mitushio H, et al. Association study between the -141C Ins/Del and TaqI A polymorphisms of the dopamine D2 receptor gene and alcoholism. Alcohol Clin Exp Res 1998;22(4):845–8.
Joe KH, Kim DJ, Park BL, Yoon S, Lee HK, Kim TS, et al. Genetic association of DRD2 polymorphisms with anxiety scores among alcohol-dependent patients. Biochem Biophys Res Commun 2008;371(4):591–5.
Jönsson EG, Nöthen MM, Grünhage F, Farde L, Nakashima Y, Propping P, et al. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol Psychiatry 1999;4(3):290–6.
Kaasinen V, Nagren K, Hietala J, Farde L, Rinne JO. Sex differences in extrastriatal dopamine d(2)-like receptors in the human brain. Am J Psychiatry 2001;158(2):308–11.
Khusnutdinova E, Bermisheva M, Kutuev I, Yunusbayev B, Villems R. Genetic landscape of the central Asia and Volga–Ural region. In: Dobretsov N, Kolchanov N, Rozanov A, editors. Biosphere origin and evolution. New York: Springer; 2007. p. 373–82.
Köhnke MD, Batra A, Kolb W, Köhnke AM, Lutz U, Schick S, et al. Association of the dopamine transporter gene with alcoholism. Alcohol Alcohol 2005;40(5):339–42.
Laakso A, Vilkman H, Kajander J, Bergman J, Paranta M, Solin O, et al. Prediction of detached personality in healthy subjects by low dopamine transporter binding. Am J Psychiatry 2000;157(2):290–2.
Laurin N, Feng Y, Ickowicz A, Pathare T, Malone M, Tannock R, et al. No preferential transmission of paternal alleles at risk genes in attention-deficit hyperactivity disorder. Mol Psychiatry 2007;12(3):226–9.
Lee HS, Kim SH, Lee HJ, Kim L, Lee SK, Jang DW, et al. Gender-specific molecular heterosis of dopamine D2 receptor gene (DRD2) for smoking in schizophrenia. Am J Med Genet 2002;114(6):593–7.
Lee HJ, Lee HS, Kim YK, Kim L, Lee MS, Jung IK, et al. D2 and D4 dopamine receptor gene polymorphisms and personality traits in a young Korean population. Am J Med Genet B Neuropsychiatr Genet 2003;121(1):44–9.
Lee SH, Ham BJ, Cho YH, Lee SM, Shim SH. Association study of dopamine receptor D2 TaqI A polymorphism and reward-related personality traits in healthy Korean young females. Neuropsychobiology 2007;56(2–3):146–51.
Lin SC, Wu PL, Ko HC, Wu JY, Huang SY, Lin WW, et al. Specific personality traits and dopamine, serotonin genes in anxiety–depressive alcoholism among Han Chinese in Taiwan. Prog Neuropsychopharmacol Biol Psychiatry 2007;31(7):1526–34.
Ling D, Niu T, Feng Y, Xing H, Xu X. Association between polymorphism of the dopamine transporter gene and early smoking onset: an interaction risk on nicotine dependence. J Hum Genet 2004;49(1):35–9.
Manchia M, Viggiano E, Tiwari AK, Renou J, Jain U, De Luca V, et al. Smoking in adult attention deficit/hyperactivity disorder: interaction between 15q13 nicotinic genes and Temperament Character Inventory scores. World J Biol Psychiatry 2010;11(2 Pt 2):506–10.
Mazei MS, Pluto CP, Kirkbride B, Pehek EA. Effects of catecholamine uptake blockers in the caudate–putamen and subregions of the medial prefrontal cortex of the rat. Brain Res 2002;936(1–2):58–67.
Mignone F, Gissi C, Liuni S, Pesole G. Untranslated regions of mRNAs. Genome Biol 2002;3(3) reviewS0004.
Miller GM, Madras BK. Polymorphisms in the 3′-untranslated region of human and monkey dopamine transporter genes affect reporter gene expression. Mol Psychiatry 2002;7(1):44–55.
