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ASSOCIATION ANALYSIS OF SEROTONIN SYSTEM GENE POLYMORPHISMS (*5-HTT, HTR1B, HTR2A, HTR2C, AND TPH1*) WITH THE RISK OF PARKINSON'S DISEASE IN TATARS

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Disruption of serotonin metabolism may play a role in the pathogenesis of Parkinson's disease (PD). An analysis of the association of polymorphic variants of the genes of the serotonergic system was carried out: *Stin2* and *5-HTTLPR* loci of the *5-HTT* gene (serotonin transporter), *rs6296* of the *HTR1B* gene, *rs6311* of the *HTR2A* gene, *rs6318* of the *HTR2C* gene (serotonin receptors) and *rs1800532 TPH1* gene (tryptophan hydroxylase) with PD and its clinical forms in patients of Tatar ethnicity living in the Republic of Bashkortostan. The study included 257 patients with sporadic PD and 368 healthy individuals. As a result of the study with the development of PD in general and with its akinetic-rigid subtype, associations of the *rs1800532*G* allele and the *rs1800532*G/G* genotype of the *TPH1* gene were established. Associations of the *rs6296*G/C* genotypes of the *HTR1B* gene and *rs6318*C/C* of the *HTR2C* gene were also revealed with the akinetic-rigid subtype of PD. The association of the *STin2*12* allele of the *5-HTT* gene was found with PD and the akinetic-rigid subtype with tremor (mixed subtype). An analysis of the influence of the studied polymorphic variants of genes on the age of PD manifestation revealed an association of the *STin2*12* allele of the *5-HTT* gene with a later age of disease development (after 60 years), and an association of the *rs6318*C* allele of the *HTR2C* gene (in men) and the *rs1800532*G* allele of the TPH1gene with the onset of the disease from 45 to 60 years old.

Keywords: Parkinson's disease, serotonin, polymorphic variants of the gene, tryptophan, serotonin transporter, serotonin receptors.

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Introduction. The interaction of dopamine and serotonin with each other has been studied for many years, but the role of serotonergic transmission in dopaminergic neurons activity modulating has not yet been precisely determined (18). It has been shown that there is a decrease the serotonergic neurons number and Lewy bodies in them in PD patients (19; 12). It is known that the level of serotonin and the expression of the serotonin transporter are reduced in PD (15), but there is an increase in the level of expression of 5-HT2C receptors (7). It was noted that the loss of the transporter does not correlate with the duration of the disease and disability (21). Previously, we presented the results of a large associative study of the influence of the genes of the dopaminergic system on the PD development in ethnic Tatars living in the Republic of Bashkortostan (RB), one of the most numerous ethnic groups of the Republic's population (2).

Purpose: to investigate the effect of six polymorphic variants of genes of the serotonergic system: serotonin transporter (5-HTT), serotonin receptors (HTR1B, HTR2A, and HTR2C) and the enzyme tryptophan hydroxylase (TPH1) on the development of PD and features of the clinical course of the disease; to determine genetic markers of PD risk in Tatars.

Materials and methods. The material for the study was DNA samples from 257 patients with Parkinson's disease and 368 healthy individuals of the control sample, corresponding to the sample of patients by sex and average age. Voluntary informed consent was obtained from patients and controls. This study was approved by the Ethics Committee of the Bashkir State Medical University (Ufa). The persons included in the study live in the territory of the RB and belong to the Tatar ethnic group. The diagnosis of Parkinson's disease was established according to the clinical diagnostic criteria of the UK Parkinson Disease Society Brain Bank Criteria (4). The assessment of the severity of PD was determined using the Hen-Yar scale (11); the clinical form and age of the onset of the disease were also taken into account (these signs remained undefined in some patients, as a result of which a different number of DNA samples were included in the calculations). Genotyping for VNTR loci of the 5-HTT gene was performed by polymerase chain reaction (PCR) for DNA synthesis and subsequent electrophoresis in polyacrylamide gel, at polymorphic loci rs6311 and rs6318 - by the method of restriction fragment length polymorphism (RFLP), by the rs006325 and rs186296 and amplification loci and fluorescence detection using a CFX amplifier (Bio-Rad, USA).The results were statistically processed using a two-sided version of the Fisher test. All statistical tests were performed for a two-tailed level of significance; differences were considered statistically significant at $p < 0.05$.

