Dopamine-related receptors, substance dependence, behavioral problems and personality among juvenile delinquents

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1. Introduction

Although it is well established that genetic factors influence human psychiatric disorders and personality traits, the degree of this influence often remains unclear (Hess et al., 2009; Reuter, Kupper, & Hennig, 2007). It is therefore important to identify possible genetic *risk* factors within this research area. However, the identification of such genetic risk factors is complicated due to the multifaceted mode of inheritance, gene-environment influences, clinical and genetic heterogeneity, and genetic pleiotropy, each contributing a limited effect on the overall risk (for a review, see Oreland et al, 2018; Lohoff et al., 2008). With regard to drug dependence, it has been estimated that for certain forms of addiction in men (heavy use, abuse, and dependence), genetic factors could explain up to 60 - 80 % of the variance and heritability estimates are high (Kendler, Karkowski, Neale, & Prescott, 2000; Uhl et al., 2008), with gene-dependent dopamine regulation being one of the most important contributing factors (Vereczkei et al, 2013; Kienast, & Heintz, 2006).

Dopamine is an important neurotransmitter involved in many neuropsychological functions, such as motivation, pleasure, cognition, memory, learning, and fine motor control. In addition, dopamine is involved in the modulation of neuroendocrine signaling (Iversen & Iversen, 2007). It has been suggested that dysfunctional dopamine regulation can result in a number of adverse effects, including psychiatric, behavioral, and personality disturbances (Grigorenko et al., 2010; Thompson et al., 2011).

There are at least five subtypes of dopamine receptors, where the D1-like family (D_1 and D_5) mediates a reduction in the drive to seek reinforcement, whereas the D2-like family (D_2, D_3, and D_4) mediates both reward and reinforcement (for a review, see Beaulieu & Gainetdinov, 2011). The regulation of dopamine levels is critically dependent on several mechanisms, including the presynaptic dopamine active transporter (*DAT*), which terminates dopamine signaling at the synapse through reuptake of released dopamine in the synaptic cleft (Salatino-Oliveira, Rodhe, & Hutz, 2018) and the enzyme Catechol-*O*-methyl transferase (*COMT*), which is involved in the degradation of catecholamines, including dopamine (Finberg, 2019).

Various studies have attempted to link development and reinforcement of substance dependence to genetic variation in both specific dopamine receptors, such as *DRD1*, *DRD2*, *DRD3* and *DRD4* (Jacobs et al., 2013; Sullivan et al., 2013; Mallard, Doorley, Esposito-Smythers, & McGeary, 2016; Chmielowiec et al., 2018; Sznabowicz et al., 2018; Wang et al., 2016), and other genes involved in the dopamine turnover, most notably *DAT* (Sullivan et al., 2013; Chmielowiec et al., 2018) and *COMT* (Lohoff et al., 2008; Vereczkei et al., 2013). In particular, the addictive effects of drugs have been linked to a substantial increase in extracellular dopamine and subsequent stimulation of neurons in brain regions regulating reward and reinforcement, both through inhibition of *DAT* (Pinsonneault et al., 2011) and regulation of the speed of dopamine degradation (Goldman, Oroszi, & Ducci, 2005).

Thus, previous research has suggested that the regulation of dopamine signaling is implicated in the development of substance dependence, and that specific functional dopaminergic gene variants may impact symptom severity of substance dependence. There are however inconsistencies in the literature (Nemoda, Szekely, & Sasvari-Szekely, 2011; Oreland et al., 2018), and one explanation for this might be that in the majority of studies, genes were investigated with regard to a single polymorphism. In the present study each gene was sampled multiple times taking both multiple markers and haplotypes (i. e., combination of markers within one gene) into consideration. More specifically, the purpose of the present study was to investigate the associations between genetic polymorphism in the *COMT*, *DAT*, and *DRD4* and 1) substance dependence, and 2) different types of self-reported psychiatric disturbances, behavioral problems, and personality traits.

