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Association between suicidal behavior and genes of serotonergic system confirmed in men with affective disorders

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ABSTRACT

Background. Suicidal behavior is a crucial clinical problem in many groups of psychiatric patients. It occurs most often in affective disorders, psychotic disorders, substance abuse/dependence and personality disorders. Although not all patients with these diagnoses present suicidal behavior, it is very important to find the most vulnerable subgroups. The extensive number of studies shows that suicidal behavior (completed and attempted suicide) is associated with changes in functioning of serotonergic system. Tryptophan hydroxylase (TPH) is rate-limiting enzyme in biosynthesis of serotonin. Serotonin transporter (5-HTT) is the main factor removing serotonin from the synaptic space. Genetic studies confirm that suicide behavior has a genetic component independently of major psychiatric disorders.

Aim. The aim of this study is to look for association between selected candidate genes and suicidal behavior in affective disorders.

Material and methods. In the study we included 597 patients meeting DSM-IV criteria for bipolar disorder or unipolar disorder and 563 healthy controls. Polymorphism of serotonin transporter gene 5-HTTLPR and single nucleotide polymorphisms – SNPs (rs1799913 and rs1800532) in tryptophan hydroxylase 1 (TPH1) gene were analyzed. We used in computation Statistica 8.0 package (STATSOFT, Poland) (tests: The two-tailed Pearson's chi-square ($\chi 2$) test and Fisher's exact test).

Results. Main positive findings are an association between TPH1 polymorphisms and bipolar disease type I (BPI) diagnosis in men and an association between TPH1 polymorphisms and suicidal attempts in male patients. In all group we did not find nor allelic neither genotypic associations of selected polymorphisms and diagnosis or suicide attempts.

Conclusions. Our findings partially confirm that serotonergic system plays a role in affective disorder and suicidal behavior, but the association needs further investigation.

Key words: suicide, affective disorder, serotonergic system genes.

Introduction

Suicidal behavior is a crucial clinical problem. Studies indicated that around 60% of suicide cases suffered from depression [1], but not all patients who suffer from mood disorder commit or attempt suicide. Around 50% of bipolar patients attempt suicide during their lifetime [2] and 20% commit suicide [3] Growing data show many clinical risk factors and indicate genetic predisposition both to psychiatric illness and suicide. Family, twin and adoption studies demonstrate that predisposition to suicide is transmitted

within families and is independent from psychiatric morbidity [4, 5].

Arguments on serotonergic hypothesis of depression (proposed by Lapin and Oxenkrug in 1969) have been investigated for 40 years. The large number of studies shows that suicidal behavior is associated with changes in functioning of serotonergic system [6–12].

Arango et al. performed quantitative autoradiographic study of prefrontal cortex in suicide victims compared to matched controls. They found that binding of serotonin 5-HT1A receptor (postsynaptic in cortex) was higher and serotonin transporter binding was lower in the suicide group. Serotonin transporter and 5-HT1A binding were negatively correlated in ventrolateral prefrontal cortex (VLPFC). That may suggest common regulatory factors [7]. Findings concerning binding of 5-HTT in depressive patients, who committed suicide, were similar: binding to 5-HTT was lower in the ventral PFC of suicides compared with nonsuicides [8]. Results of Stanley et al. were consistent: they revealed upregulated 5-HT2A receptors in ventral PFC of suicide victims [9].

Asberg et al. viewed the studies concerning levels of monoamines and its metabolites in suicidal persons. Authors revealed low levels of serotonin and 5-hydroxyindoleacetic acid (5-HIAA) in suicide victims [10].

Cooper et al. measured 5-HIAA in cerebrospinal fluid (CSF) from 30 schizophrenic patients and observed the group during 11 years. Patients who attempted suicide had lower levels of 5-HIAA in CSF than non attempters [11]. Moreover response to fenfluramine was reduced in patients with attempted suicide in lifetime history [12].

Association studies are focused on genes related to monoamines, especially serotonin. Serotonin is synthesized from tryptophan by tryptophan hydroxylase (TPH). TPH1 gene is located on chromosome 11p15.3-p14. It has two single nucleotide polymorphisms in intron 7: A779C and A218C. The meta-analysis performed by Bellivier et al. revealed an association between the TPH1 A218C polymorphism and suicidal behavior [13].

