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Serotonin transporter gene linked polymorphism (5-HTTLPR) determines progredience of alcohol dependence in Belarusian young males

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ABSTRACT

Purpose: Allelic duality and functional impact of degenerate repeat at 5′- flanking promoter region in *SLC6A4* gene of the serotonin transporter (5-HTTLPR), have been in the focus of investigations over the years. Various outcomes regarding an association of its polymorphism with risks of alcohol dependence syndrome (ADS) were presented. Such studies have not been conducted in the Eastern European population e.g. Belarus. We therefore checked: the association of 5-HTTLPR polymorphism with ADS, and functional impact of the polymorphism on progredience of ADS in Belarusian population.

Material and methods: The study involved 499 Belarusian males: 377 subjects with ADS (AG), and a control group (CG) with 122 subjects without alcohol-related problems. The ADS group was further divided into two groups of individuals with rapid (AG (R)) and delayed (AG (D)) progression of ADS. Clinical diagnosis was carried-out using ICD-10 criteria, Belarusian Addiction Severity Index, "B-ASI" and Alcohol-Use-Disorders-Identification-Test (AUDIT). PCR-RFLP analysis was performed.

Results: There were no significant differences in the distribution of frequencies of either the *5-HTTLPR* genotype or the short and long allele among AG and CG. However, the ADS *5-HTTLPR* genotype and allele distribution frequencies differ significantly by the variation in progression of ADS.

Conclusions: There is no significant association between polymorphism of serotonin transporter gene and risk of ADS. However, the polymorphism significantly determines progredience of ASD in subjects with pathological patterns of alcohol consumption. Findings from this study carry preliminary significance as a facility to effective alcohol addiction treatment, rehabilitation and preventive services in the Eastern Europe.

1. Introduction

5-hydroxytriptamine, 5-HT (serotonin) is a monoamine neurotransmitter abundant in the enterochromaffin cell of the gastro-intestinal tract (GIT), on platelets and in the central nervous system (CNS). At these locations accordingly, 5-HT regulates intestinal movement, serves as vasoconstrictor, regulates hemostasis and blood clotting, and engages in regulation of mood, appetite and sleep. Serotonin metabolism is ensured via interaction of several enzyme systems. Tryptophan hydroxylase located in the presynaptic neuron, controls the activity of conversion of tryptophan to serotonin, monoamine oxidase (MAO) located in the presynaptic neuron is responsible for the breakdown of serotonin into 5-hydroxyindoleacetic acid (5HIAA), while serotonin transporter (5HTT) in the presynaptic membrane, carries the reuptake of serotonin from the synaptic cleft into the presynaptic neuron [1].

5HTT is a protein belonging to the family of sodium-and-chloride-dependent solute carrier family 6, member 4 (*SLC6A4*). The protein selectively transports serotonin, along with sodium and chlorine into the cell and potassium out of cell, thus conducting serotonergic signal transmission. In humans, the serotonin transporter 5HTT gene is located on q11.1-q12 region of chromosome 17. In 5HTT gene several polymorphic loci were found, one of them has a linked polymorphic region with two variants (rs25531 and rs25532) of single nucleotide polymorphism (SNP) of the serotonin transporter, *5-HTTLPR* (rs4795541). The functional biallelic repetitive element in the 5′

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Table 1
General Characteristics of the sample; ADS -alcohol dependence syndrome, the alcoholic group (AG), Alcohol-Use-Disorders-Identification-Test (AUDIT), the control group (CG), a subgroup of AG (R) -individuals with a rapid progression of ADS (duration < 3 years), a subgroup of AG (D) -men with delayed progression (duration > 10 yrs).

Parameters		AG(R) n = 245 1	CG n = 122 2	AG (D) n = 132 3	Significance
Age (years)		22.93 ± 0.5	21.59 ± 0.23	37.2 ± 0.8	P1,2-3 < 0.05
Education	College (%)	56.3	52.3	39.2	P1,2-3 < 0.05
	College/professional (%)	42.2	31.3	53.3	P1-3 < 0.05
	Higher (%)	1.5	16.4	7.5	P2-1,3 < 0.05
Duration (yrs.) of ADS formation		2.95 ± 0.16	–	10.46 ± 0.56	P1-3 < 0.05
Age of commencement of alcohol consumption (yrs.)		15.02 ± 0.18	16.01 ± 0.57	17.1 ± 0.6	P1-3 < 0.05
Duration of ADS (yrs.)		3.54 ± 0.2	–	12.4 ± 1.6	P1-3 < 0.05
Alcohol dependence hereditary load (%)		67.6	40.6	57.5	P1,3-2 < 0.05
Place of residence town/village (%)		59.9	75.0	49.2	P2-1,3 < 0.05
		40.1	25.0	50.8	
AUDIT (scores)		25.9 ± 0.6	4.13 ± 0.5	29.2 ± 0.8	P2-1,3 < 0.05

