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Original Article

Single-nucleotide Polymorphism of CTLA-4 (rs5742909) in Correlation with Schizophrenia Risk Factor

Riyadi Sumirtanurdin[1], James P. Laksono[1], Haafizah Dania[2,4], Fitri N. Ramadhani[2], Dyah A. Perwitasari[4], Rizky Abdulah[2,3], Melisa I. Barliana[1,3]

[1]Department of Biological Pharmacy, Biotechnology Pharmacy Laboratory, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia, [2]Department of Pharmacology and Clinical Pharmacy, Clinical Pharmacy Laboratory, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia, [3]Center of Excellence in Higher Education for Pharmaceutical Care Innovation, Universitas Padjadjaran, Bandung, Indonesia, [4]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

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Background: Cytotoxic T protein lymphocyte antigen-4 (CTLA-4) plays a key role in regulating the T-cell system, where occurrence of disturbances in the system seen by imbalance in Th1 and Th2 levels is believed to be one of the etiologies of schizophrenia. Single-nucleotide polymorphisms (SNPs) at rs5742909 in the *CTLA-4* gene (C→T) might affect the expression level of CTLA-4 protein. **Aims and Objectives:** The aim of this study was to determine the genotype distribution of the *CTLA-4* gene (rs5742909) in patients with schizophrenia at Rumah Sakit Jiwa Prof. Dr. Soerojo Magelang and identify the correlation of these genetic polymorphisms as the risk factors of schizophrenia. **Materials and Methods:** This research was conducted through the stage of submitting ethical approval, primer design, chromosomal DNA isolation, optimization of polymerase chain reaction conditions, and data analysis. **Results:** Based on the results of the study, the CC genotype was shown in 36 patients (78.26%), TT genotype in 10 patients (21.73%), and no TT genotypes. However, statistical analysis using Fisher's exact and binary logistic regression statistical test showed no significant relationship between genetic polymorphism of the CTLA-4 rs5742909 against risk factors for schizophrenia ($P = 0.05$; $\alpha = 5\%$). **Conclusion:** SNP at rs5742909, C-to-T-allele transition, was not significant associated with the risk of schizophrenia.

Keywords: *Genetic polymorphism, Magelang, symptom based, T cell*

Introduction

Schizophrenia is a complex syndrome with a combination of heterogeneous symptoms, which positive, negative, and cognitive symptoms.[1] People with schizophrenia are reported to have a life span that tends to be shorter than the general population.[2] On average, the life expectancy of schizophrenics decreases by 20 years as compared with healthy people. Several specific risk factors have been identified related to the development of schizophrenia, including prenatal and perinatal events, paternal age, sex, environment, drug abuse,[3] and immunity.[4]

The change in the immune system in patients with schizophrenia is shown by a decrease in cellular immune system activation.[5] Another study also illustrated

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Address for correspondence: Dr. Melisa Intan Barliana, Department of Biological Pharmacy, Biotechnology Pharmacy Laboratory, Faculty of Pharmacy, Universitas Padjadjaran, Jl. Batununggal Mulia V/6, Bandung 40267, West Java, Indonesia. E-mail: melisa.barliana@unpad.ac.id

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that immunological disorders play an important role in the occurrence of psychosis symptoms in patients with schizophrenia.[6] Furthermore, a study by Soderlund *et al.*[7] showed that there is activation of the immune defense system in the brain in patients with schizophrenia as well as various other data that support that there are similar characters that occur between schizophrenic and autoimmune patients.[8] The T-cell system is a critical component that regulates the immune response so that its role is appropriate. The role of regulation of this system is very necessary for peripheral tolerance, a condition that guarantees that B and T cells do not cause autoimmune.[9] Abnormalities related to the T-cell system, especially disorders of interleukin (IL)-2, -6, and -10, have been reported to be associated with the incidence of schizophrenia.[10]