Results and discussion. The distri-

Table 1

Distribution of allele and genotype frequencies of the studied polymorphic loci of genes of the serotonergic system in PD patients and in the control group

1	2			3					4
5-HTT (STin2)	Allels, n (%)			Genotypes, n (%)					N
Sample	**9*	**10*	**12*	**9/10*	**9/12*	**10/10*	**10/12*	**12/12*	
Controls	21 (3.33)	240 (38.9)	369 (58.57)	11 (3.5)	9 (2.86)	57 (18.1)	116 (36.83)	122 (38.73)	315
PD cases	8 (1.59)	166 (33.07)	328 (65.34)	3 (1.2)	5 (1.99)	33 (13.15)	97 (38.65)	113 (45.02)	251
Tremor-dominant subtype	5 (2.72)	74 (40.22)	105 (57.06)	2 (2.17)	3 (3.26)	18 (19.57)	36 (39.13)	33 (35.87)	92
Akinetic-rigid subtype	0	19 (29.69)	45 (70.31)	0	0	3 (9.38)	13 (40.62)	16 (50.0)	32
Mixed subtype	2 (1.64)	27 (22.13)	93 (76.23)	1 (1.64)	1 (1.64)	5 (8.2)	16 (26.23)	38 (62.3)	61
<45 age at onset	3 (7.5)	15 (37.5)	26 (65.0)	1 (5.0)	2 (10.0)	3 (15.0)	8 (40.0)	8 (40.0)	20
45-60 age at onset	3 (2.06)	47 (32.19)	96 (65.75)	0	3 (4.11)	8 (10.96)	31 (42.47)	31 (42.47)	73
> 60 age at onset	3 (1.36)	66 (30.0)	151 (68.64)	2 (1.82)	1 (0.91)	14 (12.73)	36 (32.73)	57 (51.82)	110
5-HTTLPR	Allels, n (p, %)			Genotypes, n (p, %)					N
Sample	**S*		**L*	**S/S*		**S/L*		**L/L*	
Controls	294 (54.04)		250 (45.96)	76 (27.94)		142 (52.21)		54 (19.85)	272
PD cases	162 (51.27)		154 (48.73)	38 (24.05)		86 (54.43)		34 (21.52)	158
Tremor-dominant subtype	49 (53.26)		43 (46.74)	13 (28.26)		23 (50.0)		10 (21.74)	46
Akinetic-rigid subtype	25 (56.82)		19 (43.18)	9 (40.91)		7 (21.21)		6 (27.27)	22
Mixed subtype	46 (50.00)		46 (50.00)	8 (17.39)		30 (65.22)		8 (17.39)	46
<45 age at onset	10 (41.67)		14 (58.33)	3 (25.00)		4 (33.33)		5 (41.67)	12
45-60 age at onset	31 (51.67)		29 (48.33)	7 (23.33)		17 (56.67)		6 (20.0)	30
> 60 age at onset	53 (55.21)		43 (44.79)	16 (33.33)		21 (43.75)		11 (22.92)	48
HTR1B (rs6296)	**C*		**G*	**C/C*		**G/C*		**G/G*	N
Controls	171 (35.33)		313 (64.67)	32 (13.22)		107 (44.22)		103 (42.56)	242
PD cases	158 (33.62)		312 (66.38)	31 (13.19)		96 (40.85)		108 (45.96)	235
Tremor-dominant subtype	51 (32.28)		107 (67.72)	11 (13.92)		29 (36.71)		39 (49.37)	79
Akinetic-rigid subtype	17 (29.31)		41 (70.69)	5 (17.24)		7 (24.14)		17 (58.62)	29
