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The Relation of Gene Polymorphism Interferon Gamma+874 A/T and Schizophrenia Occurred in Batak Ethnicity

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Abstract

BACKGROUND: Massive heritability occurs in schizophrenia. Gene identification which is defenceless against this disorder is difficult to be proven. The potential aspect of gen vulnerability in developing schizophrenic symptoms, for instance, is shown by several complex gene of tumor necrosis factor-alpha, interleukin (IL)-1, IL-6, and IL-10.

AIMS: The aim of the study was to investigate the relationship of gene polymorphism of interferon-gamma (IFN-γ) +874 A/T and schizophrenia symptoms to Batak's schizophrenic patients.

METHODS: This study is a case–control study involved with 248 subjects from Prof. M. Ildrem Medan Hospital. The subjects were divided into two groups, the first group (124 subjects) was recruited as the case group, while the other 124 subjects were grouped as control cases with ages of 20–55 years of old. The case study group was hospitalized patients in the hospital, while the control group is those donors in the blood transfusion unit at Pirngadi General Hospital, Medan, Indonesia. IFN-γ +874 A/T gene polymorphism was examined by polymerase chain reaction-restriction fragment length polymorphism method.

RESULTS: Genotype AT frequencies from gen IFN-γ +874 A/T were found higher in case study than those from control groups, which were accounted for 43.5% and 41.1%, respectively, with p = 0.005, odds ratio (OR) = 2.83 95% confidence interval (CI) 1.36–5.86. The allele T was displayed higher in case group compared to control groups contributed for 46.0% and 33.5%, respectively, with p = 0.006, OR = 0.59 95% (CI) 0.41–0.85, (p = 0.006).

CONCLUSIONS: There was a relationship between gen IFN-γ +874 A/T and schizophrenia on Batak ethnicity with schizophrenic disorder. The genotype AT contributes for increasing schizoprenic risk up to 2.83 times.

Introduction

In global population, around 1% of people have suffered chronic schizophrenia disorders. This disorder is indicated by acute conditions in cognitive, emotions, and social functions [1,2]. The unclear etiology causes schizophrenia to be one of the complicated diseases. It is estimated that the interaction between gene and environment factors can cause the development of schizophrenia. On the other hand, psychosocial factors could have contributed to schizophrenia [3], [4].

In terms of heritability, schizophrenia has a broad feature due to the difficulties of the evidence in confirming the risks. Although no genes that have been identified particularly for schizophrenia, several candidates have been known to have relations to the vulnerability of schizophrenia and they can be used as indicators for schizophrenic pathophysiology [5], [6]. Many genes that have selected as the indicator have been extensively to have relations to schizophrenia. Those genes that can affect the development of schizophrenia are coded-cytokines genes which relate to the central nervous system. The communication between peripheral cytokines and brain cells due to pathological conditions may have been caused by passive transportations, secondary messenger, active transportation, and nerve terminals. Due to the stress-effect of cytokines regulations, this protein might have played roles that are relevant to the main psychiatry disorders [4]. Potential reason for genes vulnerability in developing schizophrenia, for instance, could have been shown in several complex genes such as tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-1, IL-6, and IL-10. Several studies have reported the involvement of interferon-gamma (IFN-γ) in neuropsychiatry disorders [7].

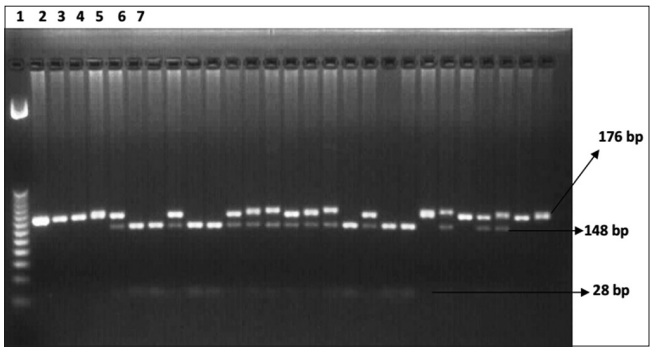
IFN is a pleiotropic cytokines that have antivirus characteristics, antiproliferative, and immunomodulator activities [8]. The IFN has a function as an indicator of molecular immunes, while the gamma IFN is a pro-inflammation cytokine considered as genes for causing the emergence of psychosis [1]. A study has reported that the decrease of IFN-γ and IL-2 productions in schizophrenic patients (ODS) [7].