Cytotoxic T lymphocyte antigen-4 (CTLA-4) protein expressed by genes on chromosome 2q33 is a protein that plays a role in forming and maintaining peripheral tolerance of T cells, which control the activation and reactivity of T cells.[11,12] The *CTLA-4* gene comprises three exons and expresses co-stimulatory molecules, which will then be expressed on the surface of activated T cells and inhibit the activity of the T cells themselves.[13]

Polymorphism that occurs at several loci in the CTLA-4 protein-coding gene is known to be associated with autoimmune disease.[14] One point of polymorphism that is known to be in the promoter of the *CTLA-4* gene which can affect the expression of CTLA-4 protein is rs5742909, where C allele is a wildtype and T allele is mutant form. T allele at rs5742909 are responsible for the elevation of CTLA-4 protein expression.[13] Based on the role of CTLA-4 protein in regulating T cells and evidence that immunity factors play a role in the risk of schizophrenia, it may be possible that genetic polymorphisms in the *CTLA-4* gene (rs5742909) that causes changes in protein expression levels have a relationship between risk factors for schizophrenia.

Materials and Methods

Subject

A group of participant comprising 46 patients who were newly diagnosed with schizophrenia or who had undergone therapy for a maximum of 1 year at Rumah Sakit Jiwa Prof. Dr. Soerojo Magelang and 51 subjects in healthy conditions who did not have neuropsychiatric symptoms were included in this study. The exclusion criteria of the study included schizophrenia patients involved in alcohol/drug abuse, mental and neurological disorders other than schizophrenia, patients with medical records that cannot be traced, and patients who are not willing to approve the study (inform consent). Ethical approval for this study was obtained from the Ethics and Law Committee of Rumah Sakit Jiwa Prof. Dr. Soerojo Magelang (Protocol no. KEH/001/01/2019). The sample used in this study was whole blood and stored at 4°C until analysis.

Single-nucleotide polymorphism analysis

The CTLA-4 rs5742909 genetic polymorphism was determined using the tetra-amplified refractory mutation system-polymerase chain reaction (T-ARMS-PCR) method. The specific primers used are listed in Table 1.[15] The T-ARMS-PCR method was able to identify both variation (single-nucleotide polymorphisms [SNP]) alleles using only one PCR reaction. In T-ARMS-PCR, a normal (outer) primer pair will produce a control amplicon that is not specific to the allele and two other allele- specific primer (inner) is designed in the opposite orientation to amplify precisely at the point of polymorphism. Each of these produces an amplicon-specific allele. These amplicon-specific alleles will have different lengths and can be separated by standard gel electrophoresis as depicted in Figure 1. DNA isolation and amplification was done using Wizard® Genomic DNA Purification Kit (Promega, Fitchburg, Wisconsin) and GoTaq® Green Master Mix (Promega, Fitchburg, Wisconsin), respectively. DNA visualization from amplification process was carried out by scanning under ultraviolet light at a wavelength of 312 nm following electrophoresis on agarose gel (2%) with ethidium bromide stain.

Table 1: T-ARMS-PCR specific primer for CTLA-4 rs5742909 genotype identification

Name	Primer sequence	Amplicon (bp)
318Fo	5′-CAATGAAATGAATTGGACTGGATG-3′	K 296
318Ro	5′-TGCACACACAGAAGGCTCTTGAATA-3′	
318Fi(C)	5′-CTCCACTTAGTTATCCAGATC***T***TC-3′	C 201
318Ri(T)	5′-ACTGAAGCTTCATGTTCACT***C***TA-3	T 141

F = forward, R = reverse, o = outer (common), i = inner (allele-specific), K = size of the control amplicon The specificity of nucleotides is indicated by parentheses[15]

Data analysis

Genotype distribution (CC, TT, or CT) in healthy subjects was analyzed using the Hardy–Weinberg equilibrium equation. Furthermore, to identify the relationship between genetic polymorphism and risk factors for schizophrenia, the Fisher's exact statistical test and binary logistic regression were used. The allele count method is based on previous research by Frydecka *et al*.[26] Each CC genotype means a double number for the C allele as well as on TT genotype, whereas in the CT genotype each number will provide one C and T allele.