regulatory region of the serotonin transporter gene, 5-*HTTLPR*, provides polymorphism of the gene encoding 5HTT. It results in a characteristic serotonin turnover function at serotonergic synapses, and thus significantly determines individual psychosocial characteristics, contributing to the vulnerability of individuals to the development of alcohol dependence syndrome. By its nature, 5-HTTLPR has an insertion-deletion polymorphism, which includes repetitive sequences of 22 nucleotides in the promoter of the gene presented by two allelic variants: L (long) and S (short - with deletion) [1–8].

Studies have found the modulatory role in the serotonin system on corticotrophin releasing hormone (CRH) and in reciprocal interaction between the limbic-hypothalamic-pituitary-adrenal (LHPA) axis and central serotonergic activity [8,9]. Serotonergic system plays a major role in food, sex and exploration behavior, participates in the formation of affective components of behavior, self-control and emotional stability [6]. Increased serotonergic activity creates a sense of mood elevation, its insufficiency - causes decrease in mood. Reduction in the central serotonergic functioning has been associated with high levels of impulsivity and aggression [10]. Serotonin controls the expression of aggressive behavior and severity of anxiety manifestation [11]. Le-Marquand et al. [12] observed a growing evidence of involvement of the serotonergic system in alcohol dependence, established association of deficits in the serotonergic system with higher alcohol intake and suggested that the level of 5-HT functioning may impact the behavioral effect of alcohol. In a 2002 review, increased baseline activity of serotonin in platelets, as measured in alcoholics and children of alcoholics, was found to have met basic criteria as neurochemical trait marker of vulnerability to alcoholism [13]. Two separate studies identified significant reduction in 5-HTT in the living and post mortem brains of alcoholics [14,15]. The sedative and hypnotic effects of ethanol were demonstrated to be potentiated by the reduced 5-HTT functioning in animal models [16]. Various studies have implicated 5-HTT in the pathophysiology of neuropsychiatric diseases including alcoholism and mood disorders [4,5,17,18].

The aim of this study was therefore to check if there is any association of 5-HTTLPR polymorphism with ADS and if there is a functional impact of the polymorphism on progredience of ADS in a Belarusian population.

2. Materials and methods

In 2011, there were 179,014 individuals listed on the ADS control register in the Republic of Belarus. Of these, 16,972 were adolescents below 18 years of age under preventive supervision, 65 of them having verified diagnosis of ADS. According to the WHO, the Republic of Belarus is one of nine countries with extremely high rate of alcohol consumption (equivalent to > 15 l of ethanol per person per year). The prevalence of ADS has a bimodal pattern, characterized by two peaks, both observed in men within the age of 20–39 years and 45–59 years [19–21].

This study involved a sample of 499 male subjects grouped to achieve objectives of the study. The alcohol dependent group (AG) consisted of 377 male subjects with ADS, recruited during their therapy at the Units of the Alcohol Dependence Therapy in the State Narcology Wards of Minsk, Brest, Gomel and Mogilev regional narcology wards; or at Psychiatric Research and Practice Center of Minsk and Lepel regional psychiatric hospital. The second group - control group (CG) - consisted of 122 volunteers with no problems with alcohol (level of use does not meet clinical criteria for abuse or dependence), from the general population, including workers of the State Narcology Wards of Minsk, Brest, Gomel and Mogilev regional narcology wards, as well as workers of the Psychiatric Research and Practice Center of Minsk and Lepel regional psychiatric hospital. To investigate the hypothesized impact of polymorphism of serotonin transporter *5-HTTLPR* gene on progredience of alcohol dependence syndrome, the AG group was further divided into two subgroups: subgroup AG (R) comprising 245 individuals with a rapid progression of alcoholism (duration < 3 years) and subgroup AG (D) comprising 132 men with delayed progression (duration > 10 yrs). Demographic characteristics of the sample are presented in Table 1.