Monakhov M, Golimbet V, Abramova L, Kaleda V, Karpov V. Association study of three polymorphisms in the dopamine D2 receptor gene and schizophrenia in the Russian population. Schizophr Res 2008;100(1–3):302–7.
Müller SE, Weijers HG, Böning J, Wiesbeck GA. Personality traits predict treatment outcome in alcohol-dependent patients. Neuropsychobiology 2008;57(4):159–64.
Munafò MR, Matheson IJ, Flint J. Association of the DRD2 gene Taq1A polymorphism and alcoholism: a meta-analysis of case–control studies and evidence of publication bias. Mol Psychiatry 2007;12(5):454–61.
Munafò MR, Johnstone EC, Murphy MF, Aveyard P. Lack of association of DRD2 rs1800497 (Taq1A) polymorphism with smoking cessation in a nicotine replacement therapy randomized trial. Nicotine Tob Res 2009;11(4):404–7.
Munro CA, McCaul ME, Wong DF, Oswald LM, Zhou Y, Brasic J, et al. Sex differences in striatal dopamine release in healthy adults. Biol Psychiatry 2006;59(10): 966–74.
Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Hum Mutat 2004;23(6):540–5.
Nisoli E, Brunani A, Borgomainerio E, Tonello C, Dioni L, Briscini L, et al. D2 dopamine receptor (DRD2) gene Taq1A polymorphism and the eating-related psychological traits in eating disorders (anorexia nervosa and bulimia) and obesity. Eat Weight Disord 2007;12(2):91–6.
Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. Arch Gen Psychiatry 1991;48(7):648–54.
Noble EP, Ozkaragoz TZ, Ritchie TL, Zhang X, Belin TR, Sparkes RS. D2 and D4 dopamine receptor polymorphisms and personality. Am J Med Genet 1998;81(3):257–67.
Noble EP. D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. Am J Med Genet B Neuropsychiatr Genet 2003;116(1):103–25.
Peroutka SJ, Price SC, Wilhoit TL, Jones KW. Comorbid migraine with aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NcoI alleles. Mol Med 1998;4(1):14–21.
Pohjalainen T, Rinne JO, Nagren K, Lehikoinen P, Anttila K, Syvälahti EK, et al. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. Mol Psychiatry 1998a;3(3):256–60.
Pohjalainen T, Rinne JO, Någren K, Syvälahti E, Hietala J. Sex differences in the striatal dopamine D2 receptor binding characteristics in vivo. Am J Psychiatry 1998b;155(6): 768–73.

Ponce G, Jimenez-Arriero MA, Rubio G, Hoenicka J, Ampuero I, Ramos JA, et al. The A1 allele of the DRD2 gene (TaqI A polymorphisms) is associated with antisocial personality in a sample of alcohol-dependent patients. Eur Psychiatry 2003;18(7):356–60.
Pooley EC, Fineberg N, Harrison PJ. The met(158) allele of catechol-O-methyltransferase (COMT) is associated with obsessive–compulsive disorder in men: case–control study and meta-analysis. Mol Psychiatry 2007;12(6):556–61.
Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81(3):559–75.
Raygorodskiy DY. Practical psychodiagnostics. Principles and tests. Samara: Bahrah-M; 2003 [372 p].
Ritchie T, Noble EP. Association of seven polymorphisms of the D2 dopamine receptor gene with brain receptor-binding characteristics. Neurochem Res 2003;28(1):73–82.
Rowe DC, Van den Oord EJ, Stever C, Giedinghagen LN, Gard JM, Cleveland HH, et al. The DRD2 TaqI polymorphism and symptoms of attention deficit hyperactivity disorder. Mol Psychiatry 1999;4(6):580–6.
Samochowiec J, Rybakowski F, Czerski P, Zakrzewska M, Stepień G, Pełka-Wysiecka J, et al. Polymorphisms in the dopamine, serotonin, and norepinephrine transporter genes and their relationship to temperamental dimensions measured by the Temperament and Character Inventory in healthy volunteers. Neuropsychobiology 2001;43(4):248–53.