Results

Identification of the genetic polymorphism of the CTLA-4 rs5742909 was carried out by the T-ARMS-PCR method, where each genotype was determined based on the size of the band from the electrophoresis separation process [Figures 2 and 3]. However, identification of genotype rs5742909 in patients with schizophrenia, not in healthy subjects, cannot be performed using the T-ARMS PCR method. This is due to the appearance of unknown band with approximately 100-bp length when visualization of DNA amplicon in patients with schizophrenia is being done. This band is might be the results of cross-dimers between one of the primer pairs. Therefore, the process of re-identification of genotypes was carried out in the schizophrenic DNA sample, by separating 318Fo and 318Fi(C) primers so that identification of C and T alleles was carried out on two different tubes [Figure 4].

Table 2 shows that the genotype distribution of rs5742909 genetic polymorphism in normal subjects was 45 subjects having CC (88.23%), 4 subjects with CT (7.84%), and 2 subjects with TT (3.92%) genotype. However in patients with schizophrenia, there were

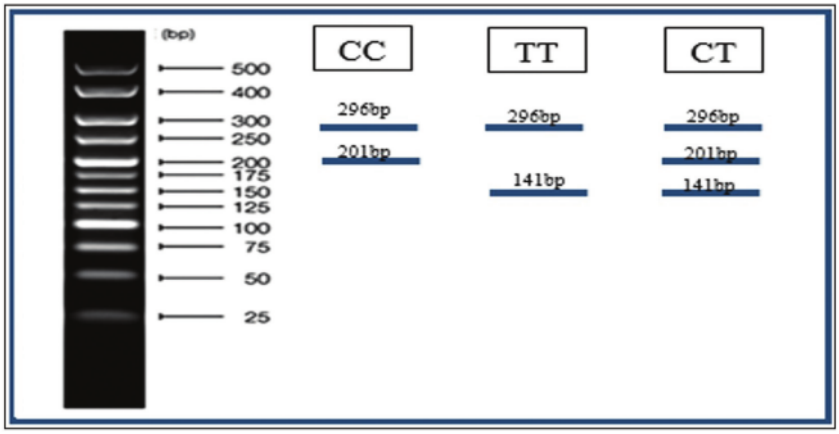

Figure 1: Illustration of band separation, based on genotype difference, following gel electrophoresis

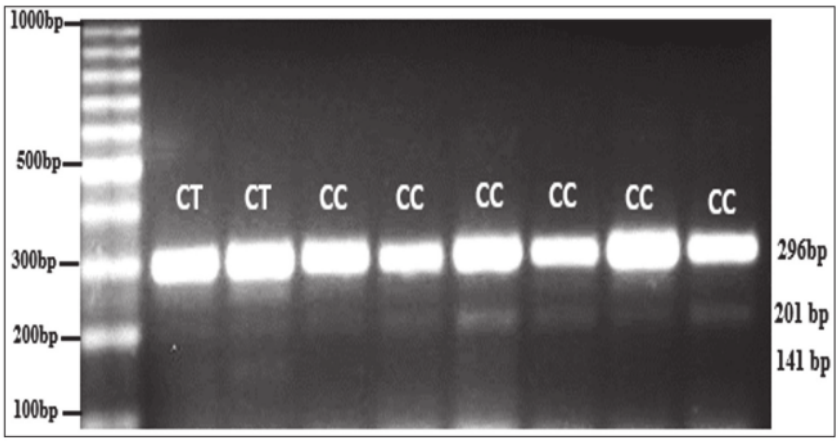

Figure 2: Visualization of DNA amplicon (healthy subjects) with CT and CC genotypes in the CTLA-4 gene rs5742909