Clinical diagnosis of alcohol dependence and abuse was made in accordance with ICD-10 and AUDIT criteria [11]. Severity of addiction to alcohol and structure of alcohol-related problems were assessed, and socio-demographic data obtained using Belarusian addiction severity index for clinical use and training “B-ITA” [21].

To achieve the set goals recent publications and reviews from available sources of literature including databases of Medline, Research Gate and OMIM were explored. In the explored literature there were no findings from studies on the variation of progredience of alcoholism with polymorphism of the serotonin transporter, *5-HTTLPR* gene.

2.1. Protocol of genetic analysis

DNA was extracted from peripheral blood leukocytes by standard methods using proteinase K, phenol-chloroform was used for treatment, precipitated with ammonium acetate and ethanol, dried and dissolved in sterile distilled water. All DNA samples were stored frozen at −18 °C. Polymerase chain reaction was carried out in the amplifier MyCycler™ thermocycler (BIORAD). The following primers were used: [F] - 5′-GGCGTTGCCGCTCTGAATTGC-3′, [R] - 5′-GAGGGACTGAGCTGGAC AACCCAC-3′.

DNA extraction was carried out by using reagents: a 15 ml mixture containing 30–40 ng DNA matrix and 1 µl (10 pmol/ml primers concentration) of each primer (Table 5), 0.7 µl MgCl2 (2.5 mM), 1.5 µl mixture of dNTP (2.5 mM), 1.5 µl of 10x buffer (750 mmol/l Tris − HCl (pH 8.8), 200 mmol/1 (NH4)2SO4, 0.1% Triton X-100, 10 mol/1 Tartrazine, 5% Fikol 400) 1 µl DMSO, 0.15 µl (0.75 units) taq-DNA

polymerase (DIALAT) and 7.15 ml of sterile de-ionized water. Then amplification was carried out under the following conditions:

95° - 5 minutes
95° - 30 seconds } for 33 cycles
61° - 45 seconds
72° - 1 minute
72° - 10 minutes
4° - ∞

After amplification, PCR products 484 bp in size (S allele) and 528 bp (L allele) were applied to a 2% agarose gel containing ethidium bromide (0.0001%). Separation of fragments was performed in the apparatus for horizontal gel electrophoresis in 1xTAE buffer at a voltage of 100 V. The resulting electrophoregram was recorded with the help of gel documentation system Vilber Lourmat (France).

The study was conducted with the subjects' consent, not earlier than 10 days after the last use of alcohol, in the absence of clinical signs of withdrawal state which are confirmed by laboratory diagnostic methods.

2.2. Exclusion criteria

We excluded from the study patients with acute and chronic mental (except of ADS) and somatic conditions, severe cognitive impairment and patients who refused to participate in the study.

2.3. Ethical issues

The study was approved by the local Bioethical Committee of the Belarusian State Medical University in Minsk, Belarus (protocol: 4/3.11.2011) and conducted in accordance with the Helsinki Declaration, with its later amendments.

3. Results

Initially, the distribution frequencies of variable genotype of the serotonin transporter, *5-HTTLPR* gene, were compared in the AG and CG groups. Comparative analysis by means of contingency tables revealed no statistically significant differences between the AG and CG ($\chi 2 = 0.2$; $P = 0.9$) (Tables 2 & 3).

Subsequently, we investigated the distribution of polymorphic variants of the serotonin transporter *5-HTTLPR* gene among patients in the AG (R) and AG (D) groups. The CG was meanwhile excluded from this analysis. Results obtained are presented in Table 4. Patients in the AG (R) group have statistically significant content of the LL polymorphic variant of the serotonin transporter *5-HTTLPR* ($\chi 2 = 10.1$, $P = 0.04$).

Further, we analyzed the frequencies of occurrence of the alleles S and L in both the AG and CG groups. Distribution of genotype frequencies in both groups did not deviate from Hardy-Weinberg equilibrium. Analysis of distribution of allelic frequencies using multiplicative genetic model revealed no statistically significant predominance of S or L allele in any of the group. Allelic frequencies distribution, results of the Hardy-Weinberg test for genotype frequencies distribution in the AG and CG groups, and tested multiplicative genetic model of allelic occurrences in the population sample and within the AG group are presented in Tables 5 and 6.

