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ORIGINAL ARTICLE

The correlation between polymorphism of interleukin 3 receptor alpha Rs6603272 G/T gene with negative symptoms in Bataknese schizophrenia patients

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ABSTRACT

Aim There are many studies about the correlation between Bataknese and schizophrenia patients, one of the most common ethnic groups in Indonesia. Cytokine and its receptor disorder is one of the scopes of immunology research in schizophrenia. Interleukin 3 (IL-3) is an important cytokine with various biologic roles in immune response. We would like to determine the association between the polymorphism of IL3RA gene with negative symptoms in Bataknese schizophrenia patients.

Methods This study used comparative case control approach. The negative symptoms were assessed using Positive and Negative Syndrome Scale (PANSS). Blood sampling and deoxyribonucleic acid (DNA) isolation used salting out method followed by IL3RA RS6603272 G/T genotype identification using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The data were analysed using $\chi 2$ and Kruskal Wallis test. A $p<0.05$ was considered statistically significant.

Results Two hundred participants were divided into schizophrenia and healthy control groups evenly. G alleles (49.5% and 50.5%) and GT genotypes (49% and 53%) were the most common alleles and phenotypes in both groups with no significant difference in both groups ($p>0.05$). The analysis also did not reveal significant correlation between the polymorphism of IL3RA RS6603272 G/T with the negative symptoms of schizophrenia ($p > 0.05$).

Conclusion There was neither significant difference of the presence of G and T alleles, also GG, GT, and TT genotypes between two groups nor the correlation between polymorphism of IL3RA RS6603272 G/T with schizophrenia negative symptoms.

Keywords: Bataknese, IL3RA RS6603272 G/T gene, polymorphism, schizophrenia negative symptoms

INTRODUCTION

Schizophrenia is a chronic and complex neuropsychiatric disorder with a significant impact on the quality of life of patients and their families. Schizophrenia spectrum disorders affect more than 21 million people globally. Seven out of 1,000 people have schizophrenia spectrum disorder during their lifetime, and the symptoms typically appear in the second or third decade of life. The most common onset of schizophrenia is late adolescence and 20s, but males usually have an earlier onset than females (1,2).

The prevalence of schizophrenia had been increasing from 13.1 million in 1990 to 20.9 million cases in 2016, and most cases (70.8% or 14.8 million) were found in the age group of 25 – 54 years old. East Asia and South Asia had the highest schizophrenia cases, about 7.2 million and 4.0 million, respectively, in 2016. National Basic Health Survey in 2018 revealed that Bali and North Sumatra are provinces with the highest schizophrenia prevalence in Indonesia (11% and 5%, respectively). Medan city has a household prevalence of schizophrenia, in which 6.77% of household members had schizophrenia (2-6). Bataknese is one of the most common ethnic groups in Indonesia, particularly in North Sumatra province, and it is between mountains and a lake that has an island in the middle. Bataknese is the oldest Proto-Melayu ethnicity that has retained its language and tradition for a thousand years, and the use of the native language can still be found. Bataknese was divided into six categories: Mandailing, Angkola, Toba, Dairi or Pakpak Dairi, and Simalungun (7,8).

There are various studies about the correlation between genes and schizophrenia (9). A study in the Psychiatry Department Dr. Soetomo Regional General Hospital Surabaya revealed the high prevalence of COMTVal158Met polymorphism (6.7%) with heterozygote alleles of 21,946 (40%), nucleotide variance

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of T substitute to A of 21,971 (3.3%), and G nucleotide variance in the polymorphism of DISC1 gene in schizophrenia patients (10,11). The investigation of the correlation of 174G/C interleukin-6 polymorphisms with schizophrenia in Batak population showed 174G/C polymorphism as a risk factor (12). It was also demonstrated that there was a strong correlation between interferon gamma +874 A/T in schizophrenia. A significant correlation between the polymorphism of the interleukin-10 1082 G/A gene in Bataknese was found (13,14). Various studies have demonstrated significant correlations between genetic variants in schizophrenia patients (13-16) .