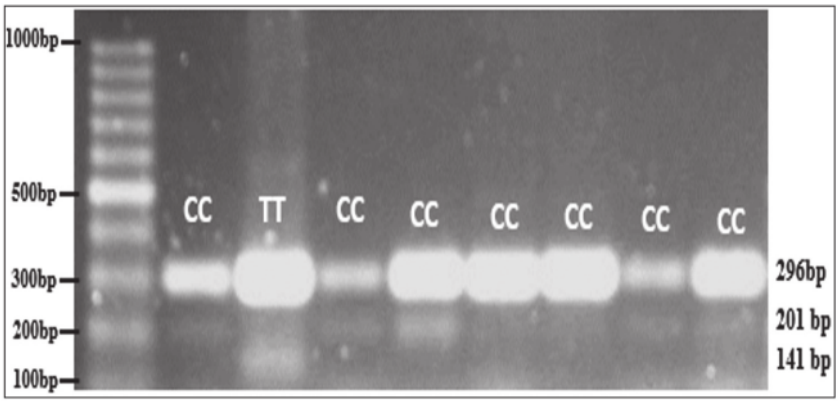

Figure 3: Visualization of DNA amplicon (healthy subjects) with TT and CC genotypes in the CTLA-4 gene rs5742909

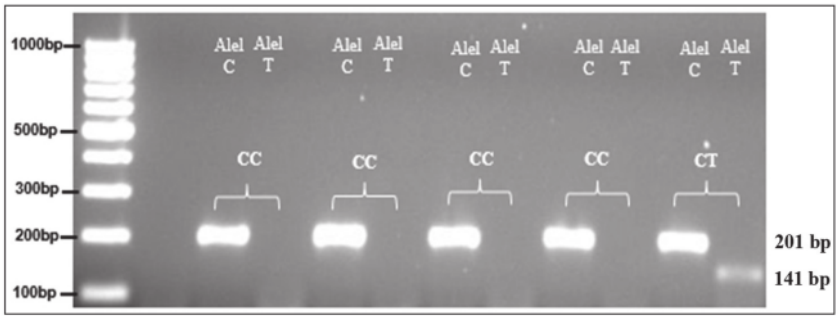

Figure 4: Visualization of DNA amplicon (patient with schizophrenia) in CTLA-4 rs5742909 gene with CC and CT genotypes after primer separation

Table 2: Genotype distribution of genetic polymorphisms of the CTLA-4 gene (rs5742909) in healthy subjects

Genotype	*N*	C allele	T allele	Observed frequency (*nl*%)	Expected frequency (*nl*%)
CC	45	90	0	45 (88.23)	43.31 (84.92)
CT	4	4	4	4 (7.84)	7.37 (14.45)
TT	2	0	4	2 (3.92)	0.31 (0.60)
Total	51	94	8	51 (100)	50.99 (100)

Table 3: Results of statistical tests on the relationship of genetic polymorphism rs5742909 to risk factors for schizophrenia

Genotype	Schizophrenia (*n*%)	Healthy subject (*n*%)	Fisher's exact/ Odds ratio value	*P* value
CC	36 (78.26)	45 (88.23)	4.869	0.050
CT	10 (21.73)	4 (7.84)		
TT	0 (0)	2 (3.92)		
Allele				
C	82 (89.13)	94 (92.15)	2.000	0.097
T	10 (10.86)	8 (7.84)		

36 subjects with CC (78.26%), 10 subjects with CT (21.73%), and no TT genotypes. Genotypic distribution in healthy subjects cannot be analyzed by the Hardy–Weinberg equilibrium test because there are cells in the expected frequency, which have values less than 1.

Furthermore, the results of statistical analysis of the relationship between genotypic variation and the risk of schizophrenia show that there was no significant relationship between genotypic variation and the risk of schizophrenia [Table 3].