2. Methods

2.1 Study sample

The participants, 174 male juvenile delinquents (14-18 years of age; mean age 16.2), form part of a larger study that assessed psychopathology in incarcerated juvenile delinquents who had been court-ordered to the only juvenile detention facility in the Arkhangelsk region of Northern Russia, a catchment area with a population of 1.5 million (for further information, see Ruchkin, Schwab-Stone, Vermeiren, Koposov, & King, 2003). The region is ethnically homogeneous, with approximately 98% of the population of Russian ancestry,

which reduces the risk of genomic population stratification. Most participants had multiple convictions (about 70 %), with imprisonment at the time of the study predominantly for theft, but also violent crime, rape or other forms of sexual violence, and murder. The mean length of sentence was 4.3 years. At the time of the data collection, all participants had been incarcerated for at least 6 months.

2.2 Measures and assessments

2.2.1 Assessment of psychiatric disorder

A semi-structured interview inventory, the Schedule for Affective Disorders and Schizophrenia, K-SADS-PL (Kaufman et al., 1997), a widely used inventory of psychopathology, was applied for diagnostic purposes in establishing substance dependence among the male adolescent delinquents.

2.2.2 Assessment of self-reported psychiatric disturbances and behavioral problems

The Child Posttraumatic Stress Reaction Index, CPTS-RI (Pynoos, Frederick, & Nader, 1987), was used to assess post-traumatic stress symptoms; the Beck Depression Inventory, BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), to address current symptoms of depression; and the Youth Self-Report, YSR (Achenbach, 1991), a standardized instrument to measure children's competencies and problem behaviors, including externalizing and internalizing symptoms. Psychometric qualities for the self-reports, as assessed by the internal consistency coefficients, were comparable to those reported in the original studies.

2.2.3 Assessment of self-reported personality

Personality traits were assessed by means of the Temperament and Character Inventory (TCI, Cloninger, 1994; Cloninger, Svrakic, & Przybeck, 1993), based on Cloninger's unified biosocial theory of personality (Cloninger, 1987). TCI measure four independent, largely genetically determined temperament dimensions, as well as three character dimensions predominantly determined by socialization processes during the life span as related to different concepts of the self (Cloninger, Przybeck, Svrakic, & Wetzel, 1994). TCI is a widely used instrument and comparisons with other well-known personality dimensions are reported (Zuckerman & Cloninger, 1996). In the present study, the short version of the TCI was applied with 125 items to be answered as true or false. Four scales for temperament: novelty seeking (NS), harm avoidance (HA), reward dependence

(RD), and persistence (P); and three scales of character: self-directedness (SD), cooperativeness (C), and self-transcendence (ST) are included. Cronbach alphas in our study was for NS .61, for HA .67, for RD .59, for SD .68, for C .64, and for ST .75. Due to low level of Cronbach alpha for P, it was not included in the present analysis.

2.3 Procedure

All participants were evaluated for the presence of psychiatric disorders by two trained child and adolescent psychiatrists, using a semi-structured clinical interview, K-SADS-PL. Inventories for self-reported psychiatric disturbances, behavioral problems and personality were administered individually by trained research staff members prior to the donation of biospecimens. All staff members who administered the self-report inventories were blind to the genetic data. For the purpose of genetic analyses, a venous blood sample was obtained. No particular inclusion/exclusion criteria were applied when recruiting the biochemical sample. Two nurses obtained blood samples from the participants. DNA was extracted from samples collected via 5mL vacutainer tubes containing ethylenediaminetetraacetic acid (Oreland). An aliquot of DNA was sent to another laboratory (Grigorenko), where it was subsequently amplified with Repli-G or Genomiphi technologies. Since amplified DNA was genotyped in all cases, the quality of the DNA was homogeneous across the sample and there were no group/collection method based biases. Once a sufficient amount of DNA was available from each sample, all markers were genotyped using the ABI TaqMan platform (Grigorenko). All DNA samples were genotyped by the same machinery, using the same procedures and the same internal controls.

