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Association of Dopamine Receptor D4 (*DRD4*) Gene Polymorphism with Cardiovascular Disease Risk Factors

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Abstract—Dopamine receptor genes are known to be candidate genes, mutations of which may be involved in the development of cardiovascular diseases. The human D4 receptor gene (*DRD4*) contains a variable number (two to ten copies) of tandem 48-bp repeats in exon 3. The goal of the study was to analyze the association of *DRD4* gene polymorphism with cardiovascular disease risk factors in the Russian population: blood pressure (BP), high-density (HDL) and low-density (LDL) lipoprotein cholesterol levels, and the triglyceride level. We genotyped 257 women and 425 men for variable number tandem repeat polymorphism in *DRD4*. The subjects were Novosibirsk residents of Slavic ethnicity. They were divided either into 7+ (those having the allele of seven or eight repeats) and 7– (two to six repeats) groups or into 2+5+ (two or five repeats) and 2–5– (three, four, six, seven, or eight repeats) groups. We found associations between the 7+ allele and elevated systolic and diastolic BP in women but not in men. Neither sex showed associations between the long variants of the *DRD4* gene and pulse blood pressure. The presence of the 2– or 5– allele of the *DRD4* polymorphism was associated with low HDL cholesterol levels in women and low total cholesterol levels in men. The polymorphism exerted no significant effects on LDL, HDL, or triglyceride levels in men.

Keywords: dopamine, receptor, *DRD4* gene, polymorphism, tandem repeat, blood pressure, lipoprotein, sex, association, medical genetics

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INTRODUCTION

Arterial hypertension is commonly ranked among the main risk factors for atherosclerosis, myocardial infarction, stroke, and kidney failure (Graham, 2014). Although arterial blood pressure variation in a population appears to be genetically determined by 30–50%, the identification of the genes controlling blood pressure is a tough problem (Wang et al., 2011). It is known that rare monogenic forms of arterial hypertension are associated with anomalies in sodium transport in the kidneys (Louis-Dit-Picard et al., 2012). Many cases of essential hypertension may be caused by an innate sodium transport anomaly in nephrons, which perform glomerular filtration and sodium reabsorption in renal tubules and collecting ducts.

Dopamine is a known paracrine regulator of gene transport in kidneys (Zeng et al., 2007). For example, a dopamine release directly in the kidneys elevates sodium excretion after salt load in normotensive individuals, and this effect is weaker in patients with essential hypertension. An association of the A48G SNP in the *DRD1* dopamine receptor gene with hypertension has been found in several ethnic groups (Orun et al., 2011; Cipolletta et al., 2012). The *TaqI* polymorphism in the *DRD2* dopamine receptor gene is associated with hypertension in the Chinese population (Fang et al., 2005).

It appears that both D1 and D2 receptors affect systemic arterial pressure via local physiological processes in the kidneys. Receptors D1 are likely to inhibit Na-K-ATPase activity in the basolateral membrane and Na–H antiport in the luminal membrane of tubules, whereas receptors D2, in contrast, enhance Na-K-ATPase activity (Sen et al., 2005). Thus, a genetic defect of either DRD1-mediated inhibition or DRD2-mediated stimulation of sodium reabsorption in kidneys may stimulate hypertension development.

The D4 dopamine receptor belongs to the family of D2-like dopamine receptors. Mice with knocked out *DRD4* display elevated anxiety (Keck et al., 2013) and a shorter lifespan (Grady et al., 2013). However, no data on the cardiovascular system in such mice have been reported. The polymorphism for the variable number of 48-bp tandem repeats (VNTR) located in

exon 3 of the gene is the best-studied polymorphic site in the human *DRD4* gene (Wu et al., 2012). Each repeat encodes a polypeptide of 16 amino acid residues in the third intracellular loop of the D4 receptor protein. It is thought that this domain of the protein participates in the interaction with G proteins and affects the intracellular cAMP level (Nemoda et al., 2011).