Mixed subtype	40 (33.33)		80 (66.67)	4 (6.67)		32 (53.33)		24 (40.0)	60
<45 age at onset	6 (21.43)		22 (78.57)	1 (7.14)		4 (28.57)		9 (64.29)	14
45-60 age at onset	25 (27.17)		67 (72.83)	5 (10.84)		15 (32.61)		26 (56.52)	46
> 60 age at onset	51 (38.64)		81 (61.36)	12 (18.18)		27 (40.91)		27 (40.91)	66
HTR2A (rs6311)	**A*		**G*	**A/A*		**A/G*		**G/G*	N
Controls	247 (33.56)		489 (66.44)	49 (13.32)		149 (40.48)		170 (46.2)	368
PD cases	189 (36.77)		325 (63.23)	39 (15.18)		111 (43.19)		107 (41.63)	257
Tremor-dominant subtype	60 (34.48)		114 (65.52)	14 (16.09)		32 (36.78)		41 (47.13)	87
Akinetic-rigid subtype	24 (36.36)		42 (63.64)	7 (21.21)		10 (30.30)		16 (48.49)	33
Mixed subtype	49 (39.52)		75 (60.48)	7 (11.29)		35 (56.45)		20 (32.26)	62
<45 age at onset	10 (31.25)		22 (68.75)	1 (6.25)		8 (50.0)		7 (43.75)	16
45-60 age at onset	35 (35.0)		65 (65.0)	11 (22.0)		13 (26.0)		26 (52.0)	50
> 60 age at onset	65 (40.63)		95 (59.37)	17 (21.25)		31 (38.75)		32 (40.0)	80
HTR2C (rs6318)	**C*		**G*	**C/C*		**G/C*		**G/G*	N
Controls (men)	28 (11.57)		214 (88.43)	14 (11.57)		0		107 (88.43)	121
Controls (women)	60 (13.42)		387 (86.58)	3 (1.43)		27 (12.86)		180 (85.71)	210
PD cases (men)	28 (15.56		152 (84.44)	14 (15.56)		0		76 (84.44)	90
PD cases (women)	18 (8.82)		186 (91.18)	3 (2.94)		12 (11.76)		87 (85.29)	102
Tremor-dominant subtype (men)	12 (16.67)		60 (83.33)	6 (16.67)		0		30 (83.33)	36
Akinetic-rigid subtype (men)	4 (22.22)		14 (77.78)	2 (22.22)		0		7 (77.78)	9
Mixed subtype (men)	4 (11.76)		30 (88.24)	2 (11.76)		0		15 (88. 24)	17
Tremor-dominant subtype (women)	4 (5.00)		76 (95.00)	0		4 (10.0)		36 (90.0)	40
Akinetic-rigid subtype (women)	7 (26.92)		19 (73.08)	1 (7.69)		5 (38.46)*		7 (53.85)	13
Mixed subtype (women)	1 (1.92)		51 (98.08)	0		1 (3.85)		25 (96.15)	26
<45 age at onset (men)	0		12 (100.0)	0		0		6 (100.0)	6
45-60 age at onset (men)	8 (40.0)		12 (60.0)	4 (40.0)		0		6 (60.0)	10
> 60 age at onset (men)	8 (12.12)		58 (87.88)	4 (12.12)		0		29 (87.88)	33
<45 age at onset (women)	0		16 (100.0)	0		0		8 (100.0)	8
45-60 age at onset (women)	8 (9.76)		74 (90.24)	1 (2.44)		6 (14.63)		34 (82.93)	41
> 60 age at onset (women)	5 (6.76)		69 (93.24)	0		5 (13.51)		32 (86.49)	37