One of the complexities of schizophrenia is the lack of a central pathophysiology mechanism and a main biological marker. The most common hypothesis is the combination of genetic and environmental factors during early life, which is consistent with the neurodevelopmental hypothesis. Although the schizophrenia gene component has a huge impact, most genetic architectures remain unknown. Schizophrenia is a multifactorial disorder that includes interactions of various susceptible genes, epigenetic processes, and environmental factors (17-19). The dysfunction of the immune system and inflammation contribute to the development of schizophrenia. The specific mechanism regarding the correlation of the neuroimmune system and schizophrenia is being investigated, but it is believed that immune dysregulation may impact brain development and function, potentially contributing to the onset of schizophrenia and its clinical manifestations (20,21).

The disorder of cytokines and their receptors is one of the research focuses regarding immunology in schizophrenia (22). Interleukin-3 (IL-3) is an important cytokine that has various biologic roles in immune response. It affects inflammation response in the adult brain development through the regulation of activated microglia, altering the susceptibility of nerve inflammation, and schizophrenia patients have abnormal serum IL-3 levels. A study in China demonstrated that the polymorphism of the Interleukin-3 Receptor Alpha (IL-3RA) gene was correlated with schizophrenia. Furthermore, the IL-3RA rs6603272 gene also plays a role in schizophrenia (20,22).

The correlation between schizophrenia and nerve degeneration in schizophrenia is a complex study. The exact mechanism is still unknown, but there was evidence that nerve inflammation and degeneration contribute to the negative symptoms in schizophrenia (23). However, the specific cause-and-effect relationship between nerve inflammation, degeneration, and negative symptoms in schizophrenia requires further research for better comprehension (24).

The aim of this study was to investigate the correlation of polymorphism of the IL-3RA gene to negative symptoms in the Bataknese schizophrenia and healthy control groups.

PATIENTS AND METHOD

Patients and study design

The study was conducted in the Prof. Dr. M. ldrem Psychiatry Hospital for case group sampling, Blood Transfusion Unit of Medan City for control group sampling, and Integrated Laboratory of Faculty of Medicine, Universitas Sumatera Utara for gene polymorphism examination between April and July 2024. We wanted to determine the association between the polymorphism of interleukin 3 receptor alpha RS6603272 G/T gene with negative symptoms in Bataknese schizophrenia patients.

Consecutive sampling was applied in this study. The inclusion criteria were as follows: Bataknese patients with schizophrenia whose diagnoses were established according to the third edition of the Guidelines for the Classification and Diagnosis of Mental Health Disorders (25); individuals with Bataknese ancestry up to two generations; aged 18–60 years; presenting predominantly negative symptoms (N score < 21); and who were cooperative and agreed to participate in the study. The exclusion criteria included a history of neurological, endocrine, or autoimmune diseases; a history of alcohol or substance use other than nicotine and caffeine; and current or previous use of immunosuppressive drugs (including corticosteroids or cancer treatment regimens).

The participants were divided into schizophrenia and healthy control groups.

We gave a brief explanation to participants before data collection, and they were asked to sign informed consent. The data were kept confidential.

This study had been approved by the Ethics Committee of Faculty of Medicine of (Number: 362/KEPK/USU/2024).

Methods

After informed consent was obtained, the schizophrenia group was asked to fill out the Bahasa version of the Positive and Negative Syndrome Scale (PANSS) (26). The healthy control group was asked to fill out the Mini International Neuropsychiatric Interview (Mini ICD-10) (27) first to exclude other psychiatric disorders. After that, 7 mL of blood was withdrawn from the median cubital vein in stable schizophrenia patients. For the control group, blood was withdrawn just before the donor process. Blood was examined in the Integrated Laboratory of Medicine Faculty at Universitas Sumatra Utara.

After the blood was withdrawn, it was placed in a vacutainer containing ethylenediamine tetraacetic acid (EDTA) and stored at a temperature of 4–80 °C until deoxyribonucleic acid (DNA) isolation was performed. DNA was isolated using the salting-out method (28). After the DNA isolation, IL3RA RS6603272 G/T genotypes were identified using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method (29). Fragments in 133 base pairs (bp), 25 bp, and 158 bp from IL3RA RS6603272 G/T were amplified using forward primer 5 ACGACCTGTACTTGAACGTTGCCAAGTAGGTGGGC-3, reverse primer: 5-AGCATCCGTTTTGTAGTGAAGAC-3. The PCR products were stored at 37 °C overnight with amplified and digested DNA fragments using the EcoR01091 enzyme and then separated in a 3% agarose gel that was stained with ethidium bromide (24). The examination of DNA concentration, check, and purity were conducted using a nanophotometer n-50 with a mean of 1.8.