Abbar et al. analyzed 7 polymorphisms in TPH1 gene. 231 individuals who had attempted suicide and 281 controls were included in the study. Authors found (among others) association between 218A allele and violent suicidal behavior. The association was strongest in individuals, who had a history of major depression [14].

Serotonin is removed from synapse by serotonin transporter (5-HTT), sodium-dependent reuptake molecule. Its gene is located on chromosome 17q11.1–12. Due to ins/del of the 44bp fragment in serotonin transporter linked polymorphic region (5-HTTLPR), 5-HTT polymorphism has two alleles: long (L) and short (S). Homozygous LL genotype is associated with higher expression of 5-HTT [15]. It was hypothesized that S allele is associated with lower 5-HTT binding sites as it was found in suicide patients. Association between S allele and suicide was confirmed in several studies [16–18]. Other papers were not consistent: Du et al. observed higher frequency of L allele in suicide victims with depression [19]. In Mann's study authors did not find association between level of 5-HTT binding in prefrontal cortex and polymorphism of 5-HTT [8].

Aim

The aim of this study is to investigate an association between selected polymorphisms and suicide attempts exclusively in affective disorders. Based on previous published abundant literature [www. gmes.mcgill.ca, date of access: 04.2013] polymorphisms of TPH1 and 5-HTT were selected to the analysis.

Material and methods

Subjects

We included 597 patients (367 female, 230 male), aged 18–84 (mean = 47, SD ± 14) that met DSM-IV criteria for bipolar disorder BP (391 BPI, male n = 174; 104 BPII, male n = 33) or unipolar disorder UP (102 UP, male n = 23) living in Wielkopolska region of Poland. The diagnosis was established using SCID-I (Structured Clinical Interview for Axis I clinical disorders for DSM-IV). Attempted suicide was defined as self-destructive behavior with at least some intentions to end one's life [6]. In the interview we asked patients about the number and methods of attempted suicide. Among patients with BP, 197 persons had a history of suicide attempt(s), among UP – 28 persons had a history of suicide attempt(s). Suicide attempters were divided into two groups according to the suicide method: violent (n = 71; hanging, jumping from height or in front of vehicle, shotgun, exsanguination, sinking) or non violent [20,21]. We excluded patient who suffered single affective episode and patients, who committed suicide during clinical observation. Observed duration of disease in our group was: min: 1 year, max: 54 years (mean 15 years, SD 11). Time period between the onset of the disease and suicide attempt is illustrated at Figure 1.

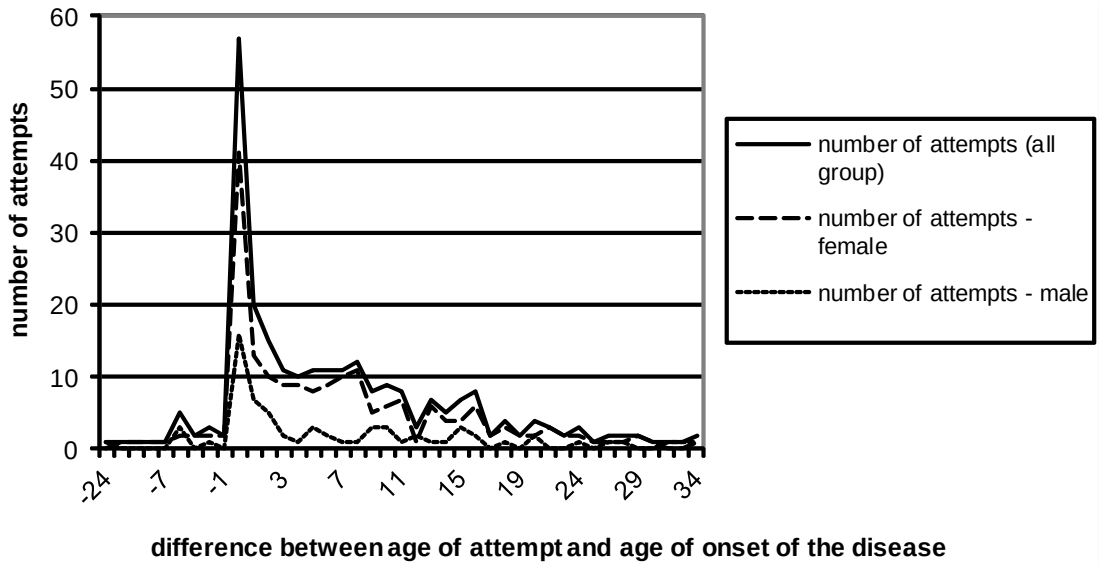

Figure 1. Time period between the onset of the disease and suicide attempt

The control group consisted of 563 healthy subjects (333 female, 230 male), aged 18–83 years (mean = 42 years, SD ± 13), from Wielkopolska region of Poland. Controls were recruited from blood donors, hospital staff, students and other volunteers.