Samochowiec J, Kucharska-Mazur J, Grzywacz A, Jabłoński M, Rommelspacher H, Samochowiec A, et al. Family-based and case–control study of DRD2, DAT, 5HTT, COMT genes polymorphisms in alcohol dependence. Neurosci Lett 2006;410(1):1–5.
Sarkar G, Kapelner S, Grandy DK, Marchionni M, Civelli O, Sobell J, et al. Direct sequencing of the dopamine D2 receptor (DRD2) in schizophrenics reveals three polymorphisms but no structural change in the receptor. Genomics 1991;11(1):8–14.
Sawada H, Shimohama S. Neuroprotective effects of estradiol in mesencephalic dopaminergic neurons. Neurosci Biobehav Rev 2000;24(1):143–7.
Serý O, Drtílková I, Theiner P, Pitelová R, Staif R, Znojil V, et al. Polymorphism of DRD2 gene and ADHD. Neuro Endocrinol Lett 2006;27(1–2):236–40.
Smillie LD, Cooper AJ, Proitsi P, Powell JF, Pickering AD. Variation in DRD2 dopamine gene predicts Extraverted personality. Neurosci Lett 2010;468(3):234–7.
Strous RD, Nolan KA, Lapidus R, Diaz L, Saito T, Lachman HM. Aggressive behavior in schizophrenia is associated with the low enzyme activity COMT polymorphism: a replication study. Am J Med Genet B Neuropsychiatr Genet 2003;120B(1):29–34.
Thompson J, Thomas N, Singleton A, Piggott M, Lloyd S, Perry EK, et al. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. Pharmacogenetics 1997;7(6):479–84.
Ueno S, Nakamura M, Mikami M, Kondoh K, Ishiguro H, Arinami T, et al. Identification of a novel polymorphism of the human dopamine transporter (DAT1) gene and the significant association with alcoholism. Mol Psychiatry 1999;4(6):552–7.
Uher R, Huezo-Diaz P, Perroud N, Smith R, Rietschel M, Mors O, et al. Genetic predictors of response to antidepressants in the GENDEP project. Pharmacogenomics J 2009;9(4):225–33.
Vandenbergh DJ, Persico AM, Hawkins AL, Griffin CA, Li X, Jabs EW, et al. Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. Genomics 1992;14:1104–6.
VanNess SH, Owens MJ, Kilts CD. The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density. BMC Genet 2005;6:55.
van Dyck CH, Malison RT, Jacobsen LK, Seibyl JP, Staley JK, Laruelle M, et al. Increased dopamine transporter availability associated with the 9-repeat allele of the SLC6A3 gene. J Nucl Med 2005;46(5):745–51.
van Strien T, Snoek HM, van der Zwaluw CS, Engels RC. Parental control and the dopamine D2 receptor gene (DRD2) interaction on emotional eating in adolescence. Appetite 2010;54(2):255–61.
Wacker J, Reuter M, Hennig J, Stemmler G. Sexually dimorphic link between dopamine D2 receptor gene and neuroticism–anxiety. NeuroReport 2005;16(6):611–4.
Yoo HJ, Kim M, Ha JH, Chung A, Sim ME, Kim SJ, et al. Biogenetic temperament and character and attention deficit hyperactivity disorder in Korean children. Psychopathology 2006;39(1):25–31.
Zhang Y, Bertolino A, Fazio L, Blasi G, Rampino A, Romano R, et al. Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. Proc Natl Acad Sci USA 2007;104(51):20552–7.
Zhu J, Bardo MT, Bruntz RC, Stairs DJ, Dwoskin LP. Individual differences in response to novelty predict prefrontal cortex dopamine transporter function and cell surface expression. Eur J Neurosci 2007;26(3):717–28.
Zuo Y, Gilbert DG, Rabinovich NE, Riise H, Needham R, Huggenvik JI. DRD2-related TaqIA polymorphism modulates motivation to smoke. Nicotine Tob Res 2009;11(11):1321–9.