J Biomed. 2016 September; 1(3):e8044. doi: 10.17795/jmb-8044.

Published online 2016 September 28. **Research Article**

Analysis of *TAP1*^{333}, *TAP1*^{637}, *TAP2*^{379} Polymorphisms in Patients with Schizophrenia

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Received 2016 July 31; **Revised** 2016 August 16; **Accepted** 2016 August 27.

Abstract

Background: Polymorphism of inflammatory cytokines is an underlying mechanism for the schizophrenia (Scz) development.
Objectives: The aim of this study is Analysis of *TAP1*^{333}, *TAP1*^{637}, *TAP2*^{379} polymorphisms in patients with Scz.
Methods: One hundred healthy controls along with 110 cases were assessed in this study. Genotype analyzing of *TAP1*^{333}, *TAP1*^{637}, *TAP2*^{379} polymorphisms was done by Amplification-refractory mutation system (*ARMS*) *PCR*.
Results: Our finding indicated that *TAP1-333* polymorphism (OR: 0.1; 95% CI: 0.12-0.813; P: 0.031) and *TAP2-379* polymorphism (OR: 2.55; 95% CI: 1.44-4.50; P: 0.001) significantly increased the risk of Scz. However, there was no association between *TAP1-637* polymorphism with Scz.
Conclusions: To the best our knowledge, this study for the first time showed the polymorphisms of *TAP1*^{333}, *TAP1*^{637}, *TAP2*^{379} in the Scz patients. We proposed further investigations with advanced techniques as next generation sequencing for finding new polymorphisms in larger sample sizes in various populations.

Keywords: *TAP1*^{333}, *TAP1*^{637}, *TAP2*^{379}, Polymorphism, Scz

1. Background

Schizophrenia (Scz) is a disturbing mental illness, characterized by distorted thoughts, hallucinations, and feelings of fright (1). According to the population based studies, the prevalence ranges from four to seven per 1,000 persons (2). The involvement of immunological mechanisms in the development of schizophrenia have been widely reported in previous studies (3).

There are ample examples of genetic polymorphisms in *IL-10, TLR2, IL-6, TNFα, IL1-β CRP, TGFβ1, IL-12, IL-1* and *TAP* genes leading to Scz (4-13). Observation of the Sunil Vasu Kalmady et al. 2014 for the first time suggested a significant relationship between *IL-6 rs1800795* and reduced hippocampus volume in Scz (13). On the other hand, D. Frydecka 2013 did not support the role of *IL-2, IL-6, IFN-gamma and TGF-beta* gene polymorphisms in the predisposition to Scz in the Polish population (14). However, the results have remained disputable.

Data are sparse regarding the polymorphism of *TAP1*, *TAP2* genes which are involved in antigen processing pathway and over expressed in response to inflammatory cytokines strongly associated with Scz (15). *TAP*, located on 6p21.3 within HLA class II region, is a heterodimer of *TAP1* and *TAP2* that belongs to the ATP-binding cassette transporters family and allocates to deliver cytosolic peptides to class I molecules in the ER (15, 16). Linkage studies emphasize the possible role of 6p21.3 region in Scz, but the exact involved locus is not yet obvious (17). Up to the present time, at least eight such polymorphisms in *TAP2* and six such coding polymorphisms in *TAP1* have been identified in humans (18). Tae-Youn Jun et al. 2004 found no significant relationship between *TAP2*^{379}, *TAP2*^{565} *and TAP2*^{665} SNPs with Korean schizophrenic patients (19).

This study for the first time analyzed the *TAP1* and *TAP2* polymorphic residues at positions *TAP1*^{333}, *TAP1*^{637}, *TAP2*^{379} in Iranian patients with schizophrenia.

2. Methods

2.1. Study Subjects

We studied 110 healthy controls (52 women and 48 men, mean age of 25.47 $\pm$ 3.28 years), along with 100 schizophrenic patients (47 women and 63 men, mean age of 24.70 $\pm$ 8.81 years). The socio-demographic characteristics of the case and control groups were described in Table 1.

