Annals of Depression and Anxiety

Austin Publishing Group

Open Access Full Text Article

Research Article

Association between Suicidal Behavior and TPH1 and TPH2 Genes of Serotonergic System in Polish Affective Group

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Received: August 08, 2014; **Accepted:** September 02, 2014; **Published:** September 05, 2014

Abstract

Suicide stayed important practical problem in psychiatry. Looking for genetic predisposition to suicide we considered polymorphisms of *TPH1* and *TPH2* genes, a rate limiting enzyme in serotonin synthesis. We focused on affective patients, most vulnerable to suicide psychiatric group. In the study were included 549 unrelated patients and 370 healthy controls. The selected polymorphisms were genotyped using the Taq Man single-nucleotide polymorphism (SNP) allelic discrimination method after extracting the DNA from blood sample. The Pearson's chi-square (χ^2) test and Fisher's exact test were applied to test the genotypic and allelic associations. The results were divergent with respect to the diagnosis and suicidal behavior. *TPH1* gene polymorphisms rs1800532 and rs1799913 revealed an association to diagnosis in group of male BP and MDD patients. Also rs7933505 was associated to the diagnosis of BP type I in males. *TPH2* polymorphisms rs1386483 and rs4448731 turn out be associated to BP type II. There were genotypic associations to suicide attempts in four *TPH1* SNPs (rs1800532, rs1799913, rs7933505, rs684302) in male group, but we found no statistically significant associations between *TPH2* polymorphisms and suicidal attempts. Our results partly confirm the role of serotonergic neurotransmission in predisposition to suicide and bipolar disorder. The serotonergic system plays a great role in behavior regulation and our results support that the role may partly differ according to sex.

Keywords: Suicide; Affective disorder; TPH

Introduction

Serotonin is the neurotransmitter involved in such brain functions as mood regulation, aggressiveness, anxiety, sex, sleeping, cognition, memory and learning [1]. It plays important role in inhibition of behavior undertaken upon an impulse. Reduced serotonergic releasing into synaptic cleft in the ventral prefrontal cortex may result in weaker inhibition of acting on powerful emotions [2,3]. The role of serotonergic system in etiopathogenesis of depression was postulated 40 years ago by Lapin and Oxenkrug [4] and is now very widely documented [5]. Moreover serotonin is main neurotransmitter associated with suicidal behavior [6-8]. Epidemiological studies have demonstrated that suicidal behavior is, at least partially, genetically determined with a pattern of transmission independent of psychiatric disorders [9].

Serotonin (5-hydroxytryptamine, 5-HT) elicits a wide array of physiological effects by binding to several receptor subtypes, including the 5-HT2 family of seven-transmembrane-spanning, G-protein-coupled receptors, which activate phospholipase C and D signaling pathways. TPH is a member of the aromatic amino acid hydroxylase family. The enzyme catalyzes the first and rate limiting step in the biosynthesis of serotonin. There are two isoforms of the TPH, which are coding by different genes: TPH1 (11p15.3–p14) and TPH2 (12q21.1). Both isoforms are expressed in human brain [10]. TPH-1 is expressed in such regions as frontal cortex, thalamus, hippocampus, hypothalamus and amygdala [11]. A second TPH form (TPH-2) is mainly expressed in the raphe nuclei and to a lesser extent in the cortex, thalamus, hippocampus, hypothalamus and amygdala. A significant difference in gene expression with higher TPH-1 than TPH-2 mRNA levels has been shown in the amygdala and hypothalamus, which are relevant brain areas in BP [12].

Aim of the study was to investigate the possible association between suicidal behavior and selected genetic polymorphisms in a sample of patients with diagnosis of affective disorders. In the present paper we analyzed intronic SNPs within the *TPH1* and *TPH2* genes. It was shown that an intronic *TPH2* SNP was related to gene expression levels [13], so potentially may influence serotonergic neurotransmission.

Material and Methods

Subjects

In the study were included 549 unrelated patients with bipolar affective disorder (BP) and Major Depression (MDD) (328 female, 221 male), aged 18-84 (mean=47.04, SD±13.97). Patients were recruited in mental health center of Department of Psychiatry and hospitalized at inpatient clinic, Department of Adults Psychiatry, University of Medical Sciences, Poznan. Consensus diagnosis was established by two psychiatrists using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [14]. Among patients 216 persons (142 females and 74 males; 147 BPI, 48 BPII and 21 MDD; see supplementary

Citation: Pawlak J, Dmitrzak-Weglarz M, Szczepankiewicz A, Wilkosc M, Skibinska M, et al. Association between Suicidal Behavior and TPH1 and TPH2 Genes of Serotonergic System in Polish Affective Group. Ann Depress Anxiety. 2014;1(3): 1014.

table) had a suicide attempt in lifetime history. We excluded patients, who committed suicide during clinical observation period, to avoid phenotypic heterogeneity. The control group consisted of 370 subjects (183 female, 187 male), aged 19-64 (mean=35.37, SD±12.24). We used Polish version of Mini International Neuropsychiatric Interview screen to exclude mental diseases in controls [15]. Attempted suicide was defined as self-destructive behavior with at least some intentions to end one's life [16].