Discussion

Various studies showed that patients with schizophrenia tend to have disorders related to T cells, especially

cytokines associated with these cells.[6,10,16] Patients with schizophrenia have a Th1 and Th2 level imbalance as indicated by a decrease in Th1 cytokines (reduced levels of IFN-γ and IL-12) and an increase in Th2 cytokines (increased levels of IL-4, IL-6, and IL-10).[17-19] Th1 cytokines play a key role in stimulating cell-mediated immunity and are generally pro-inflammatory, whereas Th2 cytokines such as IL-4 function in stimulating humoral immunity.[20]

CTLA-4 is an inhibitory receptor that affects T-cell function and plays an important role in the initial phase of the immune response.[21] Following activation of T cells by binding with CD28, CTLA-4 is transported and expressed on the surface of T cell.[22,23] The stronger the stimulation signal through TCR, the more CTLA-4 is expressed and translocated to the surface of T cell.[24] When on the cell surface, signal inhibition from CTLA-4 is transmitted through a bond between B7-1 and B7-2 on active B cells and monocytes. When compared with CD28, binding of CTLA-4 has a higher affinity and prevents subsequent co-stimulation.[25]

Polymorphism at rs5742909 in the form of the C allele transition to T based on previous studies has been known to cause an increase in CLTA-4 protein expression and has the potential to have a protective effect on the risk of schizophrenia.[13] However, the results of this study at the same point of polymorphism failed to show similar results ($P = 0.05$; $\alpha = 0.05$). In this study, it was also found higher C allele percentage in healthy subjects as compared with patients with schizophrenia, whereas the T allele vice versa, which is contrary to the results of a previous study by Kordi-Tamandani *et al.*[13] ($P = 0.097$; OR = 2000).

What can explain this difference is that the genetic-related relationships found in schizophrenia occur specifically.[26] There are numerous studies that showed a significant relationship between genetic polymorphisms with each subtype,[27] syndrome,[28] or even different symptoms in schizophrenia.[29] This suggests that the various clinical phenotypes in schizophrenia are inherited independently and represent one or a particular set of genes found in a individual.[30] It is therefore considered that the symptom-based approach is the best way to identify molecular pathophysiology in schizophrenia.[26]

The study by Frydecka *et al.*[26] that linked genetic polymorphism to the *CTLA-4* rs5742909 with schizophrenic psychopathology through a symptom-based approach showed that the group of patients with schizophrenia who experienced co-occurrence psychostic and affective symptoms had a higher percentage of T alleles as compared with the group of healthy subjects ($P = 0.0057$; OR = 2.34).[26] Another study by Liu *et al.*[31] at the same point of polymorphism carried out in the Chinese Han population also showed that the percentage of T alleles was higher in patients with schizophrenia as compared with healthy subjects, although the correlation with risk factors was not significant ($P = 0.2849$; OR = 0.9128). The results of the aforementioned studies resemble the results of the studies we have conducted in patients with schizophrenia at Rumah Sakit Jiwa Prof. Dr. Soerojo Magelang.

The transition from the C (wild type) allele to the T (mutant) allele in the polymorphism rs5742909 is known to play a role in increasing the expression of CTLA-4 proteins.[13] This increase in CTLA-4 expression will cause a decrease in the IL-2 and IFN-γ.[4] On the contrary, IFN- γ is antagonistic to IL-10[32] so that the decrease of IFN-γ may cause IL-10 levels to no longer be suppressed. An increase in IL-10 that occurs in cerebrospinal fluid has been reported to have a very strong association with the emergence of negative symptoms of schizophrenia.[33] This also might lead to differences in the results of this study with previous studies by Kordi-Tamandani *et al.*,[13] where the dominance of symptoms for the initial diagnosis in patients with schizophrenia involved in the two studies was different so that it influenced the pattern of genotypes and alleles distribution. In conclusion, our results showed that SNP at rs5742909, C-to-T-allele transition, was not significant associated with the risk of schizophrenia.

In our study, patients with schizophrenia still were not selected through symptom-based approach as in Frydecka *et al.*'[26] study, where it was expected that these procedure can be done in future studies. On the contrary, it is necessary to increase sample number and also sequencing procedures to confirm the nucleotide sequence in order to improve the strength of study result.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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