Several studies have been carried out to locate specific chromosome in ODS genes. Possibility features that have been proven are polymorphism cytokines, which show vulnerability in the development of schizophrenic due to the infection of or ischemia related to the process of nerve development [9]. An evidence

of polymorphism of +874 A/T in the first intron genes that have IFN-γ sequence is related to the production of this molecule. The presence of AA genotypes is related to the low cytokines productions, while the genotypes AT and TT, respectively, have relations in producing medium and high cytokines productions [10].

Studies that have investigated the relationship between polymorphism promotor to the gene encoding IFN-γ and the development of schizophrenia are still rare. A study conducted by Samojedny *et al*., 2010, for Polish population, involved 179 ODS and 196 healthy control patients showed no relationships. This study used allele-specific method polymerase chain reaction (PCR), and this study found the relations between gen polymorphism IFN-γ +874 T/A to the paranoid schizophrenic cases of male schizophrenic patients; however, no relationships were found to female schizophrenic patients to the odds ratio (OR) 10.53 (2.75–40, 30, 95% confidence interval [CI]) [7]. In contrast, Tamandani *et al*., 2019, in Iran have investigated by performing amplification mutation system PCR, which found different results from the other studies, and this study also found no relations between gen polymorphism IFN-γ (+874 A/T) and schizophrenia case in Iranian population [9]. On the other hand, Jemli *et al*., 2016, carried out a similar study to investigate the presence of related polymorphism gen and schizophrenic cases of Tunis people. This study involved 218 ODS and 162 control group by performing PCR-restriction fragment length polymorphism (PCR-RFLP) in finding the genotype, and this study found the presence of gen polymorphism IFN-γ (+874 A/T) with the schizophrenic Tunis patients, which contributed for 1.40 times of risks due to the presence of allele T and 2.64 times of risks from genotype TT [11].

The identification of genes that cause schizophrenia still needs to be confirmed [6], [12], [13] due to the inconsistent results from several studies [14-16]. These inconsistencies could have caused by the small size effects, heterogeneity within the samples, unsuitable hypothesis, as well as the limited knowledge in genetic understanding. Moreover, the diversities of the results perhaps are affected by specific ethnicities or uncertain backgrounds [3]. A logical approach to investigate these uncertain inconsistencies is by carrying a replication study to obtain required information including different number of samples, more homogeneity of samples from different ethnic so that it can help to identify different genes that are suspected to schizophrenic disorders [9]. Based on the above introduction, this study aims to investigate the effect of gen polymorphism IFN-γ (+874 A/T) in Batak ethnics.



AQ4 *Figure 1: Electrophoresis of agarose gel restriction fragment length polymorphism interferon-gamma +874 A/T single-nucleotide polymorphism*

Research Methodologies

Population

This study is a case–control study design for Batak ethnicities, which is one of the local tribes in North Sumatera, Indonesia. One hundred and twenty-four of Batak's schizophrenic patients and 124 healthy control group of Bataknese were recruited. All subjects are original Batak people from the second generation.

Case

Study cases are hospitalized patients from the Mental Hospital of Prof. Muhammad Ildrem Medan, North Sumatera Province, Indonesia. The diagnosis of schizophrenia was conducted based on the criteria of the diagnostic and statistical manual of mental disorder, fifth edition [17], and they were diagnosed by three independent psychiatrists. Positive and negative symptom scale scores were measured by well-trained residents, and the cases had 20–55 ages which have been prescribed with risperidone antipsychotic.

Control

The control group was recruited from hospital donors at the blood transfusion unit of Pirngadi general hospital, Medan, North Sumatera, Indonesia. This group was interviewed based on the mini international neuropsychiatric interview to avoid other psychiatric symptoms. The inclusion criteria included ages between 20 and 55 years of old without experience mental disorders, hypertension condition, auto-immune illnesses, and family heritability of mental disorders.