The study was approved by the Ethics Committee, University of Medical Sciences in Poznan. All patients gave the written informed consent.

Genotyping

The selected intronic polymorphisms of TPH1 gene (rs1800532 and rs1799913) were genotyped using the TaqMan single-nucleotide polymorphism (SNP) allelic discrimination method with the ABI 7900HT system. In the serotonin transporter-linked promoter region (5-HTTLPR) we provided genotyping described by Stoltenberg et al. (2002) of the functional polymorphism of the serotonin transporter gene (5-HTT) [22].

The results of genotype and allele frequencies in patients and healthy controls with different TPH1 and 5-HTTLPR polymorphisms were analyzed using Statistica 8.0 package (STATSOFT, Poland) (tests: the two-tailed Pearson's chi-square ($\chi 2$) test for genotypic frequency analysis and Fisher's exact test for allelic frequency analysis). In all analyses $p < 0.05$ was considered statistically significant.

The discrepancy in the size of analyzed groups between "subjects" and tables are due to missing data in genotyping. The sample success rate for the genotyped polymorphisms was 97%. The reproducibility of the genotyping was 100%.

In genotypic analysis, we compared groups of all patients, BPI, BPII and UP to controls (Table 1) and we also compared suicide attempters and non attempters (accordingly to suggestions of Saetre et al. 2010 [23] (Table 2).

Results

The distributions of genotypes for all analyzed polymorphisms were in Hardy–Weinberg equilibrium in patients as well as in healthy controls ($p > 0.05$). Power analysis was performed using Quanto version 1.2.4. Power of association analysis obtained in our study was in range 0.05–0.26 (on the assumption that BP and UP prevalence is 2.1% and 17% respectively).

We found an association between TPH1 polymorphisms and BPI diagnosis in men. CA genotype of A779C polymorphism was significantly more frequent in male BPI patients than in controls. An A allele was significantly more frequent in male BPI patients ($p = 0.024$), and C allele was significantly more frequent in controls ($p = 0.029$). A218C CA genotype was significantly more frequent in male BPI patients than in controls. There is no significant allelic A218C association. We found no association between 5-HTTLPR polymorphism and diagnoses. Data on allelic frequency are not shown in tables.

The association between suicide attempts and genotype was investigated. We found an association between TPH1 A779C and A218C polymorphisms and suicidal attempts in men (Table 2), but it was not statis-