Table 2
Distribution frequencies of variable genotype of serotonin transporter, *5-HTTLPR* gene among patients with ADS and healthy individuals; ADS -alcohol dependence syndrome, the alcoholic group (AG), the control group (CG).

Study Group	Size	Genotype of serotonin transporter *5-HTTLPR*			Total
		S/S	*S/L*	*L/L*	
AG	Total, persons	48	170	159	377
	%	12.7%	45.1%	42.2%	100.0%
CG	Total, persons	17	56	49	122
	%	13.9%	45.9%	40.2%	100.0%

Table 3
Differences in distribution frequencies of variable genotype of serotonin transporter, *5-HTTLPR* gene between patients and control group.

Genotype	OR	95%CI	Se	Sp	AUC	P
S/S	0.9	0.49-1.63	0.13	0.86	0.49	> 0.05
S/L	0.96	0.64-1.45	0.45	0.54	0.49	> 0.05
L/L	1.08	0.71-1.64	0.42	0.59	0.51	> 0.05

Table 4
Distribution frequencies of variable genotype of serotonin transporter, *5-HTTLPR* gene among patients with rapid and delayed alcohol dependence syndrome (ADS) formation; a subgroup of alcoholic group - AG (R) -individuals with a rapid progression of ADS (duration < 3 years), a subgroup of AG (D) -men with delayed progression (duration > 10 yrs).

Study Sub-group	Genotype of the serotonin transporter *5-HTTLPR*			Total
	S/S	*S/L*	*L/L*	
AG (R)	23	92	130	245
	9.4%	37.5%	53.1%	100.0%
MG (D)	22	68	42	132
	16.7%	51.5%	31.8%	100.0%

4. Discussion

Having adopted a design purposely to investigate the 5-HTTLPR genetic polymorphism factor potentiating risk of ADS and the impact of such factor on progression of the disease in young Belarusian men, this study ruled out considerations to investigate psychological, psychopathological, socio-economic and other factors that could influence the course and outcomes of regular consumption of alcohol.

In earlier studies the central 5-HT uptake function was linked to a role in brain development and plasticity, as well as to the processes underlying the development of substance dependence and neurodegeneration [5]. Findings from an association study were not supportive of the association of *5-HTTLPR* genotype with alcoholism [22]. On the contrary, a recent study by Taraskina et al. [23], implicated allelic variants of genes of the transporter involved in serotonergic neurotransmission in the formation of alcohol dependence and found its impact on clinical features in the course of the dependence. Others have also associated the *5-HTTLPR* polymorphism with ADS and certain neuropsychiatric disorders such as anxiety and depression, that often co-exist with the ADS [15,24].

Table 5
Distribution of occurrence frequencies of S and L alleles in the studied population sample ($\chi 2$ test: df = 1); the alcoholic group (AG), the control group (CG).

Allele	Studied population sample		Total
	AG	CG	
S	266	90	356
	74.7%	25.3%	100%
L	488	154	642
	76.0%	24%	100%

Table 6
Distribution of occurrence frequencies of S and L alleles within sub-groups of AG ($\chi 2/2$ test: d = 1); a subgroup of alcoholic group (AG) (R) -individuals with a rapid progression of alcohol dependence syndrome (ADS) (duration < 3 years), a subgroup of AG (D) -men with delayed progression of ADS (duration > 10 yrs).

Allele	Sub-groups of AG		Total
	AG (R)	AG (D)	
S	138	112	250
	55.2%	44.8%	100%
L	352	152	504
	69.8%	30.2%	100%

The *5-HTTLPR* long allele (L) has been associated with a higher level of gene expression and a greater intensity of metabolism of serotonin in comparison with the short allele (S) [25], with ADS in a non-European study [26] and with a compulsive craving [5]. It is obvious that alcohol use disorders develop in contingence with alcohol use and it was studied in relationship with the 5-HTTLPR in countries of the central and eastern Europe [1–8]. The *5-HTTLPR* S allele exhibits a 2- to 2.5-fold reduced basal transcription rate compared to the L allele and reduces 5-HTT functioning in the same proportion [2]. Short allele has also been associated with a reduction in the reuptake of serotonin, which increases the duration of serotonergic activity, with alcohol dependence and with the risk of relapse in abstinent alcohol-dependent patients [18,27–34].