2.4 Statistical analyses

All statistical analyses were performed with SPSS-22. The Pearson chi-square test and an extended version of Fisher's exact test for a $m^x n$ table was used, applying a network algorithm by Metha and Patel (1983) when the expected value of any of the cells was < 5, to evaluate possible differences in selected dopamine polymorphisms between substance dependence groups. Further, a test of proportion observed frequencies for testing differences between genotypes pairwise within significant polymorphisms was performed. If expected value of a cell <5, we used Fishers exact test. In order to predict substance dependence with significant

polymorphisms, exact binary logistic regression analysis was applied. The results are shown as odds ratio (OR) with 95 % confidence interval (CI). Finally, one-way analysis of variance (ANOVA) and Scheffé post-hoc tests were used to compare DRD4 C_1611535 polymorphism genotypes on self-reported psychiatric disturbances, behavioral problems, and personality scale scores.

3. Results

3.1 Dopamine-related polymorphisms and their associations with substance dependence

Of those 174 participants who provided their venous blood sample, 40 (23 %) adolescents received a diagnosis of substance dependence. As shown in Table 1, results of Chi-square and Fisher exact tests in a 2 x 3 table indicated that delinquents with substance dependence differed significantly from the other delinquents in terms of observed and expected frequency, as well as relative percent observed units, concerning four different polymorphisms, namely *COMT* rs737865, *DAT* rs6347, *DRD4* C_1611535, and *DRD4* exon III in that more subjects with substance dependence than could be expected by chance were obtained for the *COMT* rs737865 GG, *DAT* rs6347 TT, *DRD4* C_1611535 GG and the *DRD4* exon III 2 genotypes, respectively. Test of proportions between groups for those genotypes row wise were all significant ($p< 0.05$), especially the *DRD4* C_1611535 GG differed highly significantly, indicating higher relative proportion among individuals with substance dependence ($p< 0.0001$, Fisher's exact test). The four significant polymorphisms were then recoded into dummy variables, so that 3 allele combinations (variants) of each polymorphism were recoded into 2 dummy variables (one of the 3 genotypes vs others, e.g. AA vs others and GG vs others, see Table 2). These dummy variables were used in the exact binary logistic regression analysis as predictors for substance dependence. Results are presented in Table 2. All these polymorphisms, except for *DRD4* exon III, were associated with significantly increased risk to meet criteria for substance dependence. For example, (as shown in Table 2), results indicated a more than four times higher odds to develop substance dependence for subjects with the *COMT* rs737865 GG genotype (OR = 4.28), than for subjects with the other variants (AA + AG). Moreover, for those with the *DAT* rs6347 TT genotype, there was almost three times higher odds (OR = 2.66), than for subjects with other variants (CC + CT). In addition, for subjects with the *DRD4* C_1611535 GG

genotype, there was markedly higher odds (OR = 10.55) to meet criteria for substance dependence than for those with other variants (AA + AG). Among those with the *DRD4* exon III variant 2 (presence of two 7 repeats) vs other variants (0 + 1) there was a tendency to be more likely (OR = 10.59, $p < 0.08$) to meet diagnostic criteria for substance dependence, however the width of the confidence interval was large.

Insert Tables 1-2 about here

3.2 Dopamine-related polymorphisms and their associations with self-reported psychiatric disturbances, behavioral problems and personality