After a detailed description of study procedures informed written consent was obtained from all subjects. The protocol of the study was approved by the Ethics Committee, Poznan University of Medical Sciences.

Genotyping

The included polymorphisms fulfilled the following criteria: Minor Allele Frequency (MAF) above 0.10 and genotypic correlation (ρ) across the genotypes of maximal 0.85. DNA was extracted from blood samples using the salting out protocol. The selected polymorphisms were genotyped using the TaqMan Single-Nucleotide Polymorphism (SNP) allelic discrimination method with the ABI 7900HT system. In the Real-Time PCR reaction the commercially available TaqMan Genotyping assays (Applied Bio systems, Foster City, CA) were used. Gene variants included in the study are depicted in Table1.

Computations

Statistical analyses were performed using Statistical 8.0 package (STATSOFT, Poland). The concordance of genotypes with Hardy-Weinberg equilibrium was assessed using "Utility Programs for Analysis of Genetic Linkage". The Pearson's chi-square (χ^2) test and Fisher's exact test were applied to test differences in the genotypic and allelic (respectively) distribution between groups of patients and controls. Graph Pad software was used to calculate odds ratios (OR) for the alleles. Power analysis was performed using Program Quanto. As regards association with the diagnosis the following groups: BP+MDD, BPI, BPII and MDD were compared to controls. As regards association with the suicide behavior were compared attempters to controls and also compared suicide attempters and non attempters (accordingly to suggestions of [17]).

Supplementary Table: Gender, diagnosis and suicide attempters' numbers.

	BPI	BPII	MDD
Male (N of attempters/ total N)	57 / 173	13 / 33	4 / 15
Female (N of attempters/ total N)	90 / 214	35 / 68	17 / 46

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). Using the Bonferroni correction the significance cut-off at p<0.01 was established.

We found genotypic association between *TPH1* rs1800532 and rs1799913 polymorphisms and diagnosis of affective disorder in male group. In pure BP type I group rs1800532, rs1799913 and rs7933505 genotypes were associated to the diagnosis in males. No significant associations were found in BPII and MDD groups.

Among *TPH2* polymorphisms we found genotypic association between rs1386483 and rs4448731 and diagnosis of BP type II in whole group. Association between rs4448731 and BPII was confirmed in male subgroup.

In terms of allelic associations we found differences in rs1800532 and rs1799913 polymorphisms between male affective patients and controls. In both SNPs G allele was significantly more frequent in patients (rs1800532: p=0.0049, OR: 0.6463, CI: 0.4789-0.8722 and rs1799913: p=0.0049, OR: 0.6463, CI: 0.4789-0.8722). There were no other significant allelic associations to the diagnosis.

Significant associations between diagnosis of affective disorder and genotype are shown in Table 2.

Then the association between suicide attempts and genotype was investigated. We found an association between *TPH1* rs684302 polymorphism and suicidal attempts in comparison of suicide attempters vs. controls (Table 3), but it was not statistically significant when we compared suicide attempters to non attempters. More differences were found between suicide attempters and controls in male group. There were genotypic associations to suicide attempts in four *TPH1* SNPs (rs1800532, rs1799913, rs7933505, rs684302). There

Table 1: Gene variants included in the study.

Gene	Polymorphism	rs #	chromosome	position	MAF	TaqMan probe	Type
TPH1	A218C C>A	rs1800532	11p15.3-p14	18047816	0.39 (A)	C_8940793_10	Intronic
	A779C C>A	rs1799913		18047255	0.45 (T)	C_2645661_10	Intronic
	T>G	rs211105		18055304	0.32 (G)	C_2645667_10	Intronic
	G>A	rs7933505		18045987	0.40 (A)	C_2645659_10	Intronic
	C>T	rs684302		18060353	0.46 (T)	C___2298453_20	Intronic
TPH2	G>A	rs1386483	12q21.1	72412494	0.28 (A)	C_8872255_10	Intronic
	T>G	rs1843809		72348698	0.13 (G)	C_11479729_10	Intronic
	C>T	rs1386493		72355179	0.13 (T)	C_8872331_10	Intronic
	G-703T G>T	rs4570625		72331923	0.20 (T)	C_226207_10	5' near gene
	C>T	rs2171363		72360264	0.36 (T)	C__15836061_10	Intronic
	G>C	rs1386491		72362378	0.22 (C)	C___8872320_10	Intronic
	T>G	rs6582078		72374891	0.33 (G)	C__31110916_10	Intronic
	C>T	rs4448731		72329106	0.43 (T)	C__31110841_10	
	G>A	rs1352250		72397784	0.38 (A)	C___8376101_20	Intronic

Table 2: Association between diagnosis of affective disorder and genotype (bolded are p values significant after correction p<0.01).