DNA isolation

In isolating the DNA, first, the amount of 3 ml of EDTA was centrifuged at 3000 rpm for 10 min. Then, the amount of obtained plasma was separated so that the leukocyte was obtained. This white blood cell was collected for 300 μL, which was then placed into 1.5 ml of the Eppendorf tube. Next, the sample was added by 900 μL of EL Buffer and it was mixed by turning the tube up and down. Afterward, the sample was incubated

for 10 min, and it was followed by centrifugation within 13,000 rpm for 3 min to obtain white supernatant. After white precipitation being obtained, the tube was added by 300 µL of nuclei lysis solution to be mixed, and then as many as 100 µL of protein precipitation was added. Before the mixture was centrifuged at 13,000 rpm again at 3 min, the mixture was shaken by vortex instrument. The supernatant that was obtained after centrifugation was placed into another Eppendorf tube that was already contained 300 µL of isopropanol. The tube then was turned up and down to obtain thread-like DNA. This mixture was centrifuged again at 13,000 rpm for 1 min, and the supernatant was removed which is followed by the addition of 70% of ethanol. This mixture was centrifuged again at 13,000 rpm for 1 min so that the separation between ethanol and precipitation was occurred. The ethanol liquid was collected by pipetting and it was heated to be dry for 1 h. After being dried, the dried-sample was poured by 100 µL of DNA and rehydration solution, and it was incubated at 40°C for a night. Finally, the DNA sample was stored inside a freezer at −20°C until the PCR-RFLP step was carried out.

The PCR-RFLP

The method of PCR-RFLP was performed according to Jemli *et al*. [11] and Zambon *et al*. [18] using patients and control genotypes within the variant of IFN-γ +874 A/T. Total of 176 bp IFN-γ +874 A/T, forward primer 5'-GATTTTATTCTTACAACACAAAATCAAGAC-3' and backward primer 5'-GCAAAGCCACCCCACTATAA-3' are used. The PCR was performed by these steps. First, denaturation was carried out at 10 min at 95°C which was followed by 35 cycles of denaturation within 30 s at 95°C and anil within 1 min at 53°C. Then, the denaturation step was extended for 1 min and 30 s at 72°C. The final extension step of the cycle was conducted for a minute at 72°C. The PCR reaction was done within 25 µL of volume reaction, with 0.2 mM dNTPs, 1.5 mM $MgCl_2$, 1 × Taq buffer of polymerase 1 U Taq DNA polymerase (Wizard genomic DNA purification kit, AS), 1 µM and respective primer, and 100 ng genomic DNA. The PCR product (176 bp) was incorporated by HinfI enzymes for 4 h at 370°C. The restriction fragment (176 bp for A allele, 148 bp, and 28 bp for T allele) was separated throughout electrophoresis in 3% of agarose gel, and it was colored by ethidium bromide.

The first line is a marker, 25 base pair ladder. The second line is PCR product, and the third, fourth, and fifth lines are AA homozygotes. The sixth line is AT heterozygote, while the seventh line is TT homozygote. Meanwhile, the RFLP 176 bp is for A allele, and both of 148 and 28 bp are for T allele (Figure 1).

Statistical analysis

Regarding the invariant genotype is not depending on times, this study utilized case–control to examine the genetical association of INF-γ +874 A/T to schizophrenia. The distribution of genotype frequencies which is in accordance with Hardy–Weinberg Equilibrium was analyzed by the Chi-square test. The OR with trust interval for 95% CI was used to estimate the relation of schizophrenic risks and gene polymorphism, and it was evaluated using the logistic regression analysis. Statistical significances were classified as $p < 0.05$. SPSS software analysis was utilized to determine the qualitative and quantitative data analysis.

Ethics

This study was carried out after receiving the written consent agreed by all of the subjects. The study was designed in accordance with Helsinki Declaration and it has been accepted by the Committee Ethics of Research of Medical Faculty of Universitas Sumatera, Indonesia

Results

Demographic characteristics

In Table 1, it was found that no significant differences among ages and genders of the case and control group. The other demographical characteristics of both groups are presented in Table 1.