Table 1. Association between diagnosis of affective disorder and genotype

Polymorphism		TPH A779C rs1799913			p	TPH A218C rs1800532			p	5-HTTLPR			p
Genotype		CC	CA	AA		CC	CA	AA		SS	SL	LL	
BP+UP (n = 581)	T	33.27/32.35*	51.60/48.71	15.12/18.93	0.235	32.92/3.62	51.60/51.29	15.48/17.10	0.743	14.29/10.86	49.05/48.31	36.66/40.82	0.145
	F	34.68/30.63	48.84/50.63	16.47/18.75	0.489	34.88/30.53	48.55/53.57	16.57/16.20	0.427	14.04/9.55	47.47/47.77	38.48/42.68	0.170
	M	31.02/34.82	56.02/45.98	12.96/19.20	0.070	29.82/33.18	56.42/48.43	13.76/18.39	0.201	14.67/12.73	51.56/49.09	33.78/38.18	0.595
BPI(n = 356)	T	33.70/32.35	52.33/48.71	13.97/18.93	0.145	33.15/31.62	52.33/51.29	14.52/17.10	0.574	13.84/10.86	50.65/48.31	35.51/40.82	0.173
	F	39.51/30.63	45.85/50.63	14.63/18.75	0.094	39.90/30.53	45.32/53.27	14.78/16.20	0.085	14.55/9.55	47.42/47.77	38.03/42.68	0.181
	M	26.25/34.82	60.62/45.98	13.13/19.20	**0.017**	24.69/33.18	61.11/48.43	14.20/18.39	**0.048**	12.94/12.73	54.71/49.09	32.35/38.18	0.471
BPII (n = 102)	T	35.64/32.35	46.53/48.71	17.82/18.93	0.810	35.64/31.62	46.53/51.29	17.82/17.10	0.659	14.71/10.86	46.08/48.31	39.22/40.82	0.536
	F	27.94/30.63	48.53/50.63	23.53/18.75	0.658	27.94/30.53	48.53/53.27	23.53/16.20	0.352	10.14/9.55	49.28/47.77	50.58/42.68	0.948
	M	51.52/34.82	42.42/45.98	6.06/19.20	0.078	51.52/33.18	42.42/48.43	6.06/18.39	0.063	24.24/12.73	39.39/49.09	36.36/38/18	0.196
UP (n = 96)	T	29.17/32.35	54.17/48.71	16.67/18.93	0.614	29.17/31.62	54.17/51.29	16.67/17.10	0.862	15.63/10.86	45.83/48.31	38.54/40.82	0.406
	F	27.40/30.63	57.53/50.63	15.07/18.75	0.549	27.40/30.53	57.53/53.27	15.07/16.20	0.801	16.22/9.55	45.95/47.77	37.84/42.68	0.243
	M	34.78/34.82	43.48/45.98	21.74/19.20	0.952	34.78/33.18	43.48/48.43	21.74/18.39	0.883	13.64/12.73	45.45/49.09	40.91/38.18	0.948

BP – bipolar; UP – unipolar; BPI – bipolar type I; BPII – bipolar type II; T – total; M – males; F – females
** % of cases / % of controls*
bold numbers were used for statistically significant results; underlying was used for statistical trends (0.05<p < 0.06)

tically significant when we stratified suicide attempters by diagnosis. CA genotype of A779C polymorphism was significantly more frequent in suicide attempters (BP and UP together) than in controls, and AA genotype was significantly more frequent in controls. Similarly CA genotype of A218C polymorphism was significantly more frequent in suicide attempters (BP and UP together) than in controls, and AA genotype was significantly more frequent in controls. There was no significant allelic A779C and A218C association. We found, that for association between TPH1 A779C polymorphism and suicidal attempts in men, the dominant model is statistically significant (p = 0.0429). Models in other associations were not significant. We found no association between 5-HTTLPR polymorphism and suicidal behavior.

We also look for association of TPH1 A779C, TPH1 A218C polymorphisms, 5-HTTLPR and singular (n = 107) or multiple (n = 91) suicide attempters (Table 3). We found an association between TPH1 A779C polymorphism and singular suicidal attempts in men. CA genotype was significantly more frequent in this subgroup of suicide attempters than in controls. We observed an association between 5-HTTLPR and singular suicidal attempts in whole group of patients. SL genotype was significantly less frequent in singular suicide attempters than in controls, LL genotype was significantly more frequent in singular suicide attempters than in controls. There was no significant allelic association in these subgroups.

We did not observe any association between violent or non violent suicide attempts and analyzed polymorphisms (data not shown in tables).

Discussion

With respect to diagnosis, the results of association studies are still not concordant. We found association of BPI diagnosis with A218C and A779C polymorphisms (both CA genotype) of TPH1 in males and lack of association of these polymorphisms with UP. Meta-analysis performed by Chen et al. also shows, that A218C polymorphism of TPH1 is associated with bipolar (BP), but not unipolar (UP) diagnosis [24]. On the contrary in the study in Korean population authors found no association between TPH1 polymorphisms and diagnosis of bipolar disorder [25]. Negative findings were also reported by Craddock, Mendlewicz and Seretti [26–28].