Polymorphism		TPH1				TPH2	
Genotype		rs1800532	rs1799913	rs7933505	rs684302	rs1386483	rs4448731
BP+MDD (n=536)	T	0.10086	0.11546	0.17760	0.07704	0.09891	0.95952
	F	0.94712	0.98048	0.99047	0.63949	0.78424	0.57426
	M	0.00896	0.00896	0.01890	0.037758	0.04765	0.46350
BPI(n=375)	T	0.08315	0.09513	0.19381	0.10644	0.78778	0.38417
	F	0.93250	0.89860	0.82240	0.74956	0.72589	0.15605
	M	**0.00370**	**0.00370**	0.00901	0.02643	0.21275	0.99857
BPII (n=100)	T	0.89108	0.89404	0.85024	0.73482	0.00252	0.00988
	F	0.55004	0.57800	0.61063	0.56205	0.08010	0.43682
	M	0.09319	0.09319	0.13392	0.07486	0.07281	0.00890

Abbreviations: BP: Bipolar; MDD: Major Depressive Disorder (separated data are not shown, because the subgroup was smaller than n=100); BPI: Bipolar type I; BPII: Bipolar type II; T - Total; M: Males; F: Females

Table 3: Association between suicide attempts and genotype in patients with affective disorders (bolded are p values significant after correction p<0.01).

Polymorphism		TPH1				TPH2	
Genotype		rs1800532	rs1799913	rs7933505	rs684302	rs1386483	rs4448731
Suicide attempt(s) in lifetime history (n=) vs controls	T	0.00731	0.00878	0.01061	0.00240	0.14057	0.94290
	F	0.31736	0.37078	0.42465	0.13352	0.80934	0.88043
	M	0.00457	0.00457	0.00433	0.00521	0.07881	0.72165
Suicide attempters (n=) vs non attempters (n=)	T	0.05074	0.05074	0.03581	0.01237	0.90501	0.94323
	F	0.09190	0.09190	0.10790	0.08854	0.99036	0.79255
	M	0.25277	0.25277	0.15607	0.07063	0.84659	0.98901
No suicide attempt(s) in lifetime history (n=) vs controls	T	0.63543	0.65242	0.82701	0.58260	0.20953	0.96466
	F	0.76197	0.69923	0.68203	0.94167	0.85351	0.46223
	M	0.11970	0.11970	0.23931	0.32952	0.12345	0.49850

T: Total; M: Males; F: Females

were no significant allelic associations. We found no statistically significant associations between *TPH2* polymorphisms and suicidal attempts both in comparison of suicide attempters vs. controls and in comparison of suicide attempters to non attempters. Patients with no suicide attempt in lifetime history did not differ to controls in terms of frequencies of investigated pollymorphisms.

Discussion

In the associative studies devoted to the association between *TPH1* and *TPH2* genes and suicidal behavior we find both positive and negative reports. We aimed to replicate them in well clinically characterized group. SNPs located in intron regions of genes seemed interesting. As regards to serotonergic system: Perroud et al. showed that rs10748185 located in intron 2 of *TPH2* gene, was statistically significantly associated with mRNA levels. Authors also measured *SLC6A4*, *TPH1*, and *TPH2* mRNA levels in the ventral prefrontal cortex suicide victims. Only *TPH2* mRNA levels were found significantly increased in suicide completer's vs. controls [13].

To find polymorphisms linked to suicide behavior, we in first step of the study checked if the investigated SNPs were associated to the disease in our group. *TPH1* gene polymorphisms rs1800532 and rs1799913 revealed an association to diagnosis in group of male BP and MDD patients. Taking into account only BP type I males also rs7933505 was associated to the diagnosis. *TPH2* polymorphisms rs1386483 and rs4448731 turn out be associated to BP type II. There were no significant associations to MDD. We take this result with caution (data on MDD not shown in tables) because of low number of MDD included. The results are also consistent to the meta-analysis performed by Chen et al. [18]. Authors proved that polymorphism of *TPH1* gene (rs1800532) were associated with bipolar (BP), but not unipolar (UP) diagnosis. *TPH1* and *TPH2* genes were investigated in Korean population, authors included to the study 103 BP patients and 86 controls. In this (not large) group no positive findings revealed [19]. Close scores, which we obtained for rs1800532 and rs1799913 associations, may result from coupling of these SNPs in the chromosome [20]. Jin Gao et al. performed a meta-analysis of association studies on *TPH2* gene and major depressive disorder [21] and concluded that there are evidence for linkage of the disease and at least one of investigated SNPs (rs4570625). Our results confirm the role of serotonergic system in predisposition to affective disorders, especially bipolar disorder.

