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The association of polimorphic TH01 marker with schizophrenia in Poland

R. Jacewicz [a,*], S. Szram [a], P. Galecki [b]

[a] *Department of Forensic Medicine, Medical University of Lodz, Sedziowska 18a, 91–304 Lodz, Poland*
[b] *Department of Psychiatry and Neurosis Disorders with Crisis Intervention Ward, Medical University of Lodz, Poland*

Abstract. TH01 locus, used for personal identification, is a polymorphic microsatellite region located in the first intron of the tyrosine hydroxylase gene (TH). This non-coding tetranucleotide repetitive marker is the subject of numerous studies on neuropsychiatric disorders, main schizophrenia and affective disorders. For the first time in the Polish population we conducted a comparative analysis of polymorphism in TH01 locus between a group of patients with psychiatric disorders and their regionally matched healthy subjects.

Keywords: Association study; TH01; Schizophrenia; Poland

1. Introduction

The polymorphism in TH01 tetranucleotide sequence correlates with quantitative and qualitative changes in binding by specific protein ZNF191 and may be involved in regulation of TH gene expression. This gene codes the enzyme limiting synthesis of brain catecholamines. This neurotransmitter plays a crucial role in pathophysiology of psychiatric disorders. The biochemical conception of schizophrenia implies the existence of signs of dopaminergic transfer hyperactivity. The association between this disease and polymorphism of TH01 marker has been reported in a group of neuropsychiatric patients from France, Tunisia and Sweden [1,2]. The results of these investigations are often contradictory and therefore they do not determine unambiguously the case in question. We attempted our own population study to compare distribution of allele frequencies in TH01

* Corresponding author. Tel.: +48 42 6544536; fax: +48 42 6544293.
E-mail address: r.jacewicz@post.pl (R. Jacewicz).

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locus in a group of neuropsychiatric patients from Poland and their regionally matched healthy subjects.

2. Materials and methods

90 patients affected by schizophrenia took part in the study. The neuropsychiatric patients were diagnosed by two psychiatrists according to the DSM-IV criterions. The control was recruited from among healthy individuals after the age of 45 with negative family history of psychiatric disorders. Bioethics Committee of Medical University in Lodz gave its assent to the research with the decision No. RNN/03/03/KB. Genomic DNA was isolated by the salt extraction procedure. Amplification of TH01 locus was carried out using following sequences of primers: 5′-GTG GGC TGA AAA GCT CCC GAT TAT-3′, 5′-ATT CAA AGG GTA TCT GGG CTC TGG-3′. Florescent detection was performed on the ABI Prism 377 sequencer with standard LIZ 500 using Gene Scan version 3.7. Distributions of alleles were compared using RXC program created by G. Carmody (University of Ottawa, Canada). Relative Risk (RR) of the disease was calculated according to the formula given by Dyer and Werrens.

Table 1
Alleles and genotypes distribution for TH01 polymorphism

Locus TH01	Psychiatric patients, $N=90$ (%)	Controls, $N=350$ (%)
Allele[a]		
6	42 (23.33)	158 (22.57)
7*	37 (20.55)	84 (12.00)
8	20 (11.11)	80 (11.43)
9	38 (21.11)	148 (21.14)
9.3**	43 (23.89)	222 (31.71)
10	0 (0.00)	8 (1.14)
Genotypes		
6–6	2 (2.22)	23 (6.57)
6–7***	9 (10.00)	14 (4.00)
6–8	3 (3.33)	21 (6.00)
6–9	14 (15.55)	32 (9.14)
6–9.3	12 (13.33)	43 (12.29)
6–10	0 (0.00)	2 (0.57)
7–7	2 (2.22)	7 (2.00)
7–8	5 (5.55)	13 (3.71)
7–9	9 (10.00)	14 (4.00)
7–9.3	10 (11.11)	28 (8.00)
7–10	0 (0.00)	1 (0.29)
8–8	2 (2.22)	3 (0.86)
8–9	4 (4.44)	18 (5.14)
8–9.3	4 (4.44)	22 (6.29)
9–9	2 (2.22)	16 (4.57)
9–9.3	7 (7.78)	48 (13.71)
9–10	0 (0.00)	4 (1.14)
9.3–9.3	5 (5.55)	40 (11.43)
9.3–10	0 (0.00)	1 (0.29)

Statistical significance of differences in χ^2 test was marked with *.

3. Results

Allelic and genotype frequency distributions of the psychiatric patients were compared to those of control in Table 1. The chi-square tests showed a significant differences in overall TH01 allele distribution between afflicted and control subjects ($\chi^2 = 12.640$; $p = 0.028 \pm 0.005$). 7 allele is present significantly more often in the group of patients ($\chi^2 = 8.837$; $p = 0.003 \pm 0.002$) and its presence increases the risk of psychiatric diseases almost twofold (RR = 1.90). Apart from 7 allele also 6–7 genotype occurs statistically significantly more often in the afflicted population ($\chi^2 = 4.166$; $p = 0.041 \pm 0.006$). Contrary to that, the frequency of ten-repeat sequence (allele 9.3) is found significantly more rarely in the patients than controls ($\chi^2 = 5.202$; $p = 0.028 \pm 0.005$) and its presence decreases the risk of schizophrenia (RR = 0.67).

4. Discussion

Studies of association between schizophrenia and the polymorphism of TH01 marker have been previously performed in France, Tunisia and Sweden. The results of association analysis in a Polish sample are at variance with Meloni et al. [1]. We did not observe any rare perfect 10-repeat allele $(TCAT)_{10}$ among schizophrenic patients in a case control study. Our research is in agreement with the results obtained by Jönsson et al. [2], who estimated the polymorphism of TH01 in the Swedish population. They showed a trend to lower 10 allele frequency as well as statistically lower frequency of 9.3 allele among schizophrenics. The revealed differences in the susceptibility to psychiatric disorders depending on polymorphic allele variants in TH01 locus may be associated with its function of a regulatory element in the process of TH gene transcription. Albanese et al. [3] showed, that tetranucleotide TCAT sequence in TH01 locus within TH gene acts as a transcriptional repressor.

The obtained results allow us to conclude that an allele with a higher number of repeats, i.e. 9.3 and 10, perform a protective function in susceptibility to schizophrenia and presence of 7 allele increases the risk of this disease. Because of a small sample of patients our findings need further investigation.

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