Table 1. The Socio-Demographic Characteristics of the Case and Control Groups

Variables	Cases (N = 100)	Controls (N = 110)	P Value
Sex			
Females	47	52	
Males	63	48	
Age	43.36	42.5	0.128
BMI	24.70 ± 8.81	25.47 ± 3.28	0.708
Educational level			0.0
Illiteracy	70	18	
literacy	17	49	
Job status			0.0
Unemployed	94	43	
Self-employment	4	24	
Employe	2	33	
Smoking status			0.0
Smokers	50	15	
Non smokers	50	85	
Marital Status			0.0
Single	78	9	
Married	32	101	

2.2. DNA Isolation and Polymerase Chain Reaction (PCR)

Blood samples were collected from Behravan and Iran hospitals and were kept in EDTA-coated tubes (20). We used Cinnapure DNA purification kit for DNA extraction. Tetra amplification refractory mutation system (T-ARMS) PCR method was used for polymorphisms assessment. Amplification of $TAP1^{333}$, $TAP1^{637}$, $TAP2^{379}$ SNPs were set according to the following PCR conditions: 10 μL premix master mix (including of Taq, dNTP, Buffer and Mg^{2+}), 1.5 μL of each outer primer and 2 μL of each inner primer (10 mmol/L), and 5.5 μL of RNase-free double distilled water. The PCR was heated at 95°C for 5 minutes, followed by 30 cycles at 95°C for 30 seconds, annealing at 50.8°C ($TAP2^{379}$), 64°C ($TAP1^{333}$), 60°C ($TAP1^{367}$) for 30 seconds, extension at 72°C for 30 seconds and final extension by incubation at 72°C for 10 minutes. All the reactions were performed in 20 μL total volume and were done based on previous study (21). Primers sequence and annealing temperature of $TAP1^{333}$, $TAP1^{637}$, $TAP2^{379}$ SNPs were listed in Table 2.

2.3. Statistical Analysis

SPSS software version 20 and Epical version 3.2 were used for statistical analysis. Categorical data were evaluated by Pearson's x^2. The relationship between candidate polymorphisms of *TAP* in this study and the risk of Scz were tested by estimating odds ratios (OR) and 95% confidence intervals (95% CI).

3. Results

Even though the results indicated no association between $TAP2^{637}$ SNP with Scz, allele frequency for $TAP2^{379}$ and $TAP1^{333}$SNPs showed that there was statistically significant different between case and controls (P = 0.01 and P = 0.03, respectively) Table 3. Our finding in allele frequency was in line with the genotype evaluations. As demosterated in Tables 4 and 5 the AG genotype of $TAP2^{379}$ (OR = 2.55; 95% CI = 1.44 - 4.50; P = 0.001) and GG genotype of $TAP1^{333}$ (OR: 0.1; 95% CI: 0.12-0.813; P: 0.031) significantly increased the risk of Scz. Also there were no association between TAP^{637} genotypes with the risk of Scz (AG: OR = 0.532; 95% CI = 0.274 - 1.03; P = 0.06, GG: OR = 1.98; 95% CI = 0.34 - 11.63; P = 0.45) Table 5.

4. Discussion

Schizophrenia is a serious neurodegenerative disorder that people have an altered perception of reality (22, 23). About 40 percent of people who suffer from schizophrenia have increased inflammation in an area of the brain

Table 2. Primers Sequence and Annealing Temperature

Genes	Primers	Product (size)
$TAP2^{379}$	Forward inner GAGACCTGGAACGCCTTGTACCTGCGCG	420
	Reverse inner ACAACCACTCTGGTATCTTACCCTCCTGAT	220
	Forward outer GGAAGTGCTTCGGGAGATCCAGGATGT	581
	Reverse outer TTAAAAGAAGAAATAAAGCCCAAGGCC	581
$TAP1^{333}$	Forward inner GGGCAGAAGGAAAAGCAGAGGCAGGGTCAC	351
	Reverse inner GATCAGTGTCCCTCACCATCACCCGGAG	241
	Forward outer CCCTGCACTGAGAGATTTGCAGCCTGGAG	533
	Reverse outer ACCTGGGAACATGGACCACAGGGAGAGGGT	533
$TAP1^{637}$	Forward inner CATCTTGGCCCTTTGCTCTGCAGAGGTACA	307
	Reverse inner ACCCCCTGACAGCTGGCTCCCAGCCTCCC	180
	Forward outer CATCTTCCCAGAATCACCCCTATCCAGCTA	429
	Reverse outer TGGGGAGGCATCCAATGGAACTGGATTTGG	429

Table 3. Allele Frequency and Number of $TAP2^{379}$, $TAP1^{333}$ and $TAP1^{367}$ in Scz Patients and in Healthy Controls