The number of tandem repeats in the polymorphic site varies from two to ten. Variants with four and seven repeats are predominant in people of the Caucasian race (Nikolaidis et al., 2010). The presence of at least one "long" allele (seven, eight, or ten repeats) in a genotype is associated with attention deficit/hyperactivity disorder (Gold et al., 2014), a predisposition to alcohol addiction (Maxwell et al., 2013), and a personality trait, novelty seeking (Munafo et al., 2008).

As for cardiovascular diseases, the presence of "long" alleles in the *DRD4* of Euro-Americans is associated with elevated systolic and diastolic pressure (Sen et al., 2005). Alleles with two and five repeats are associated with elevated HDL cholesterol in men and reduced LDL cholesterol level in women in the Finnish population (Elovainio et al., 2005). We previously found associations of *DRD4* polymorphism with various psychosocial features of cardiovascular diseases in Novosibirsk residents (Gafarov et al., 2013).

The processes of signal transduction in synapses and lipid metabolism are tightly connected. Neurons form very few synapses that are not mediated by glial cells. Cholesterol is the signaling substance released from glial cells to induce synaptogenesis (Orth, Bellosta, 2012). Cholesterol is essential for the formation of synaptic vesicles and postsynaptic receptor clusterization (Dason et al., 2014). It has been conjectured that a decrease in plasma cholesterol level decreases cholesterol content in brain cell membranes, which, in turn, suppresses the activity of serotonergic neurons (Ainiyet and Rybakowski, 2014). Also, a reduced plasma cholesterol level increases neuron membrane fluidity, favoring serotonin reuptake in synapses and a decrease of its binding by receptors on the postsynaptic membrane (Pucadyil and Chattopadhyay, 2006). It appears that lipid and dopamine metabolism are controlled by common genetic factors. An association between the VNTR polymorphism in *DRD4* and some lipid metabolism parameters has been detected in a Finnish population (Elovainio et al., 2005).

We did not find publications concerning the association of tandem repeat copy number polymorphism in *DRD4* with blood pressure or lipid composition in Russian populations. The goal of our study was to analyze the association of certain polymorphic variants of the *DRD4* gene with three blood pressure indices and four blood lipid profile indices among residents of Novosibirsk, Russia.

MATERIALS AND METHODS

The study is based on strictly standardized unique information on trends in the rates of morbidity and mortality of cardiovascular and other therapeutic diseases and their major risk factor in Novosibirsk. This information was collected under the auspices of the MONItoring of Trends and Determinants in CArdiovascular Disease (MONICA) project of the World Health Organization (Luepker, 2012) from 1984 to 1994. A random sample was constructed according to the regulations of the MONICA protocol by applying a random number table to the register of voters. About 82.1% of invitees accepted the invitation. Written informed consent was taken from all subjects. The study was approved by the ethics committee of the Institute of Internal and Preventive Medicine, Novosibirsk. We examined men ($n = 419$) aged 25–65 years (mean age 46.3 ± 0.5 years) and women ($n = 257$) aged 25–64 years (mean age 43.1 ± 0.7 years). According to the questionnaire data, ethnic Russians constituted 92.3% of the sample.

Measurements of blood pressure were conducted by one doctor, who had received training and obtained the appropriate certificate. Two measurements were conducted manually for each patient with a standard mercury blood pressure meter. The study dealt with the arithmetic mean values. The pulse blood pressure was taken to be the difference between the measured systolic and diastolic pressures.

For lipid analysis, blood samples were taken from the median cubital vein in the morning in a fasting state no earlier than 12 h after meal. Total cholesterol (CS), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were assayed by the enzymatic method with standard kits Biosub-CHOL, Biosub TG (Biocon, Germany), and HDL/LDL (Herbos dijagnostik, Croatia) in an FP-901 analyzer (Labsystems Oy, Finland).