The end of the table 1

1	2		3			4
TPH1 (rs1800532)	**G*	**T*	**G/G*	**G/T*	**T/T*	N
Controls	381 (51.77)	355 (48.23)	93 (25.27)	195 (52.99)	80 (21.74)	368
PD cases	288 (59.26)	198 (40.74)	87 (35.8)	114 (46.92)	42 (17.28)	243
Tremor-dominant subtype	108 (60)	72 (40.00)	34 (37.78)	40 (44.44)	16 (17.78)	90
Akinetic-rigid subtype	32 (61.54)	20 (38.46)	14 (45.16)	14 (45.16)	3 (9.68)	31
Mixed subtype	58 (50.88)	56 (49.12)	13 (22.18)	32 (56.14)	12 (21.05)	57
<45 age at onset	16 (50.00)	16 (50.00)	6 (37.50)	4 (25.0)	6 (37.5)	16
45-60 age at onset	90 (62.5)	54 (37.50)	28 (38.89)	34 (47.22)	10 (13.89)	72
> 60 age at onset	124 (56.36)	96 (43.64)	33 (30.00)	58 (52.73)	19 (17.27)	110

n – number of allels/genotypes, N – number of persons.

bution of the frequencies of genotypes and alleles of the studied loci is shown in Table 1, and the comparative analysis according to the obtained data is shown in Table 2. The distribution of genotype frequencies of the studied polymorphic variants corresponds to the Hardy-Weinberg equilibrium in all studied groups (p> 0.05).

The serotonin transporter (5-HTT) carries out serotonergic signaling and regulates the rate of serotonin reuptake in neurons. The serotonin transporter gene (5-HTT or SLC6A4) is located on chromosome 17 (q11.1-q12) and consists of 15 exons. Polymorphic VNTR locus 2 of the intron of the 5-HTT gene (STin2) consists of many repeated copies of the 17 bp element; three alleles are known containing 9 (STin2*9), 10 (STin2*10), and 12 (STin2*12) repeat copies (16). The influence of the locus on the level of gene expression was noted: STin2*9 is associated with an increased level of 5-HTT expression (6). In our study, higher frequencies of the *12 allele were found in patients with PD (p=0.023), especially in patients with a mixed (akinetic-rigid-trembling) form of PD (p=0.0002), and with the onset of the disease after 60 years (p=0.01) in comparison with the control group (Table 2; data on the genotype *9/*9 were omitted in it due to the small size of the group). Analysis of the literature data showed that targeted studies of the role of the Stin2 polymorphic variant of the 5-HTT gene in the development of PD have not previously been carried out.

Allelic variants of another locus of the 5-HTT gene, 5-HTTLPR, contain either 16 repeats (long allele *L) or 14 repeats (short allele *S), with a 43 bp deletion (5). The presence of the long allele *L provides a higher level of gene expression and a greater intensity of serotonin metabolism, compared to the short allele *S (13). Our analysis did not reveal significant associations between allelic variants of this locus and the development of PD.

Table 2

Results of the analysis of associations of the studied polymorphic loci of genes of the serotonergic system with Parkinson's disease

1	2	3	4	5
Allels, genotypes	Study groups	P	OR	95% CI
5-HTT (STin2)				
*9/10	PD cases / Controls	0.104	0.33	0.09-1.2
*9/12		0.594	0.69	0.23-2.09
*10/10		0.132	0.69	0.43-1.1
*10/12		0.663	1.08	0.77-1.52
*12/12		0.145	1.3	0.93-1.82
*9		0.122	0.49	0.21-1.12
*10		0.081	0.8	0.63-1.02
*12		0.023	1.33	1.04-1.7
*10/10	Akinetic-rigid subtype / Controls	0.325	0.47	0.14-1.6
*10/12		0.703	1.17	0.56-2.46
*12/12		0.256	1.58	0.76-3.28
12		0.082	1.68	0.96-2.94
10		0.223	0.69	0.39-1.21
*9/10	Mixed subtype / Controls	0.699	0.46	0.06-3.63
*9/12		1.000	0.57	0.07-4.58
*10/10		0.060	0.4	0.15-1.04
*10/12		0.142	0.61	0.33-1.13
*12/12		0.001	2.61	1.48-4.59
*10		$6x10^{-4}$	0.46	0.29-0.73
*12		$2x10^{-4}$	2.27	1.45-3.55
*9/10	>60 age at onset / Controls	0.529	0.51	0.11-2.34
*9/12		0.465	0.31	0.04-2.48
*10/10		0.235	0.66	0.35-1.24
*10/12		0.489	0.83	0.52-1.31
*12/12		0.019	1.7	1.1-2.63
*10		0.034	0.69	0.5-0.96
*12		0.01	1.55	1.12-2.15
HTR1B (rs6296)				
*G/G	PD cases / Controls	0.462	1.15	0.8-1.65
*G/C		0.461	0.87	0.6-1.25
*C/C		1.000	1	0.59-1.7
G		0.586	1.08	0.83-1.41
*G/G	Akinetic-rigid subtype / Controls	0.115	1.91	0.87-4.17
*G/C		0.046*	0.4	0.16-0.97
*C/C		0.567	1.37	0.49-3.85
G		0.386	1.32	0.73-2.39