Gene	Cases (%), N = 110	Controls (%), N = 100	P Value
$TAP2^{379}$			
A	182 (83%)	158 (72%)	Ref
G	39 (17%)	62 (28%)	0.01
$TAP1^{333}$			
A	83 (37%)	97 (48%)	Ref
G	137 (63%)	103 (51%)	0.03
$TAP1^{367}$			
A	182 (83%)	171 (85%)	Ref
G	38 (17%)	29 (13%)	0.5

called the dorsolateral prefrontal cortex, a key brain region affected by the disease (24, 25). Srinivas et al. 2014 proved significant correlation between SNPs in pro-inflammatory cytokine genes *IL1A, IL6, TNFA* and *IFN*γ and schizophrenia in the Indian population (26). As well as, M. J. Schwarz et al. 2008 identified significant association between the *IL-2 - 330 TT* genotype and the *IL-4 - 590 CC* genotype with schizophrenia (27). Chowdari et al. 2001 investigated three polymorphisms at the Interleukin-1 gene cluster in Scz patients (28). Besides, Ozbey 2009 suggested that the IL-10 gene promoter polymorphism and IL-12 (p40) are susceptibility agents to progress Scz in the Turkish population (11, 29).

We candidate most important SNPs of *TAP* ($TAP1^{333}$,$TAP1^{637}$,$TAP2^{379}$) in this study that are involved in various *immunopathological* disease such as involvement of *TAP1-637* and *TAP2-379* SNPs in causing genetic susceptibility to cystic echinococcosis in Turkish population, as well as significant difference in the frequency of the genotype Asp-637/Asp-637 in hypersensitivity pneumonitis (30, 31). In addition, Kim et al. 2007 proved $TAP1^{333}$ and $TAP1^{637}$ SNPs as a contributing factor in the development of allergic rhinitis in the Korean population (32). Dogru et al. 2007 highlighted increased in *TAP1-333* and *TAP1-637* polymorphisms in the bronchiectasis (33). Lin HJ et al. 2004 indicated that $TAP1^{333}$ and $TAP1^{637}$ polymorphism are associated with primary open-angle glaucoma (34). Ozbas-Gerceker et al. 2013 suggested an association of *TAP1-333* polymorphism with multiple myeloma-MM (35). Shinde V et al. found *TAP1* gene variant (rs1135216 Asp637Gly) influences the susceptibility to leprosy patients in Indian population (36). Qiu et al. 2012 revealed that haplotype 687Gln-651 Cys-637 Gly-333 Ile was strongly associated with persistent HBV infection in a northeast Han Chinese

Table 4. Genotype Frequency and Number of *TAP2*^{379} Polymorphisms in Scz Patients and in Healthy Controls

Genotype *TAP2*^{379}	Cases (%), N = 110	Controls (%), N = 100	OR	95% CI	P Value
AA	71 (64.5)	41 (41)	Ref	-	-
AG	39 (35.5)	56 (56)	2.55	1.44 - 4.51	0.001
GG	-	3 (3)	3.82	0.00	0.99

Table 5. Genotype Frequency and Number of *TAP2*^{333} Polymorphisms in Scz Patients and in Healthy Controls

Genotype *TAP2*^{333}	Cases (%) N = 110	Controls (%), N = 100	OR	95% CI	P Value
AA	4 (3.6)	5 (5)	Ref	-	-
AG	75 (68.2)	87 (87)	1.21	0.69-2.13	0.523
GG	31 (28.2)	8 (8)	0.1	0.012-0.813	0.031

Table 6. Genotype Frequency and Number of *TAP2*^{637} Polymorphisms in Scz Patients and in Healthy Controls

Genotype *TAP2*^{637}	Cases (%), N = 110	Controls (%), N = 100	OR	95% CI	P Value
AA	74 (67.3)	75 (75)	Ref	-	-
AG	34 (30.9)	21 (21)	0.53	0.273 - 1.035	0.063
GG	2 (1.8)	4 (4)	1.98	0.338 - 11.63	0.4

population (37). Sunder et al. 2011 demonstrated that the GG genotype at *TAP1* position 333 and GA genotype at *TAP1* position 637 were strongly associated with HIV-TB co-infection (38).

Our study for the first time found the significant association of *TAP1*^{333} and *TAP2*^{379} polymorphism with the Scz development in the Iranian sample of patients. These polymorphisms cause different recognition and transport affinity to the same endogenous antigen peptide, and result in various individuals to secretion of different immune cytokines to the same endogenous antigen (39). Nevertheless, our study also had some limitations. First, it is a case-control study, all the participants in this study were Iranian people, and the possibility of ethnicity as a confounding factor could be excluded. Indeed, samples should be included subjects from different geographical and racial backgrounds that could affect the consequences of study. We suggested more studies in larger sample sizes in various populations with advanced techniques as next generation sequencing for finding new polymorphisms.

Acknowledgments

We would like to express our gratitude to the department of biology, university of Sistan and Baluchestan, for supporting this project financially.

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