We found no association of 5-HTTLPR and the diagnosis of affective disorder. Association of 5-HT-

Table 2. Association between suicide attempts and genotype in patients with affective disorders

Polymorphism		TPH A779C rs1799913			p	TPH A218C rs1800532			p	5-HTTLPR			p
Genotype		CC	CA	AA		CC	CA	AA		SS	SL	LL	
Suicide attempt(s) in lifetime history (n = 226) vs controls	T	29.44/32.35*	57.48/48.71*	13.08/18.93*	0.056	29.44/31.62*	57.48/51.29*	13.08/17.10*	0.235	13.64/10.86*	43.64/48.31*	42.73/40.82*	0.389
	F	30.77/30.63*	53.85/50.63*	15.38/18.75*	0.660	30.77/30.53*	53.85/53.27*	15.38/16.20*	0.976	13.70/9.55*	44.52/47.77*	41.78/42.68*	0.403
	M	26.76/34.82*	64.79/45.98*	8.45/19.20*	**0.013**	26.76/33.18*	64.79/48.43*	8.45/18.39*	**0.034**	13.51/12.73*	41.89/49.09*	44.59/38.18*	0.547
Suicide attempt(s) in lifetime history (n = 226) vs no suicide attempt in lifetime history (n = 371)	T	29.44/35.63*	57.48/47.99*	13.08/16.38*	0.091	29.44/35.06*	57.48/47.99*	13.08/16.95*	0.088	13.64/14.68*	43.64/52.35*	42.73/32.96*	0.057
	F	30.77/37.44*	53.85/45.32*	15.38/17.24*	0.286	30.77/37.81*	53.85/44.78*	15.38/17.41*	0.245	13.70/14.29*	44.52/49.52*	41.78/36.19*	0.556
	M	26.76/33.10*	64.79/51.72*	8.45/15.17*	0.155	26.76/31.29*	64.79/52.38*	8.45/16.33*	0.150	13.51/15.23*	41.89/56.29*	44.59/28.48*	0.052
Violent suicide attempt(s) in lifetime history (n = 65) vs controls	T	32.31/32.35*	58.46/48.71*	9.23/18.93*	0.125	32.31/31.62*	58.46/51.29*	9.23/17.10*	0.247	11.76/10.86*	42.65/48.31*	45.59/40.82*	0.676
	F	34.38/30.63*	56.25/50.63*	9.38/18.75*	0.419	34.38/30.53*	56.25/53.27*	9.38/16.20*	0.589	8.82/9.55*	55.88/47.77*	35.29/42.68*	0.660
	M	30.30/34.82*	60.61/45.98*	9.09/19.20*	0.212	30.30/33.18*	60.61/48.43*	9.09/18.39*	0.306	14.71/12.73*	29.41/49.09*	55.88/38.18*	0.090
Not violent suicide attempt(s) in lifetime history (n = 133) vs controls	T	28.57/32.35*	56.39/48.71*	15.04/18.93*	0.268	28.57/31.62*	56.39/51.29*	15.04/17.10*	0.570	13.97/10.86*	43.38/48.31*	42.65/40.82*	0.459
	F	29.41/30.63*	53.92/50.63*	16.67/18.75*	0.825	29.41/30.53*	53.92/53.27*	16.67/16.20*	0.976	14.56/9.55*	39.81/47.77*	45.63/42.68*	0.219
	M	25.81/34.82*	64.52/45.98*	9.68/19.20*	0.137	25.81/33.18*	64.52/48.43*	9.68/18.39*	0.218	12.12/12.73*	54.55/49.09*	33.33/38.18*	0.835
Suicide attempters (n = 226) vs non attempters (n = 371)	T	29.44/35.63**	57.48/47.99**	13.08/16.38**	0.091	29.44/35.06**	57.48/47.99**	13.08/16.95**	0.088	13.64/14.68**	43.64/52.35**	42.73/32.96**	0.056
	F	30.77/37.44**	53.85/45.32**	15.38/17.24**	0.286	30.77/37.81**	53.85/44.78**	15.38/17.41**	0.245	13.70/14.29**	44.52/49.52**	41.78/36.19**	0.556
	M	26.76/33.10**	64.79/51.72**	8.45/15.17**	0.155	26.76/31.29**	64.79/52.38**	8.45/16.33**	0.150	13.51/15.23**	41.89/56.29**	44.59/28.48**	0.052

BP – bipolar; UP – unipolar; BPI – bipolar type I; BPII – bipolar type II; T – total; M – males; F – females
** % of cases / % of controls*
*** % of attempters / % of non attempters*
bold numbers were used for statistically significant results; underlying was used for statistical trends (0.05 < p < 0.06)