Results of the one-way ANOVA analysis with Scheffé post-hoc test comparing the self-reported psychiatric disturbances and behavioral problems (CPTS-RI, BDI, YSR), as well as personality (TCI) scale scores between *DRD4* C_1611535 genotypes (AA, AG, and GG) are presented in Table 3 and 4, respectively. The results hence showed that the GG genotype of *DRD4* C_1611535 carriers were significantly higher on CPTS-RI scores, indicating more severe posttraumatic stress symptoms, than those with the AG genotype. They also differed significantly from both other genotypes (AA and AG) in terms of higher scores on the YSR scale Thought problems, and from the AA genotype on Aggressive behavior, demonstrating some cognitive disturbances and aspects of externalizing behavior problems (see Table 3). As presented in Table 4, the *DRD4* C_1611535 polymorphisms further differed concerning the TCI scale RD, the GG variant carriers displaying lower scores than those with the AG variant, indicating characteristics of being less socially attached and less dependent on others approval. Finally, the same gene variant was significantly associated with lower scores on SD than both other variants (AA and AG). An individual with low scores on SD is assumed to be irresponsible, aimless, and undisciplined with poor impulse control. There were no differences between *DRD4* C_1611535 polymorphisms on the other TCI scales.

Insert Tables 3-4 about here

4. Discussion

The present study aimed at exploring dopamine-related genetic polymorphisms and their associations with clinically assessed substance dependence, as well as different self-reported psychiatric disturbances, behavioral problems, and personality.

4.1 Influences of dopamine-related polymorphisms on substance dependence

A number of previous studies have implicated gene-regulated mechanisms of dopamine neurotransmission in reinforcement of drug use in individuals with substance dependence, including dopamine receptors (Grigorenko et al., 2010; Nemoda et al., 2011; Comings et al., 1999), dopamine transporter (*DAT*; Blum et al., 2012; Vereczkei et al., 2013; Chmielowiec et al., 2018), and enzymes systems (*COMT*; Levran et al., 2009; Vereczkei et al., 2013). Some studies have demonstrated that the *DAT* polymorphisms may represent an important genetic factor in the vulnerability to substance dependence (e.g. Dreher, Kohn, Kolachana, Weinberger, & Berman, 2008), thus our finding of a significantly heightened risk for substance dependence in subjects with the *DAT* rs6347 TT genotype supports those findings. However, the lack of significant associations for the other *DAT* polymorphisms examined in the present study (*DAT* rs40184 and *DAT* rs2652511) may have been related to the fact that the previous studies focused on specific types of addiction, such as cocaine or opioid dependence, whereas we have assessed a broader group of delinquent individuals with substance dependence.

The *COMT* polymorphisms have been shown to play a role in the reinforcement mechanism of addiction (Goldman et al., 2005; Haile, Kosten, & Kosten, 2008; see also Tammimäki & Männistö, 2010), and have been linked to psychiatric disorders, such as schizophrenia and bipolar disorder, as well as with aggressive behaviors (Craddock, Owen, & O'Donovan, 2006; Tunbridge, Harrison, & Weinberger, 2006; Nemoda et al., 2011), thus contributing further to comorbid addiction problems. Our study supports the previous findings regarding the potential influence of the *COMT* variation on severity of addiction problems and suggests that the *COMT* rs737865 polymorphism, especially the GG genotype, may be associated with increased risk of developing substance dependence.

Of the five types of dopamine receptors, the *DRD2* and *DRD4* polymorphisms have been most consistently linked to substance abuse. With regard to *DRD4* exon III, carriers of the *DRD4* long allele (≥ 7 repeats) have shown to indicate an increased susceptibility to alcohol dependence (Daurio, Deschaine, Modabberina, & Leggio, 2019; Park, Sher, Todorov, & Heath, 2011; van der Zwaluw, Larsen, & Engels, 2012), opioid dependence (Chen et al., 2011), and nicotine dependence (Ellis et al., 2011). Moreover, it has been suggested that the D4 receptor gene may be linked to the severity of dependence (Lusher, Ebersole, & Ball, 2000). Our results of significantly higher frequencies and observed proportion among individuals with substance dependence highlight a role of *DRD4* polymorphisms, notably the C_1611535 GG genotype, in substance dependence, which, to the best of our knowledge, has not been reported previously.