Table 1: Demographic characteristics

Variable	Patients (n=124)	Control (n=124)	p-value
Sex			
Male	100 (80.6)	96 (77.4)	0.64*
Female	24 (19.4)	28 (22.6)	
Age (years)	37 (22–59)	35 (20–52)	0.003**
Educational level			
Low	51 (41.1)	5 (4)	<0.001*
Medium	66 (53.2)	49 (39.5)	
High	7 (5.6)	70 (56.5)	
Working status			
Employed	27 (21.8)	103 (83.1)	<0.001*
Unemployed	97 (78.2)	21 (16.9)	
Onset of psychotic	29 (19–39)		
Duration of illness	8.5 (1–25)		
Positive and negative symptom scale	100 (80–120)		

*Chi-square, **Mann–Whitney U.

The genetic analysis of IFN-γ +874 A/T was examined in both case and control groups. Table 2 shows the frequency distribution of allele and genotype from both groups. The AT genotype frequencies of the case group were found to be higher than those from the control group, which contributed to 43.5% and 41.1%, $p = 0.005$, OR = 2.83, respectively. For allele frequencies, the T allele was higher in the case group compared to those from the control group which accounted for 46.8% and 33.5% $p = 0.003$, OR = 0.57, respectively.

Table 3 presents different models, such as dominant, recessive, and overdominant. In recessive

Table 2: Genotype and allele frequencies of interferon +874A/T gene polymorphism in controls and schizophrenic patients

Genotype	Patients (n=124)	Controls (n=124)	p-value	Odds ratio (95% confidence interval)
AA	39 (31.5)	57 (46)	0.005	2.83 (1.36–5.86)
AT	54 (43.5)	51 (41.1)	0.09	1.83 (0.89–3.79)
TT	31 (25)	16 (12.9)	Comparison	
Allele				
A	132 (53.3)	165 (66.5)	0.003	0.57 (0.39–0.82)
T	116 (46.8)	83 (33.5)		

model, the TT genotype frequencies were found to be higher in the case group than those from the control, while the patients who had AA-AT genotype had higher risks to develop schizophrenia compared to those who had genotype of TT.

Table 3: Odds ratio calculated assuming a different model of inheritance of the IFN +874A/T gene genotype

IFN-γ +874 A/T	Patients n=124 (%)	Control n=124 (%)	p-value	Odds ratio (95% confidence interval)
Dominant				
AA	39 (31.5)	57 (46.0)	0.02	1.00
AT-TT	85 (68.5)	67 (54.0)		0.53 (0.32–0.90)
Recessive				
TT	31 (25.0)	16 (12.9)	0.02	1.00
AA-AT	93 (75.0)	108 (87.1)		2.25 (1.15–4.37)
Overdominant				
AA/TT	70 (56.5)	73 (58.9)	0.79	1.00
AT	54 (43.5)	51 (41.1)		0.90 (0.54–1.49)

IFN: Interferon.

Discussion

This study is the first study that reports the relation between gene polymorphism of IFN-γ +874 A/T and schizophrenic disorders in Indonesia, in particular for Batak ethnicity.

One of the main concerns in an associative study is the inappropriate relation whether positive or negative could be occurred due to the differences of genetic cultural background between case and control group. Ancestor genetic, in which the case and control group was taken from two different population, might also be confused of the variety, while the heterogeneity genetics appear due to the fusion within the population. This presence of different fusion from the ancestors which continuously passed on to the offspring causes two or more than two of the original ancestors' genes. This fusion increases complexity within the structure of the population. In the second generation of the population, 1/16 individuals would have owned high risks of characteristics bestowed from their four predecessors, and the other 1/16 might have had lower risks from their predecessors [19,20]. Based on these considerations, this study recruited 248 subjects who had the same ethnic backgrounds, and they were Batak ethnic who were the second generation of their families.