Continuation of the table 2

1	2	3	4	5
*G/G	<45 age at onset / Controls	0.165	2.43	0.79-7.47
*G/C		0.283	0.5	0.15-1.64
*C/C		1.000	0.5	0.06-3.95
*G		0.156	2	0.8-5.03
*G/G	45-60 age at onset / Controls	0.105	1.75	0.93-3.31
*G/C		0.192	0.61	0.31-1.19
*C/C		0.812	0.8	0.29-2.18
*G		0.150	1.46	0.89-2.4
HTR2A (rs6311)				
*A/A	PD cases / Controls	0.559	1.16	0.74-1.83
*A/G		0.510	1.12	0.81-1.55
*G/G		0.288	0.83	0.6 - 1.15
*A *G		0.252	1.15	0.91 - 1.46
*A/A	Akinetic-rigid subtype / Controls	0.198	1.75	0.72 - 4.25
*A/G		0.272	0.64	0.3 - 1.38
*G/G		0.856	1.1	0.54 - 2.24
*A *G		0.684	1.13	0.67 - 1.91
*A/A	Mixed subtype / Controls	0.839	0.81	0.35 - 1.88
*A/G		0.028	1.84	1.07 - 3.15
*G/G		0.074	0.58	0.33 - 1.02
*A		0.220	1.29	0.87 - 1.91
*A/A	45-60 age at onset / Controls	0.129	1.84	0.88 - 3.83
*A/G		0.063	0.52	0.27 - 1.01
*G/G		0.454	1.26	0.7 - 2.28
*A		0.822	1.07	0.69 - 1.66
HTR2C (rs6318)				
*C	PD cases (men) / Controls	0.418	1.41	0.64 - 3.13
*G		0.418	0.71	0.32 - 1.58
*C	Akinetic-rigid subtype (men) / Controls	0.306	2.18	0.41 - 11.55
*G		0.306	0.46	0.09 - 2.44
*C	<45 age at onset (men) / Controls	1	0.57	0.03-10.66
*G		1	1.75	0.09-32.78
*C	45-60 age at onset (men) / Controls	0.031	5.1	1.28 - 20.32
*G		0.031	0.2	0.05 - 0.8
*C/C	PD cases (women) / Controls	0.397	2.09	0.41 - 10.54
*G/C		0.857	0.9	0.44 - 1.86
*G/G		1.000	0.97	0.5 - 1.9
*G		0.354	1.35	0.72 - 2.52
*C/C	Akinetic-rigid subtype (women) / Controls	0.215	5.75	0.56 - 59.5
*G/C		0.025	4.24	1.29 - 13.91
*G/G		0.009	0.19	0.06 - 0.6
*C		0.354	1.35	0.72 - 2.52
*C/C	Mixed subtype (women) / Controls	1	1.12	0.12 - 10.39
*G/C		0.330	0.27	0.04 - 2.07
*G/G		0.216	4.17	0.54 - 31.94
*C		0.038	0.15	0.02 - 1.13
*G		0.038	6.67	0.89 - 50.18
TPH1 (rs1800532)				
*G/G	PD cases / Controls	0.006	1.65	1.16 - 2.35
*G/T		0.160	0.78	0.56 - 1.08
*T/T		0.215	0.75	0.5 - 1.14
*G		0.012	1.36	1.08 - 1.71
*T		0.012	0.74	0.59 - 0.93
*G/G	Tremor-dominant subtype / Controls	0.025	1.8	1.11 - 2.93
*G/T		0.159	0.71	0.45 - 1.13
*T/T		0.471	0.78	0.43 - 1.41
*G		0.055	1.4	1.01 - 1.95
*T		0.055	0.72	0.52 - 1