Genomic DNA was isolated from peripheral blood by the conventional method involving proteolysis and phenol extraction. The VNTR polymorphism was analyzed as in (Nanko et al., 1993) with modifications. The fragment of the *DRD4* gene (GenBank accession L12398) 96–384 bp in size was amplified with primers 5'-AGGTGGCACGTCGCGCCAAGCTGCA-3' (positions 668–692) and 5'-TCTGCGGTGGAGTCTGGGGTGGGAG-3' (positions 1129–1105). The PCR mixture contained 0.5–1 μg of genomic DNA, 0.4 μM each of the forward and reverse primers, 0.1 mM each of the four dNTPs, 1.5 mM $MgCl_2$, 10% dimethyl sulfoxide, 0.01% Tween 20, 20 mM $(NH_4)_2SO_4$, 75 mM Tris HCl pH 9.0, and 1.25 U of Taq polymerase. The reaction volume was 25 μL. The reaction was conducted in an Eppendorf Mastercycler gradient thermocycler (Eppendorf Scientific Inc., United States). The amplification regime was as follows: predenaturation at 95°C for 4 min followed by 35 cycles: 95°C for

Table 1. Frequencies of alleles with various numbers of tandem repeats in the *DRD4* gene in ethnic Russians

Allele	Frequency		
	Novosibirsk* ($n = 676$)	Central Russia** ($n = 83$)	Volga–Urals region** ($n = 46$)
2	0.120	0.138	0.152
3	0.050	0.048	0.076
4	0.718	0.723	0.641
5	0.021	0.012	0.087
6	0.074	0.018	0
7	0.015	0.042	0.044
8	0.002	0.012	0
11	0	0.010	0

* Our data; ** data by Borinskaya et al. (2004).

1 min; 65°C for 1 min; and 72°C for 1 min. The reaction products were resolved by electrophoresis in 4% polyacrylamide gel and stained with ethidium bromide. Fragment sizes were determined against a DNA molecular weight ladder from 100 to 1000 bp with 100-bp increments (SibEnzyme, Russia).

For statistical evaluation, the subjects were divided into two groups according to genotypes with regard to associations reported in the literature. In the analysis of blood pressure indices, the group of subjects with at least one long (seven or eight repeats) allele in the genotype (Group 7+) was compared with all others (Group 7–) (Sen et al., 2005). In analysis of blood lipid profiles, the group of subjects with at least one allele with two or five repeats (Group 2+5+) was compared with all others (Group 2–5–) (Elovainio et al., 2005).

At the first step, two-way analysis of variance was done. The independent factors were the genotype for the *DRD4* gene (two experimental groups) and the sex (two experimental groups). The blood pressure and blood lipid indices were considered dependent variables. As the influence of sex or sex × genotype interaction proved to be significant for many indices studied, further analysis was done for men and women separately by one-way analysis of covariance. In the analysis of covariance, the genotype for *DRD4* (two experimental groups) was considered an independent factor, the blood pressure and blood lipid indices were considered dependent variables, and the subject age was included as a covariate. The significance of pairwise differences of the mean values between groups was estimated by the Tukey post hoc test. Statistical evaluation was done with STATISTICA 8.0 software.

RESULTS

We determined the VNTR polymorphism in *DRD4* in 676 Novosibirsk residents examined in the MONICA project (Table 1). The allele frequencies found in our study are in good agreement with frequencies for ethnic Russians found in earlier studies (Borinskaya et al., 2004).

Analysis of variance revealed a significant influence of the sex × genotype interaction on systolic ($F_{1.672} = 4.859$, $P = 0.028$) and diastolic ($F_{1.672} = 4.458$, $P = 0.035$) blood pressure. In the analysis of covariance, we found an association of the presence of alleles with seven or eight repeats in *DRD4* with elevated systolic ($P = 0.005$) and diastolic ($P = 0.001$) blood pressure in women (Table 2). No association with these parameters was found in men. Associations between the presence of long alleles and pulse blood pressure were found in neither men nor women.