4.2 Influences of dopamine-related polymorphisms on self-reported psychiatric disturbances, behavioral problems and personality

With regard to vulnerability for developing substance dependence, genetic variation of the function of the dopamine system has previously been linked not only to specific disorders, but also to behavior and personality (Mallard et al., 2016; Hess et al., 2009). Indeed, genetic variation in the dopamine D4 receptor consisting of singular nuclear polymorphisms (SNP: s), as well as the number of repeats in exon III, have been linked to externalizing behavior (Hohmann et al., 2009; McGeary, 2009), including novelty seeking, impulsive personality traits, and aggressive and delinquent behavior (see Dmitrieva, Chen, Greenberger, Ogunseitan, & Ding, 2011). An association between the long repeat allele of the dopamine D4-exon-III receptor polymorphism and NS, and RD respectively, has been reported (Ebstein, & Belmaker, 1997; Ebstein et al., 1997). It has been further concluded that there may be an association between *DRD4* and NS amongst severe substance dependent populations and that especially *DRD4* polymorphisms may predispose substance abusers to a severe dependency (Lukasiewicz et al., 2008; Lusher, Chandler, & Ball, 2001). In contrast, among the present groups of juvenile delinquents, there was no difference on NS between the *DRD4* C_1611535 GG and the other genotypes recoded together. This lack of difference between the groups are in line with results reported that NS is generally high in criminal groups (Cloninger, 1994), or that NS is not related to *DRD4*, in accordance with findings from a large study on adolescents by Nederhof and collaborators (2011).

The present results, indicating that the *DRD4* polymorphism C_1611535 GG genotype is associated with low levels of RD and SD, as well as with high levels of self-reported posttraumatic stress, thought problems, and aggressive behavior, to some extent support the findings mentioned above and results on trauma experiences among incarcerated adolescents (Kimonis, Tatar II, & Cauffman, 2012). Individuals scoring low on RD are assumed to be tough-minded, cynical, and insensitive to social pressures, and thus low scores have been associated with risk for early onset of conduct problems (Cloninger et al., 1994), drug addiction (Milivojevic et al., 2012; Zoccali et al., 2007), aggressive antisocial behavior, and coldness in social interactions (Cloninger et al., 1993), all being characteristics of psychopathy (Hare, 2003). It is noteworthy, that not only the GG *DRD4* genotype of C_1611535 was associated with low RD, but also with low scores on SD, assumed to constitute a major common feature of antisocial personality disorders (Cloninger et al., 1994). The combination obtained of low RD and low SD suggests a tendency to antisocial personality disturbances, which in turn is repeatedly found to be associated with substance abuse and dependence in both delinquent and non-delinquent groups (Bahlmann, Preuss, & Soyka, 2002; Eklund & af Klinteberg, 2009; Larsson et al., 2007; Dick & Agrawal, 2008; Neumann & Hare, 2008; Hammerton et al., 2017).

4.3 Concluding remarks

The present study is characterized by a number of strengths, such as literature-grounded hypothesis, a multi-polymorphism/haplotype-based approach to genetic variability in a single gene and ethnic and behavioral homogeneity of the sample. According to their self-reports, the participants present a limited variability in their ethnic origins, by being predominantly of Slavic ancestry and having roots in Northern Russia. However, especially given the relatively small size of the sample used, the exploratory character of the study should be emphasized. Further studies are needed to increase the precision of the degree of involvement of dopaminergic mechanisms in substance dependence, as well as their associations with addiction-related phenotypes.

Conflict of Interest

The authors have declared that no competing interests exist.

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Table(s)

Table 1 Comparison of differences, observed (O)/ expected (E) and relative frequencies (% O) percentage observed in selected dopamine polymorphisms between substance dependence groups (yes/no). Chi-square tests (χ^2 and significance level < 0.05), Fisher exact test (exact p for small cells < 5).