Nevertheless, according to the literature, the 5-HTTLPR*S/S genotype increases the risk of PD in Italians (26) and in Chinese (22), but not in Norwegians (10). The biallelic meta-analysis performed by Gao L and Gao H. did not reveal the presence of a significant association of the 5-HTTLPR locus with the development of PD (25). Thus, we see contradictory results for the studied polymorphic loci of the serotonin transporter gene 5-HTT, but suggesting that a lower level of expression of this gene may make a certain modifying contribution to the development of PD.

Serotonin receptors are also involved in the serotonergic transmission mechanisms. The rs6296 polymorphic variant of the HTR1B gene is a nucleotide substitution c.861G> C; the rs6296*C allele is associated with a 20% decrease in the average number of serotonin 1B receptors (23). Our analysis did not reveal statistically significant associations with PD in general and with its clinical forms. It was also shown that this polymorphic variant is not associated with the development of PD in two Russian papers earlier (1; 3).

The rs6311 polymorphic variant of the HTR2A gene is a nucleotide substitution --1438G> A in the promoter region of the gene. It is assumed that this variant modulates the promoter activity of 5-HTR2A, which plays a role in neuropsychiatric disorders (24). As a result of our analysis, an association of the rs6311*A/G genotype with a mixed form of PD was revealed (p=0.028). It can also be noted that the frequency of the *A/A genotype and the *A allele is slightly higher in the patient groups compared to the control, but these differences do not reach statistical significance. According to published data, the carriage of the HTR2A*A allele increases the risk of developing PD in Russians (1; 3). There is no association of this locus with the development of PD was found in the samples of Italian patients and patients from the United States (8; 9; 27).

The rs6318 polymorphic variant (nucleotide substitution c.68G> C) of the HTR2C gene located in the Xq24-q28 chromosomal region affects the gene expression: the rs6318*C allele is associated with the formation of a protein with a 2-fold lower affinity for serotonin (14). In our study, women with akinetic-rigid PD were found to have a statistically significant lower frequency of the *G/G genotype (p=0.009) and a higher frequency of the *G/C genotype (p=0.025) compared with the control (Table 2). In men with the onset of the disease from 45 to 60 years, a statistically significant

The end of the table 2

1	2	3	4	5
*G/G	Akinetic-rigid subtype / Controls	0.021	2.44	1.16 - 5.14
*G/T		0.456	0.73	0.35 - 1.52
*T/T		0.164	0.39	0.12 - 1.32
*G		0.197	1.49	0.84 - 2.65
*T		0.197	0.67	0.38 - 1.19
*G/G	<45 age at onset / Controls	0.259	1.77	0.63 - 5
*G/T		0.039	0.3	0.09 - 0.95
*T/T		0.215	2.16	0.76 - 6.12
*T		0.859	1.07	0.53 - 2.17
*G/G	45-60 age at onset / Controls	0.021	1.88	1.11 - 3.19
*G/T		0.439	0.79	0.48 - 1.31
*T/T		0.152	0.58	0.28 - 1.18
*G		0.022	1.55	1.07 - 2.24
*T		0.022	0.64	0.44 - 0.92
*G/G	>60 age at onset / Controls	0.326	1.27	0.79 - 2.03
*G/T		1.000	0.99	0.65 - 1.52
*T/T		0.350	0.75	0.43 - 1.3
*G		0.249	1.2	0.89 - 1.62
5-HTTLPR				
*S/S	PD cases / Controls	0.428	0.82	0.52 - 1.29
*S/L		0.689	1.09	0.74 - 1.62
*L/L		0.711	1.11	0.69 - 1.8
*S		0.437	0.89	0.67 - 1.17
*L		0.437	1.12	0.85 - 1.48
*S/S	Mixed subtype / Controls	1.000	1.02	0.51 - 2.04
*S/L		0.874	0.92	0.49 - 1.72
*L/L		0.842	1.12	0.52 - 2.4
*S		0.910	0.97	0.62 - 1.51
*L		0.910	1.03	0.66 - 1.6
*S/S	Akinetic-rigid subtype / Controls	0.223	1.79	0.73 - 4.36
*S/L		0.078	0.43	0.17 - 1.09
*L/L		0.413	1.51	0.56 - 4.04
*S		0.910	0.97	0.62 - 1.51
*L		0.910	1.03	0.66 - 1.6
*S/S	<45 age at onset / Controls	1.000	0.86	0.23 - 3.26
*S/L		0.245	0.46	0.14 - 1.56
*L/L		0.136	2.88	0.88 - 9.43
*S		0.296	0.61	0.27 - 1.4
*L		0.296	1.65	0.72 - 3.78
*S/S	45-60 age at onset / Controls	0.672	0.78	0.32 - 1.89
*S/L		0.703	1.2	0.56 - 2.57
*L/L		1.000	1.01	0.39 - 2.59
*S		0.785	0.91	0.53 - 1.55
*L		0.785	1.1	0.65 - 1.88
*S/S	>60 age at onset / Controls	0.490	1.29	0.67 - 2.49
*S/L		0.348	0.71	0.38 - 1.32
*L/L		0.697	1.2	0.57 - 2.51
*S		0.912	1.05	0.68 - 1.62
*L		0.912	0.95	0.61 - 1.47

