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Research Article

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

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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 (χ²) 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 hydroxylyase 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....
Supplementary Table: Gender, diagnosis and suicide attempters’ numbers.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>rs #</th>
<th>chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPH1</td>
<td>A218C C&gt;A</td>
<td>rs1800532</td>
<td>11p15.3-p14</td>
</tr>
<tr>
<td></td>
<td>A779C C&gt;A</td>
<td>rs1799913</td>
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<tr>
<td></td>
<td>T&gt;G</td>
<td>rs211105</td>
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<tr>
<td></td>
<td>G&gt;A</td>
<td>rs7933505</td>
<td></td>
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<tr>
<td></td>
<td>C&gt;T</td>
<td>rs684302</td>
<td></td>
</tr>
<tr>
<td>TPH2</td>
<td>G&gt;A</td>
<td>rs1386483</td>
<td>12q21.1</td>
</tr>
<tr>
<td></td>
<td>T&gt;G</td>
<td>rs1843809</td>
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<tr>
<td></td>
<td>C&gt;T</td>
<td>rs1386493</td>
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</tr>
<tr>
<td>G-703T</td>
<td>G&gt;T</td>
<td>rs4570625</td>
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<tr>
<td></td>
<td>C&gt;T</td>
<td>rs211363</td>
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<td></td>
<td>C&gt;G</td>
<td>rs1386491</td>
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<td></td>
<td>G&gt;A</td>
<td>rs1352250</td>
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<td>T&gt;</td>
<td>rs211363</td>
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</table>

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]).

**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 were no other significant associations in BPII and MDD groups.
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 polymorphisms.

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 especially bipolar disorder. Independently of above mentioned results, we found an association between TPH1 rs684302 polymorphism and suicidal 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.

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

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>TPH1</th>
<th>TPH2</th>
</tr>
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<tbody>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1800532</td>
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<tr>
<td>rs1799913</td>
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<tr>
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<td>rs1386483</td>
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<td>rs4448731</td>
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</table>

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
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 serotoninergic neurotransmission in predisposition to suicide. The serotoninergic 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

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References


26. Yoon HK, Kim YK. TPH2 -703G/T SNP may have important effect on susceptibility to suicidal behavior in major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2009; 33: 403-409.