Polymorphisms	Genotypes /variants	Substance dependence Yes (n=40) O/E (% O)	No (n= 134) O/E (% O)	χ^2	p <	exact p
COMT rs737865	AA	20/23.4 (51.3)	78/74.6 (62.9)	**6.33**	**.05**	
	AG	13/12.9 (33.3)	41/41.1 (33.1)			
	GG	**6/2.6 (15.4)**	**5/8.4 (4.0) ***			
COMT rs740603	AA	11/12.9 (27.5)	45/43.1 (33.6)	.72	ns	
	AG	21/20.5 (52.5)	68/68.5 (50.7)			
	GG	8/6.7 (20.0)	21/22.3 (15.7)			
COMT rs165599	AA	15/17.1 (37.5)	59/56.9 (44.4)	2.56	ns	
	AG	17/17.8 (42.5)	60/59.2 (45.1)			
	GG	8/5.1 (20.0)	14/16.9 (10.5)			
DAT rs40184	CC	9/10.5 (22.5)	36/34.5 (27.3)	2.05	ns	
	CT	25/21.2 (62.5)	66/69.8 (50.0)			
	TT	6/8.4 (15.0)	30/27.6 (22.7)			
DAT rs6347	CC	1/3.9 (2.6)	16/13.1 (12.4)	**6.82**	**.05**	**0.035**
	CT	9/12.7 (23.7)	47/43.3 (36.4)			
	TT	**28/21.4 (73.7)**	**66/72.6 (51.2)***			
DAT rs2652511	AA	4/7.8 (10.3)	29/25.2 (23.0)	3.42	ns	
	AG	20/ 19.1(51.3)	61/61.9 (48.4)			
	GG	15/12.1 (38.5)	36/38.9 (28.6)			
DRD4 C_1611535	AA	18/23.0 (45.0)	81/76.0 (61.4)	**16.53**	**.001**	**0.001**
	AG	14/14.4 (35.0)	48/47.6 (36.4)			
	GG	**8/2.6 (20.0)**	**3/8.4 (2.3)***			

DRD4 rs93661	AA	8/7.9 (20.0)	26/26.1 (19.7)	.20	ns	
	AG	15/14.0 (37.5)	45/46.0 (34.1)			
	GG	17/ 18.1(42.5)	61/59.9 (46.2)			
DRD4 exon III	0	21/26.4 (52.5)	94/88.6 (70.2)	**8.72**	**.05**	**0.016**
	1	16/12.6 (40.0)	39/42.4 (29.1)			
	2	**3/0.9 (7.5)**	**1/3.1 (0.7)***			
DRD4 rs11246226	AA	9/12.7 (23.1)	44/40.3 (35.5)	3.98	ns	
	AC	17/17.5 (43.6)	56/55.5 (45.2)			
	CC	13/8.9 (33.3)	24/28.1 (19.4)			

Note. *DRD4* exon III: 0= No ≥7 repeat; 1= presence of one ≥7 repeat; 2= presence of two ≥7 repeats.

* Test of proportion between genotypes row wise within significant polymorphism, $p < 0.05$. If any cell had an expected value <5, Fisher's exact was used for the row wise test.

Table 2 Exact binary logistic regression analysis predicting substance dependence with significant genetic polymorphisms. Odds ratio (OR) with 95% confidence interval (CI). OR=1 means Reference group

Polymorphisms	Genotypes	OR	95% CI
COMT rs737865	AA vs others	0.60	0.28-1.37
	(AG+GG)	1	Reference
	GG vs others	**4.28**	**1.02-18.90**
	(AA+AG)	**1**	Reference
DAT rs6347	CC vs others	0.19	0.004-1.32
	(CT+TT)	1	Reference
	TT vs others	**2.66**	**1.14-6.66**
	(CC+CT)	1	Reference
DRD4 C_1611535	AA vs others	0.51	0.24-1.12
	(AG+GG)	1	Reference
	GG vs others	**10.55**	**1.37-65.20**
	(AA+AG)	1	Reference
DRD4 exon III	0 vs others	0.47	0.22-1.04
	(1+2)	1	Reference
	2 vs others	10.59	0.82-570.2
	(0+1)	1	Reference