Statistical analysis

The data were collected using software statistical analysis with the following steps: variable analysis and presented in the frequency tables. The analysis comprises frequency and percentage. The comparative test ($\chi 2$ test) was conducted to assess the difference in allele and IL-3RA RS6603272 G/T genotype between Bataknese schizophrenia and healthy control groups. The odds ratios were calculated (OR>1 indicates that independent variables were not risk or protective factors; OR=1 indicates that independent variables were not risk or protective factors; and OR<1 indicates that independent variables were

the protective factor of dependent variables). The comparative tests were conducted to determine the correlation between the polymorphism of IL3RA RS6603272 G/T and schizophrenia negative symptoms using the Kruskal-Wallis test.

RESULTS

Two hundred band agarose electrophoresis gels were analysed on the IL3RA RS6603272 G/T gene, and the reading was done using the exact method with Sun et al. (20). No deviation from the Hardy–Weinberg Equilibrium was detected for the three polymorphisms (p>0.05). The analysed demographic characteristics in this study (schizophrenia group) were sex, age, onset of the disease, duration of the disease, and the total PANSS negative symptoms score, while in the healthy control group, the characteristics analysed were sex and age. The categorical data were presented in N (%). In contrast, the numeric data were presented in mean and minimum–maximum value.

Most of our participants in both groups were males, comprising 56 (56%) in the healthy control group and 79 (79%) in the schizophrenia group, respectively. The mean age in the healthy control and schizophrenia groups was 28.89 and 32.38 years, respectively. The median onset age of schizophrenia onset was 27 years, and the median duration was 5 years. Most of the schizophrenia participants in the schizophrenia group were rehospitalization patients who received polytherapy, in which clozapine was the most common antipsychotic drug (98%). Most MoCA-Ina scores indicated moderate cognitive impairment. The median of the PANSS negative symptoms score was 25 (Table 1).

Table 1. Demographic characteristics of two patient groups

Variable	Healthy control (N=100)	Bataknese schizophrenia (N=100)
Sex (No; %)		
Male	56 (57)	79 (79)
Female	44 (44)	21 (21)
Age (Mean±SD)	28.89±6.075	32.38±4.4269
	Median (interquartile range)	
Onset (age)	-	27 (14.0-41.00)
Duration (years)	-	5.00 (2.00-21.00)
The total of PANSS negative symptoms score	-	26.93 (21.00-42.00)

PANSS, Positive and Negative Syndrome Scale

The polymorphism of the IL3RA RS6603272 G/T gene consisted of two alleles: G and T. The allele variable was a categorical (nominal) variable and presented in a frequency distribution. The G allele was the most common in both groups. There was no significant difference in G and T allele presence between the two groups (p>0.05), with an odds ratio (OR) of approximately 0.961 (close to 1), indicating that the independent variable was not a risk factor for schizophrenia. The genotype variant of the IL3RA RS6603272 G/T gene consisted of a combination of the G and T alleles, represented by the GT, GG, and TT genotypes. The GT genotype was the most common in the schizophrenia and control groups (49% and 53%, respectively) (Table 2).

The result of binary binomial logistic regression analysis demonstrated no significant difference regarding the presence of the GT genotype in healthy controls and schizophrenia groups, with a p=0.479 and OR of 1.288 (GT versus TT). However, based on the OR value, the distribution of GT and GG genotypes in healthy controls was a risk factor for schizophrenia. The p=0.667 (OR 1.190)-for the GT and GG genotypes was found. This result indicates that there were no significant differences in the presence of the GG genotype between the two groups, and the OR value revealed that the difference in the distribution of GG and TT genotypes was not considered a risk factor for schizophrenia (Table 2).