Using experimental models of human and monkeys, an association between carrier genotype L/L and ADS was demonstrated [23,24]. Also animals homozygous for the *5-HTTLPR* L allele of serotonin transporter become active consumers of alcohol, regardless of external circumstances (separation from congeners, presence of other types of stress) [24]. Alcohol abstinence by heterozygous entities was significantly dependent on the conditions of detention [23]. Taraskina et al. [23] in a human study found that short allele homozygotes (S/S) were at increased risk for negative alcohol outcomes. In most of human studies, the link between allelic polymorphism of the serotonin transporter *5-HTTLPR* with alcoholism was not found, however, it was discovered that, carriers of different alleles form clinically different subgroups of alcohol consumers [23,25,26].

Some studies found an association between antisocial and impulsive-aggressive behavior that induce alcohol drinking in alcohol-dependent persons with S/S polymorphism of promoter region of the gene encoding the serotonin transporter protein [12,21,30,31]. Herman et al. [29] found a statistically significant difference in "drinking" behavior between the (LL + LS) and SS carriers. People who are homozygous for the S variant of the *5-HTTLPR*, have a higher risk of purposeful use of alcohol to an intense intoxication. This style of consumption was conditionally named “drinking to get drunk”. The authors explain this phenomenon as using alcohol by the S *5-HTTLPR* homozygotes as a tranquilizer. Observed style of alcohol consumption in carriers of L (LL + LS) *5-HTTLPR* alleles was named “binge drinking”. These findings are consistent with results of a study by Taraskina et al. [23] on a selected subgroup of persons suffering from ADS with depressive component in history and subsequent comparison with the controls which revealed an association of L allele carriers with ADS and history of depression ($\chi 2 = 4.68$, $p < 0.03$, df = 1). The risk of development of depressive states in men suffering from ADS with LL and LS genotypes of the SLC6A4 gene increased by 2.4-fold (LL + LS compared to SS), RR = 2.4 (95%CI = 1.01–3.65).

At the time of completion of this study, population distribution frequencies of polymorphic alleles of the serotonin transporter *5-HTTLPR* gene for the Republic of Belarus were not available in the international database. From our investigations, demographic characteristics of the sample do not influence the association with the risk of alcohol dependence or impact on progredience of alcoholism of the *5-HTTLPR* polymorphism among the studied population sample. Polymorphic variant LL of serotonin transporter *5-HTTLPR* gene has not been found to be statistically significantly associated with the risk of formation of alcohol dependence syndrome but it statistically significantly predisposes to a rapid progression of alcoholism, potentiating the formation of alcohol dependence syndrome among individuals with pathological patterns of alcohol use. Probably, this is mediated via depletion of serotonin from the central serotonergic synapses, as a result of expressive functional activity of the L allele of the serotonin transporter *5-HTTLPR* gene, which manifests in the increased functionality of 5-HTT with resulting amplification of serotonin neurotransmission from synaptic cleft into the presynaptic neuron. Rapid formation of ADS thus, occurs via biological and psychosocial mechanisms mediated via predisposing characteristic of serotonergic neurotransmission [29–31].

5. Conclusions

There is no established statistically significant association between polymorphism of the serotonin transporter *5-HTTLPR* gene and alcohol dependence syndrome in the studied population sample. LL genotype of the polymorphic serotonin transporter *5-HTTLPR* gene statistically significantly predisposes to a rapid progression of dependence in individuals with pathological patterns of the alcohol consumption.

Conflict of interest

The authors declare no conflict of interests.

Financial disclosure

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The author contribution

Study Design: Andrei Kapitau, Victor Obyedkov, Kirill Pavlov.
Data Collection: Andrei Kapitau, Victor Obyedkov, Kirill Pavlov.
Statistical Analysis: Kirill Pavlov.
Data Interpretation: Andrei Kapitau, Kirill Pavlov, Napoleon Waszkiewicz.
Manuscript Preparation: Andrei Kapitau, Kirill Pavlov, Sławomir Dariusz Szajda, Napoleon Waszkiewicz.
Literature Search: Inessa Goloenko, Victor Obyedkov, Kirill Pavlov, Napoleon Waszkiewicz.
Funds Collection: Andrei Kapitau.

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