A statistically significant effect of sex was demonstrated for CS ($F_{1.662} = 486.25$, $P = 0.0001$) and HDL-C ($F_{1.647} = 4.146$, $P = 0.042$). The influence of the sex × genotype interaction was significant for LDL-C ($F_{1.639} = 4.859$, $P = 0.028$). The mean age-corrected CS level in men with at least one allele with two or five repeats was significantly lower than in men carrying

Table 2. Age-corrected blood pressure indices in men and women carrying at least one *DRD4* allele with seven or eight repeats

Index	Mean ± standard error (n)		P for differences
	group 7–	group 7+	
Men			
Systolic BP, mmHg	135.11 ± 1.06 (403)	133.38 ± 5.32 (16)	0.748
Diastolic BP, mmHg	86.48 ± 0.52 (403)	89.31 ± 2.97 (16)	0.349
Pulse BP, mmHg	48.64 ± 0.76 (403)	44.06 ± 3.80 (16)	0.238
Women			
Systolic BP, mmHg	131.67 ± 1.22 (253)	159.50 ± 9.73 (4)	0.005
Diastolic BP, mmHg	83.64 ± 0.68 (253)	101.25 ± 5.42 (4)	0.001
Pulse BP, mmHg	48.02 ± 0.84 (253)	58.25 ± 6.67 (4)	0.128

Table 3. Age-corrected lipid profile indices in men and women carrying at least one *DRD4* allele with two or five repeats

Index	Mean ± standard error		*P* for differences
	group 2–5–	group 2+5+	
Men			
CS, mg/dL	208.58 ± 2.33 (316)	198.81 ± 4.16 (99)	0.041
LDL-C, mg/dL	131.88 ± 2.25 (303)	124.06 ± 3.96 (98)	0.086
HDL-C, mg/dL	54.27 ± 0.85 (307)	51.57 ± 1.52 (96)	0.120
TG, mg/dL	120.83 ± 3.87 (288)	111.58 ± 6.70 (96)	0.232
Women			
CS, mg/dL	99.75 ± 3.58 (203)	103.56 ± 7.37 (48)	0.642
LDL-C, mg/dL	117.10 ± 2.71 (195)	127.07 ± 5.51 (47)	0.104
HDL-C, mg/dL	57.88 ± 0.88 (200)	53.65 ± 1.80 (48)	0.035
TG, mg/dL	102.49 ± 3.73 (184)	107.65 ± 7.72 (43)	0.548

other alleles (Table 3). We found no significant associations of the *DRD4* polymorphism and levels of LDL-C, HDL-C, or TG in men.

Women carrying at least one allele with two or five repeats had lower HDL-C levels ($P = 0.035$) than the rest of the sample. No associations of the *DRD4* polymorphism with other lipid profile indices were found in women.

We found no associations between the presence of at least one *DRD4* allele with two or five repeats with blood pressure indices in men or women. Neither did we find associations between lipid profile indices and carriership of *DRD4* alleles with seven or eight repeats.

DISCUSSION

We genotyped 676 Novosibirsk residents examined in the course of the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project (Table 1). Most of them were ethnic Russians. The variant frequencies of the VNTR polymorphism in the *DRD4* gene found in our study were in good agreement with those previously found in Russians of central Russia and the Volga–Urals region (Borinskaya et al., 2004). As in other Russian populations, the allele with four repeats was predominant (72%), and the next most frequent allele was that with two repeats: 12%. The insignificant differences in frequencies of alleles with other copy numbers may be related to genetic features of the Russian population in different regions of Russia, the presence of subjects of other ethnicities, the progeny of cross-marriages, and the different sample sizes.

We found an association of the presence of long *DRD4* alleles (seven or eight repeats) with elevated systolic and diastolic blood pressure values in women (Table 2). As the group of female carriers of long alleles consisted of as few as four persons, this conclusion is tentative and it requires verification. However, it is consistent with the results formerly obtained in a study of Euro-American women (Sen et al., 2005). The discrepant data on men may be related to genetic features of these ethnic groups and/or unknown ambient factors.