Table 2. Differences of IL3RA RS6603272 G/T gene alleles and genotypes in healthy control and schizophrenia groups

Variable	No (%) of patients		p	OR (95% CI)
	Schizophrenia	Healthy control		
IL-3RA RS6603272 Allele				
G	102 (49.5)	104 (50.5)	0.920	0.961 (0.649-1.422)
T	98 (50.5)	96 (49.5)		
Total	200	200		
The Polymorphism IL-3RA RS6603272 Genotypes				
G/T	49 (49)	53 (53)	0.478	1.288 (0.641-2.588)
G/G	26 (26)	26 (26)	0.667	1.190 (0.538-2.636)
T/T	25 (25)	21 (21)		
Total	100	100		

Bataknese schizophrenia patients with mean scores of 27.57, 24.85, and 25.84 for the GG, GT, and TT genotypes, respectively, with p = 0.762 (> 0.05), were found. Furthermore, the mean score of the Bataknese schizophrenia group with G and T alleles was 27.41 and 26.95, respectively, with a p=0.308 (> 0.05). It can be concluded that there is no significant correlation between the polymorphism of IL3RA RS6603272 G/T with negative symptoms in the Bataknese schizophrenia group (Table 3).

Table 3. Correlation between T genotype and polymorphism of IL-3 RS 6603272 G/T gene with negative symptoms in schizophrenia patients

Variable	Genes	N	Mean	p
Genotypes (N=100)	GG	49	27.57	0.763
	GT	26	24.58	
	TT	25	25.84	
Allele (N=200)	G	102	27.41	0.308
	T	98	26.95	

PANSS, Positive and Negative Syndrome Scale

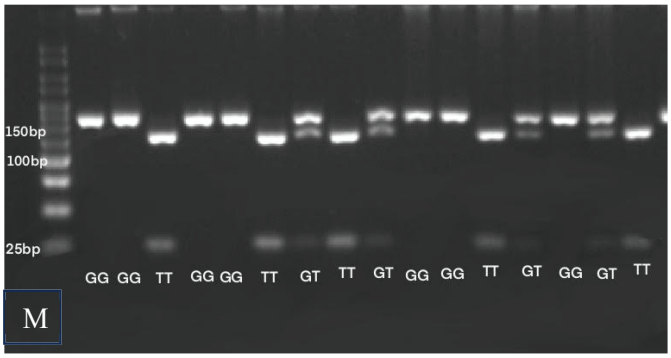

Figure 1. Agarose electrophoresis gel of the polymorphism of IL3RA RS6603272 G/T Gene

1st row = marker (M), base pair 25 = base pair ladder, base pair 158= allele G, base pair 23 and 133 = T allele; 2nd row = GG genotype; 3rd row = GT genotype, 6th row = TT genotype

DISCUSSION

Most participants in this study were males with an age range of 23 – 50 years in the schizophrenia group. It is similar with previous studies (1,19,20) although there are opposite results with no significant prevalence of schizophrenia between males and females (30). The reason for higher schizophrenia prevalence in males may be due to the lower medication adherence and higher relapse rate in males, as well as a relative difference in help-seeking between males and females, and a higher substance misuse rate in males (31,32). The analysis of age of onset in this study was in line with other studies which found that the most common onset of schizophrenia was in the age group of 19 to 51 years (33). An epidemiology study from Spain also found that the highest prevalence of schizophrenia was found in males in the age group of 35- 54 years (1,33).

There was no significant difference in the presence of the allele between the two groups. However, a study in China found a significant difference in alleles between schizophrenia and healthy control groups, in which the T allele is more common in schizophrenia patients compared to healthy controls, with a significant correlation (22). The inconsistency between those studies may be due to different inclusion criteria and ethnicity. Furthermore, environmental and lifestyle factors may play an important role in schizophrenia development, leading to the variance in results between studies. Interleukin-3 may contribute to various immunological disorders, consistent with the hypothesis that cytokine disorders in schizophrenia have a strong genetic basis. However, the functional aspect of the rs6604272 polymorphism in IL-3RA is still unknown. Further studies are required to determine if this gene polymorphism is associated with increased peripheral IL-3 value in schizophrenia patients, particularly chronic patients (33-35).

We found no significant difference in the genotype polymorphism of the IL3RA RS6603272 G/T gene between the two groups. It was not consistent with previous studies that demonstrated a correlation between the polymorphism of the IL3RA RS6603272 G/T gene and schizophrenia prevalence. The inconsistency between these studies may be due to differences in inclusion criteria, sample size, and ethnicity. Additionally, the increased serum IL-3RA level was confirmed in the studies prior to the polymorphism study. The different results of similar polymorphism may appear due to several factors, such as different effects from similar polymorphism genetic factors, which depend on the individual's whole genetic arrangement, also environmental factors, such as dietary habits, lifestyle, toxic exposure, and stress (22,36). The epigenetic modification role, such as DNA methylation and histone modification, can alter gene expression without altering the DNA sequence (37). The polymorphism regarding the disease risk may only express those risks in certain conditions. These single or combination factors may cause similar polymorphism with different results in different individuals or conditions. The different findings in this study may be influenced by factors such as varying standards for antipsychotic drugs, sample size, and differing inclusion and exclusion criteria across studies (38).