P – p value for two sided fisher exact test; OR - odds ratio, 95%CI - 95% confidence interval; * - p<0,05.

higher frequency of the *C allele (p=0.03) was found in comparison with the control (Table 2). Our data are to a certain extent consistent with the results of a study that showed the presence of a relationship between the HTR2C * C allele and drug-induced parkinsonism in men (20).

Tryptophan hydroxylase (TPH) catalyzes the conversion of tryptophan to 5-hydroxytryptophan (5-HT), being an enzyme that limits the rate of serotonin biosynthesis. The TPH2 gene is located on chromosome 12 (12q21.1); its polymorphic variant rs1800532 is a nucleotide substitution c.218A>C (17). Our analysis revealed in PD patients a statistically significant higher frequency of the *G allele and *G/G genotype: (p=0.012 and p=0.006, respectively), compared with the control (Table 2). Also, in patients with akinetic-rigid form, a statistically significant increase in the frequency of the *G/G genotype (p=0.021) is observed as compared to the control (Table 2). Also, the *G/G genotype and the *G allele are associated with the onset of the disease at the age of 45 to 60 years. Studies devoted to associations of the rs1800532 polymorphic locus of the TPH1 gene with the development of PD have not been found in the literature.

Thus, according to our data, certain polymorphic variants of genes of the serotonergic system contribute to the genetic predisposition to Parkinson's disease and have a modifying effect on the main clinical characteristics (clinical form and age of manifestation). In particular, in the ethnic group of Tatars, an association of the STin2*12 allele of the 5-HTT gene with the development of PD, especially with its mixed form, was found. Also, with the development of PD in general and with its akinetic-rigid form, associations of the rs1800532*G allele and the rs1800532*G/G genotype of the TPH1 gene were established. Associations of certain variants of the HTR1B and HTR2C genes were also revealed with the akinetic-rigid form of PD. As a result of the analysis of the influence of the studied polymorphic variants of genes on the age of PD manifestation, an association of the STin2*12 allele of the 5-HTT gene with a later age of disease development (after 60 years), the rs1800532*G allele of the TPH1 gene, and in men - the rs6318*C allele of the HTR2C gene was found - with the onset of the disease from 45 to 60 years. Analysis of literature data revealed conflicting results of studies of the association of the presented genetic variants with Parkinson's disease in different regions, which may be associated with population differences in the distri-

bution of allele frequencies of the studied genes. Therefore, given the population genetic heterogeneity, it is important to identify polymorphic variants of genes associated with the development of diseases in certain ethnic groups. Such genetic variants can be considered markers of risk or anti-risk of developing multifactorial diseases and used in the examined ethnic groups to diagnose a predisposition to their development.

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