The mechanism linking the VNTR polymorphism in *DRD4* to high blood pressure is obscure. It is known that the antipsychotic clozapine, which selectively acts on the D4 dopamine receptor, decreases blood pressure (Rotella et al., 2014). Several studies have been dedicated to the physiological effects of local D4 activation in kidneys. In cortical collecting ducts, the D4 receptor counteracts receptors to vasopressin (V2) and aldosterone and thereby reduces water and sodium reabsorption (Staruschenko, 2012). Sodium reabsorption in kidneys is also regulated by the interaction of the D4 receptor and the angiotensin II receptor type 1 (Tayebati et al., 2011).

Expression of *DRD4* mRNA was found in proximal and distal nephron tubules and in the presynaptic terminals of kidney nerves, which densely innervate glomeruli, the tunicae adventitiae of interlobar and interlobular arteries, and afferent and efferent arterioles (Ricci et al., 2002). The expression of *DRD4* mRNA in juxtaglomerular cells indicates that it may be involved in renin secretion regulation, although the blood renin level in mice with knocked out *DRD4* remained within normal limits (Zeng et al., 2008).

We found a significant association between the carriership of at least one *DRD4* allele with two or five repeats and reduced HDL-C level in women. It is consistent with data on women from a population sample in Finland (Elovainio et al., 2005). Thus, our data confirm the earlier inference deduced by Finnish scientists that *DRD4* alleles with two or five repeats are risk factors for cardiovascular diseases in women. Our data on the men of our sample show that carriers of at least one *DRD4* allele with two or five repeats have lower CS levels than men carrying other alleles. This result does not match that obtained for men in Finland (Elovainio et al., 2005), but it also supports the idea

that alleles with two or five repeats are protective against cardiovascular diseases.

The mechanism by which *DRD4* alleles with two or five repeats influence the level of CS or its fractions is unknown. According to data from the Bgee database, *DRD4* is expressed in the human liver (Bgee, 2014), and this fact indicates that the dopamine-induced activation of D4 receptors may trigger the signaling pathways modulating the expression rates of genes expressed in hepatocytes, in particular, genes for apolipoproteins or enzymes of the cholesterol synthesis pathway. The apolipoproteins entering "protective" lipoprotein particles, HDL-C, are encoded by the genes *APOA2*, *APOA54*, *APOD*, *APO*, and others (Camont et al., 2011). "Bad" cholesterol, that is, LDL, includes proteins encoded by *APOB, LPA*, and others (Diffenderfer and Schaefer, 2014). Change in the expression of one or several apolipoprotein genes may affect the levels of both CS and HDL-C.

The hypothesis of the involvement of D4 receptors in the regulation of genes controlling cholesterol level is supported by dopamine-induced inhibition of HMGCoA reductase, one of the key enzymes in the cholesterol synthesis pathway (O'Meara et al., 1992). Other studies confirm the association of the activity of the dopaminergic system (dopamine level or dopamine receptor activity) with total blood cholesterol level (Polymeropoulos et al., 2009; Brunerova et al., 2013) or with LDL-C (dos Santos Silva et al., 2011). The differences between the effects of *DRD4* alleles found by us in men and women may be related to the fact that the expression of some apolipoproteins is regulated by sex hormones, in particular, estradiol (Lamon-Fava et al., 1999). Regulation by sex hormones may interfere with dopamine-activated signaling pathways and differently modulate gene expression in men and women.

To sum up, our study was the first to demonstrate an association between long alleles of the D4 dopamine receptor with seven and eight repeats and elevated systolic and diastolic blood pressure values in Russian women. We also revealed an association of the presence of at least one allele of the *DRD4* gene with two or five repeats with reduced HDL-C levels in women and reduced CS levels in men.

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