Independently of above mentioned results, we found an association between *TPH1* rs684302 polymorphism and suicidal attempts in comparison of suicide attempters vs. controls. After the division of the studied group by gender, genotypic associations to suicide attempts in four *TPH1* gene's SNPs (rs1800532, rs1799913, rs7933505, rs684302) occurred in male group, but it was absent in female. Again results obtained for rs1800532 and rs1799913 are very similar. Among *TPH2* polymorphisms we found no associations to suicide attempts.

Saetre et al. analyzed association studies on rs1800532 and rs1799913 *TPH1* gene's polymorphisms and suicide. The group included to the meta-analysis was heterogeneous in terms of psychiatric diagnosis (schizophrenia, bipolar disorder, MDD, alcohol abuse/dependence and borderline personality disorder). In conclusion authors found no evidence for association between rs1800532 and rs1799913 and suicide [17]. Our result in male group is discordant, but in total sample it is consistent.

Maurex et al. found an association between the frequency of the *TPH-1* haplotype ACGCCG and low Iowa Gambling Task performance [22]. Authors suggest the following interpretation of the results: suicidal behavior and impulsive aggression may reflect impairments in decision-making. Deficits in decision-making occurring in subgroup of BP patients who attempted suicide may be associated with alterations in the serotonin system via *TPH1* polymorphism.

As regards results on the association of *TPH2* and suicide, we did not replicate the results of earlier studies. Fudalej et al. found TT genotype of rs1386483 associated to multiple suicide attempts and completed suicide [23]. The results of another study showed association between rs1843809 and suicide and alcohol-related suicide [24]. Both mentioned studies included completed suicide cases. In the study by Zhang et al. suicide attempters with MDD diagnosis were included. Authors investigated rs7305115 in TPH2 gene and found this polymorphism associated with risk of suicide behavior in Han nationality population [25]. Also Yoon and Kim published results that show the association between rs4570625 and suicide attempts in depressed patients. The study was performed on Korean population [26]. Perez-Rodriguez et al. described the haplotype of *TPH2* associated with borderline personality disorder, higher aggression and affect lability scores and more suicidal/parasuicidal behaviors [27]. However, in the study performed by De Luca and collaborators [28], authors found no association between *TPH2* polymorphisms and suicide attempts (what is similar to presented results). The population was close to the group included to our study: it consisted of 336 bipolar patients, mostly women, 86 of patients had a suicide attempt in lifetime history.

Many studies confirmed that the female sex is associated with a higher risk of suicide attempt than male. It was observed in adolescent [29,30] and adults in numerous populations [31,32]. Men and women differ also in suicide methods they use [33,34]. Skogman et al. investigated sex differences in completed suicide risk factors. Authors stated that risk factors for men and women were essentially different [35]. Oquendo et al. studied a group of bipolar and depressive patients and risk factors for suicide acts in two years follow up [36]. In this period 4 subjects completed suicide and 48 made a suicide attempt (16.6%). Risk factors differed in men (family history of suicidal acts, past drug use and early parental separation) and women (prior suicide attempts, suicidal ideation, lethality of past attempts, hostility, subjective depressive symptoms, and fewer reasons for living). In this clinical context we not need to be surprised by results of genetic studies. Associations to suicide observed only in one gender group were reported by many authors [20,37-40]. Our results are consistent with them and partly confirm the role of serotonergic neurotransmission in predisposition to suicide. The serotonergic system plays a great role in behavior regulation [41] and our results may support that the role may partly differ according to sex. Vulnerability to numerous suicide risk factors seems be dependent on neurotransmission. It needs further investigations if it is (indirectly) under the influence of endocrine system. In mentioned above study by Perroud, *SLC6A4*, *TPH1*, and *TPH2* mRNA levels were different between males and females, independently of suicide behavior [13].

As suggested by Skogman et al. taking the role of gender into account in the assessment of suicide risk and treatment planning could improve the prevention of future suicide [35]. Improving the effectiveness of therapeutic intervention we should be aware of genetically mediated predisposition to affective disorder and suicide behavior supported by presented results.

Acknowledgment

This research was supported by grant No 2011/01/B/NZ5/02795, financed by the Ministry of Science and Higher Education of Poland.

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Ann Depress Anxiety - Volume 1 Issue 3 - 2014
ISSN : 2381-8883 | www.austinpublishinggroup.com

Citation: Pawlak J, Dmitrzak-Weglarz M, Szczepankiewicz A, Wilkosc M, Skibinska M, et al. Association between Suicidal Behavior and TPH1 and TPH2 Genes of Serotonergic System in Polish Affective Group. Ann Depress Anxiety. 2014;1(3): 1014.