Table 3. Association between singular/multiple suicide attempts and genotype in patients with affective disorders

Polymorphism		TPH A779C rs1799913			p	TPH A218C rs1800532			p	5-HTTLPR			p
Genotype		CC	CA	AA		CC	CA	AA		SS	SL	LL	
Patients with singular suicide attempt (n = 107) vs controls	T	27.10/32.35	57.94/48.71	14.95/18.93	0.222	27.10/31.62	57.94/51.29	14.95/17.10	0.456	14.41/10.86	34.23/48.31	51.35/40.82	**0.025**
	F	30.43/30.63	52.17/50.63	17.39/18.75	0.984	30.43/30.53	52.17/53.27	17.39/16.20	0.983	14.08/9.55	32.39/47.77	53.52/42.67	0.059
	M	21.05/34.82	68.42/45.98	10.53/19.20	0.043	21.05/33.18	68.42/48.43	10.53/18.38	0.091	15.00/12.73	37.50/49.09	47.50/38.18	0.397
Patients with multiple suicide attempts (n = 91) vs controls	T	32.97/32.35	56.04/48.71	10.99/18.93	0.157	32.97/31.62	56.04/51.29	10.99/17.10	0.353	12.22/10.86	52.22/48.31	35.56/40.82	0.605
	F	30.77/30.63	56.92/50.63	12.31/18.75	0.456	30.77/30.53	56.92/53.27	12.31/16.20	0.775	12.50/9.55	54.69/47.77	32.81/42.68	0.316
	M	38.46/34.82	53.85/45.98	7.69/19.20	0.363	38.46/33.18	53.85/48.43	7.69/18.39	0.452	11.54/12.73	46.15/49.09	42.31/38.18	0.957

bold numbers were used for statistically significant results; underlying was used for statistical trends (0.05<p < 0.06)

TLPR with BP, but not with depression, were shown in meta-analysis performed by Anguelova et al. No polymorphism of TPH1 was considered in this study [29]. Brezo et al. found that TPH1 variation was relevant in the diathesis for suicide attempts and 5-HTTLPR in mood disorders [30].

We found association between TPH1 genotypes and suicidal attempts in men. In both investigated loci CA genotype was more frequent in suicide attempters, and AA genotype was more frequent in controls. The result is consistent with recent meta-analysis. Clayden et al. concluded (although it may not be so simple), that A218C polymorphism of TPH was associated only with suicide attempts, not with completed suicide [31]. Indeed several studies concerning suicide completers (regardless psychiatric morbidity) gave not consistent results (n = 247, only males, association with GG genotype in A218C SNP) [32]; (n = 160, males, only violent suicides, no allelic or genotypic association) [33].

In study performed by Tsai et al. 151 affective patients and 200 controls were included. An association between TPH A218C polymorphism and suicidal behaviors was found in depressive patients, but not in bipolar. The A allele and AA genotype were associated with suicide [34]. In recent study Galfalvy et al. genotyped 343 subjects presenting a Major Depressive Episode. The group was ethnically heterogeneous (Caucasian, African-American, Hispanic). Clinical factors and CSF-HIAA (5-hydroxyindoloacetic acid), HVA (homovanillic acid) and MHPG (3-methoxy-4-hydroxyphenylglicol) levels were also explored. Subjects have been monitored for suicide attempts for one year. AA genotype of A218C polymorphism was associated with history of high-lethality suicide attempts and predicted suicide attempts during the 1 year follow-up [35]. Association found in our group was different (CA genotype of A218C was significantly more frequent in suicide attempters than in controls).

In 1997 Mann et al. performed a study on group of 51 inpatients with major depression. 29 of them attempted suicide. Patients who had attempted suicide and patients who had not were comparable in severity of depression (rated with the 17-item Hamilton Depression Rating Scale). Persons who attempted suicide (N = 29), made an average of 2.2 attempts during their lifetime. Authors found an association between allele A and genotype AA of A779C polymorphism and suicide [36]. In our study comparing suicide attempters (n = 226) and controls (n = 544) we obtained discordant result. AA genotype of A779C was significantly more frequent in controls than in suicide attempters.

We found no statistically significant association comparing group with (n = 226) and without (n = 371) suicide attempts.