Several studies have attempted to replicate the relation of this gen in varied populations; however, the results were found to be different. Tamandani *et al*. have suggested that no involvement of the IFN-γ +874 A/T gene in developing the risks of schizophrenia, whereas Samojedny *et al*. and Jemli *et al*. have stated that the polymorphism in the first intron of this gen was related to the development of schizophrenic disorders. In this study, the results demonstrated that the case group had higher percentage of A allele compared to those found from the control group which contributed for 66.5% and 54%, respectively, while the percentage of T allele was found to be also higher in case groups than those from control group which accounted for 46% and 33.5%, respectively [9]. These proportions were different from those who were found by Samojedny *et al*. due to their results. Their findings have reported that the A and T alleles in the case group, respectively, were 51.12% and 48.88%, while in the control group was found to have 44.64% and 55.36%, respectively [7]. Our findings were in accordance with the results obtained by Jemli *et al*. [11], in which A allele was found to be higher in the control group, and the T allele was higher in the case group. In the genotype level, this study found that the AT genotype had a higher proportion among patients, while the AA genotype was higher among the control group. The trends in the case group were found to be as exact as those reported by Samojedny *et al.* [7]. In the control group, Jemli *et al*. have reported that the TT recessive genotype increased the risk of the development of schizophrenia for 2.25 times higher compared to those caused by genotype AA-AT.

Schizophrenia is a syndrome which has different pathological mechanisms, which possibly contributes to increasing abnormalities, and this indicates that the limited immune pathology in sub-case group [21]. The other explanation that perhaps points out the difference of frequencies between previous studies and our findings is the impact of polymorphism in altering the population to be vulnerable to illnesses. Polymorphism could have continuously inherited to the offspring so that the polymorphism frequencies in different ethnicities might have been different from each other [22].

In general, we found that the relation between gen polymorphism of IFN-γ +874 A/T and schizophrenia in Bataknese population in the genotype level. The AA genotype was found to increase the risks of schizophrenic disorders due to the statistical analysis results including OR = 2.83, 95% (CI) 1.36–5.86, p = 0.005. Jemli *et al*. have found that the relations between gen polymorphism of IFN-γ +874 A/T were affiliated to the increased risk of schizophrenia among Tunis people, in which the TT genotype increased the case of schizophrenia for 2.64 times [11]. Samodjeni stated that the gen polymorphism of IFN-γ +874 A/T was contributed to the presence of schizophrenia in males, but none was found in females. They focused on the presence of A allele which correlated to the higher risks of developing schizophrenia for 1.66 times in Polish males [7].

The relation between polymorphism of A/T INF-γ

+874 A/T and schizophrenia, which has been found in this study may suggest the significant ethiology from this gene polymorphism in developing schizophrenia among Bataknese populations. IFN was pro-inflammation cytokines which can cause psychosis. Although IFN is mainly secreted by the T-helper lymphocyte type 1 helper and NK cell, this molecular mechanism that IFN-γ and its receptor was produced within the body is needed by nerve system in particular for neuron and glial cells [7,11,21]. It was hypothetically coined out that demyelination might be used cooperatively with direct damages in oligodendrocytes, or the activation of macrophage, and microglia, which is determined by the expression of IFN-γ [23]. On the other hand, IFN-γ is a major histocompatibility (MHC0) which can help to act in responding to the synaptic plasticity and glial reactivity [11,24]. This gen also plays an important role in the activation of varied pathological central nervous systems because of its role in increasing the microglia by intensifying the production of several cytokines, such as TNF-α, nitrate oxides, and free radicals [4,25,26].

Conclusions

This study concludes that relationship between gen polymorphism of IFN-γ +874 A/T and schizophrenic disorders was found among Bataknese. The AA genotype increases the risk of schizophrenia to 2.83 times in Batak ethnics. In the recessive model, the TT genotype raises the risks of this disorder into 2.25 times in Batak people.