Table 3 Comparison of *DRD4* C_1611535 genotypes (AA, AG, and GG) on self-reported psychiatric disturbances (CPTS-RI, BDI) and behavioral problems (YSR) by means of ANOVA tests. F-ratio (df 2, 171), significance level ($p < 0.05$), and significant *t* (5%) for post-hoc tests between genotypes (Scheffé)

Variables	AA	AG	GG	F	p <	Post-hoc
CPTS-RI	27.46 (12.37)	23.45 (12.38)	35.91 (12.38)	**5.22**	**0.01**	**b**
BDI	19.38 (12.08)	17.84 (10.73)	21.60 (11.63)	.59	ns	
YSR:						
Withdrawal	5.09 (2.95)	4.64 (2.53)	5.88 (1.25)	.89	ns	
Somatic complaints	4.31 (3.59)	3.94 (2.82)	5.00 (2.73)	.44	ns	
Anxious/Depressed	10.03 (6.12)	10.04 (6.09)	12.38 (6.91)	.55	ns	
Social problems	5.13 (2.68)	4.57 (2.43)	5.88 (1.36)	1.35	ns	
Thought problems	4.02 (3.13)	3.79 (2.65)	6.88 (1.81)	**3.95**	**0.05**	**a, b**
Attention problems	7.30 (3.13)	7.36 (2.60)	8.38 (3.16)	.49	ns	
Delinquent behavior	8.41 (3.93)	8.08 (3.32)	9.75 (3.66)	.72	ns	
Aggressive behavior	12.82 (6.64)	14.26 (6.50)	18.88 (5.62)	**3.51**	**0.05**	**a**

Note: CPTS-RI (the Child Posttraumatic Stress Reaction Index); BDI (the Beck Depression Inventory); YSR (the Youth Self-Report). Scheffé post-hoc tests significant ($p < 0.05$) between genotypes: a) AA – GG; b) AG – GG variants.

Table 4 Comparison of *DRD4* C_1611535 genotypes (AA, AG, and GG) on self-reported personality (TCI) by means of ANOVA tests. F-ratio (df 2, 171), significance level ($p < 0.05$), and significant *t* (5%) for post-hoc tests between genotypes (Scheffé)

Variables	AA	AG	GG	F	p <	post-hoc
Novelty Seeking	11.87 (2.74)	11.30 (2.90)	11.82 (2.82)	.77,	ns	
Harm Avoidance	9.80 (3.49)	8.86 (3.58)	8.73 (3.64)	1.48	ns	
Reward Dependence	7.39 (2.10)	7.52 (1.97)	5.90 (1.38)	**3.05**	**0.05**	**b**
Self-Directedness	9.58 (3.46)	10.68 (3.71)	6.81 (3.66)	**5.78**	**0.01**	**a, b**
Cooperativeness	13.74 (3.55)	14.65 (3.65)	12.91 (2.77)	1.74	ns	
Self-Transcendence	8.13 (3.00)	8.32 (3.04)	10.27 (2.97)	2.50	ns	

Note: Scheffé post-hoc tests significant ($p < 0.05$) between genotypes: a) AA – GG; b) AG – GG variants.

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Ethical permission

All male adolescent delinquents at the facility during a period of approximately one-year were invited to participate and all participants gave their oral consent after being given a detailed description of the study. In addition, they were informed about the voluntary and confidential nature of their participation. They were further assured that the staff would not obtain any information about results, and that their treatment/management at the unit would not be affected whether they participated or not. The study was approved by the relevant Institutional Review Boards in Russia and USA.

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Highlights

(1) *COMT* rs737865 GG genotype associated with increased risk of substance dependence

(2) Results highlight a role of the *DRD4* C_1611535 GG genotype in substance dependence

(3) *DRD4* C_1611535 GG genotype associated with antisocial personality disturbances

(4) Multi-polymorphism/haplotype-based approach to variability in a single gene used