The analysis revealed no significant correlation between IL-3RA RS6603272 G/T gene alleles and genotypes with schizophrenia negative symptoms. This study is the first to determine the correlation between the polymorphism of the IL3RA RS6603272 G/T gene and negative symptoms. However, numerous studies have investigated the correlation between gene polymorphism and negative symptoms, particularly those involving immune-related genes. Several studies have reported correlated results, finding a significant positive correlation between immune-related genes and schizophrenia negative symptoms, specifically the polymorphisms of IL-1β, IL-2, IL-6, and TNF-α genes (39,40).

Several studies also demonstrated the correlation between peripheral inflammation biomarkers and negative symptoms. An increased inflammation cascade, characterized by heightened immune activity, pro-inflammatory cytokine production, and oxidative stress, was found in schizophrenia patients. The interaction between these factors contributes to serotonergic, dopaminergic, and glutamatergic neurotransmission disorders, leading to negative symptoms (21,40,41). Peripheral immune response reflects central neuroimmune status; therefore, systemic cytokine concentration is more relevant to reflect how inflammation leads to a specific symptom profile in schizophrenia. The balance between peripheral Th1 and Th2 inflammatory responses and cytokine production is crucial for efficient immune response; therefore, their imbalance may affect Th2 differentiation and secretion. Reportedly, increased IL-3 serum levels in schizophrenia patients, particularly in chronic patients, and their correlation analysis demonstrated the correlation between increased serum IL-3 levels and negative symptoms score. A genetic study also demonstrated that IL-3 and IL-3RA genes are located near the schizophrenia-associated genetic marker in pseudo-autosomal region (PAR1) from X and Y chromosomes, in which the abnormality of IL-3 and its receptor contributes to increased granulocyte-macrophage colony stimulating factor (GM-CSF), which encourages inflammation, and may play a role in the manifestation of schizophrenia symptoms (21,38,42).

Previous studies supported the hypothesis that pro-inflammatory cytokines in the peripheral body system increased in schizophrenia. However, the manifestation of schizophrenia symptoms varied and was affected by the complex interaction between genetic, epigenetic, environmental, and neuronal developmental factors. These interactions may lead to similar polymorphism in patients with different symptoms. Each person has a unique genetic arrangement, and other genetic variants may interact with polymorphisms, altering their effects. This interaction may alter how certain polymorphisms contribute to the development of symptoms. Schizophrenia-related polymorphism can lead to different symptom profiles, depending on certain life events in the environmental context (22,38,43).

This study was the first in Indonesia and Medan to investigate one ethnic group, the Bataknese, specifically reporting the demography of genotypes and alleles of the polymorphism of the IL3RA RS6603272 G/T gene in North Sumatra. This study may be the foundation of future studies regarding the correlation polymorphism of gene for another ethnic group in Indonesia or other countries with schizophrenia to extend the knowledge between gene and schizophrenia.

Our study has several limitations such as the confounding factors of cytokines that cannot be fully controlled, and the small sample size.

In conclusion, there was neither significant difference regarding the presence of G and T alleles also GG, GT, and TT genotypes between both groups nor significant correlation between the polymorphism of IL3RA RS6603272 G/T allele with negative symptoms of schizophrenia.

AUTHORS CONTRIBUTION

Conceptualization D.A.A, E.E, and M.M.A; methodology, D.A.A, E.E, and M.M.A; software, D.A.A; validation D.A.A; formal analysis, D.A.A and E.E; investigation. D.A.A; resources D.A.A and E.E; data curation D.A.A and E.E; writing (first draft) D.A.A and E.E; writing (review and editing), D.A.A, E.E, M.M.A, V.C, Z.Y; visualization D.A.A, E.E, M.M.A, V.C, Z.Y; study registration and funding, D.A.A.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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