In numerous studies no association between alleles and/or genotypes of TPH1 and suicide behavior was found. Negative results authors reported: taking into consideration association with suicide ideation [19]; in groups of suicide completers [37–40]; in groups of suicide attempters [23, 41–47].

We also did not find association between 5-HTTLPR and suicide attempts which was confirmed by many studies. In affective patients such results reported also de Luca et al. 2005, 2008 [48,49], Zalsman et al. 2006 [50], Mendlewicz et al. 2004 [26], Bellivier et al. 2000 (genotypic not significant) [17] Ho et al. 2000 [51], Ohara et al.1998 [52]. Among the papers mentioned above the study of Mendlewicz et al. stands out because of a very large investigated group (572 BP, 539 UP, 104 suicide attempters and 821 controls) and selection regarding diagnosis. The study was performed in 8 European centers.

In 1999 Du et al. reported association between L allele of 5-HTTLPR and suicide. Our results obtained in subgroup of patients, who attempted singular suicide attempt (n = 107), are consistent with it (although Du et al. considered group of only 24 suicide completers with well documented diagnosis of depression [19]). Similar results reported in 2000 Faludi et al. (n = 32) [37]. Contrary, Bondy et al. (2000) found that suicide victims were significantly more often carriers of SS or SL genotypes than controls. This group differs from our patients, because they were suicide completers with unknown psychiatric diagnosis [53]. Gorwood et al. reported association between SS or SL genotype in alcoholic patients with history of suicide attempts. Authors analyzed 110 alcohol-dependent males and 61 unaffected blood donors. It is possible that different diagnoses are important for effect of serotonin transporter polymorphism [54]. Analyze carried out by Caspi et al. showed that stressful life events predicted suicide ideation or attempt among individuals carrying an S allele but not among LL homozygotes. It suggests the importance of gene and environment interaction and its influence to depression course [55]. Coventry et al. tried to explore interactions of stressful life events and genotype in depressive patients. Self-reports of depression and an increase in depression/suicidality were significantly associated with prior personal events. They were not significantly associated with any of the genotype main effects (5-HTTLPR, 5-HTTLPR + rs25531) or interactions (stress x genotype) [56].

Concerning violent and non violent suicide attempts, we did not find association with investigated polymorphisms in these subgroups of patients. Bellivier et al. compared 194 unipolar and 43 bipolar patients (99 suicide attempters) and 187 blood donors as control group. They found no genotypic association with 5-HTTLPR and no allelic association in all suicidal groups. Authors found allelic association between S allele and subgroup of violent suicide attempters. The more severe was the phenotype (i.e. control subjects, no suicidal behavior, non violent attempt, and violent suicide attempt), the higher was the frequency of the S allele [17]. Neves et al. twice reported allelic association between S allele and suicidal and violent suicidal behavior. Firstly on group of 167 BP patients (2008) [57], and then on 198 BP patients (2010) [58]. In both papers the investigated group had different ethnicity than our group and number of suicide attempters was lower. Meta- analysis carried out by Li and He in 2007 supports the hypothesis of role of 5-HTT in the pathogenesis of suicidal behavior [59].

Our findings confirm that serotonergic system may play a role in affective disorder and suicidal behavior, but this association needs further investigation. Due to lack of statistically significant association in allelic analysis the interpretation of genotypic results is more difficult. We may suppose that the influence of polymorphic genes of serotonin neurotransmission may partly vary in male and female. Investigation performed by Perroud et al. in 2010 supports it. Authors found that females had higher TPH1 and 5-HTT transcripts levels than males. Whereas these expression levels did not differ between suicide completers and controls [60].

The results of association studies are still not concordant. Findings differ probably because of ethnicity differences, varied analyzed diagnostic groups or not homogeneous investigated groups. Investigated groups may not be representative for whole population of patients (some persons who suffer for personality disorders may refuse participation in studies) and healthy controls. One can suppose that influence of single polymorphism is so little that it is sometimes hardly noticeable because of the influence of other factors (like life events or personality traits). These elements are especially important in so complex phenomenon as suicidal behavior. Several authors suggest that genes act through intermediate phenotypes, that may be separate from psychiatric diagnosis [61].

Strategy using endophenothypes may be more useful in genetic studies than pure, but complex in signs and symptoms, diagnosis [62].

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