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References

1. Kim HJ, Eom CY, Kwon J, Joo J, Lee S, Nah SS, *et al*. Roles of interferon-gamma and its target genes in schizophrenia: Proteomics-based reverse genetics from mouse to human. Proteomics. 2012;12(11):1815-29. https://doi.org/10.1002/pmic.201100184
PMid:22623148
2. Light G, Greenwood TA, Swerdlow NR, Calkins ME, Freedman R, Green MF, *et al*. Comparison of the heritability of schizophrenia and endophenotypes in the COGS-1 family study. Schizophr Bull. 2014;40(6):1404-11.
PMid:24903414
3. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: Overview and treatment options. P T. 2014;39(1):638-45.
PMid:25210417
4. World Health Organization. Schizophrenia; 2015. Available: https://www.who.int/news-room/factsheets/detail/schizophrenia. [Last accessed on 2018 Jun 12].
5. Kanazawa T, Bousman CA, Liu C, Everall IP. Schizophrenia genetics in the genome-wide era: A review of Japanese studies. NPJ Schizophr. 2017;3(1):27. https://doi.org/10.1038/s41537-017-0028-2
PMid:28855529
6. Dai N. Investigation of Findings of Recent Schizophrenia Genome Wide Association and Linkage Studies in Indonesian Samples. Thesis School of Psychiatry and Clinical Neuroscience. Australia: The University of Western Australia; 2013. p. 1-200.
7. Paul-Samojedny M, Owczarek A, Suchanek R, Kowalczyk M, Fila-Danilow A, Borkowska P, *et al*. Association study of interferon gamma (IFN-γ) +874T/A gene polymorphism in patients with paranoid schizophrenia. J Mol Neurosci 2011;43(3):309-15. https://doi.org/10.1007/s12031-010-9442-x
PMid:20821074
8. Kontsek P, Kontseková E. Forty years of interferon. Acta Virol. 1997;41(6):349-53.
9. Tamandani DM, Najafi M, Mojahed A, Shahraki A. Analysis of IFN-? (++874 A/T) and IL-10 (-1082 G/A) genes polymorphisms with risk of schizophrenia. J Cell Mol Res. 2014;6:64-8.
10. Pravica V, Asderakis A, Perrey C, Hajeer A, Sinnott PJ, Hutchinson IV. *In vitro* production of IFN-gamma correlates with CA repeat polymorphism in the human IFN-gamma gene. Eur J Immunogenet. 1999;26(1):1-3. https://doi.org/10.1046/j.1365-2370.1999.00122.x
PMid:10068907
11. Jemli A, Eshili A, Trifa F, Mechri A, Zaafrane F, Gaha L, *et al*. Association of the IFN-? (++874 A/T) genetic polymorphism with paranoid schizophrenia in tunisian population. Immunol Invest. 2016;???:13. https://doi.org/10.1080/08820139.2016.1237523 AQ6
12. Giegling I, Hosak L, Mössner R, Serretti A, Bellivier F, Claes S, *et al*. Genetics of schizophrenia: A consensus paper of the WFSBP task force on genetics. World J Biol Psychiatry. 2017;18(7):492-505. https://doi.org/10.1080/15622975.2016.1268715
13. Machado EZ, Duarte FA. Localization of genes modulating the predisposition to schizophrenia: A revision. Genet Mol Biol. 2000;23(3):549-56. https://doi.org/10.1590/s1415-47572000000300009
14. Chen J, Cao F, Liu L, Wang L, Chen X. Genetic studies of schizophrenia: An update. Neurosci Bull. 2015;31(1):87-98.
PMid:25652814
15. Voisey J, Swagell CD, Hughes IP, Lawford BR, Young RM, Morris CP. Analysis of HapMap tag-SNPs in dysbindin (DTNBP1) reveals evidence of consistent association with schizophrenia. Eur Psychiatry. 2010;25(6):314-9. https://doi.org/10.1016/j.eurpsy.2009.11.011
PMid:20615671
16. Shi J, Gershon ES, Liu C. Genetic associations with schizophrenia: Meta-analyses of 12 candidate genes. Schizophr Res 2008;104(1-3):96-107. https://doi.org/10.1016/j.schres.2008.06.016
PMid:18715757

17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Philadelphia, PA: American Psychiatric Publishing; 2013. p. 33-40.
18. Zambon CF, Basso D, Navaglia F, Belluco C, Falda A, Fogar P, *et al*. Pro and anti-inflammatory cytokines gene polymorphisms and *Helicobacter pylori* infection: Interactions influence outcome. Cytokine. 2005;29(4):141-52. https://doi.org/10.1016/j.cyto.2004.10.013
PMid:15652446
19. Karki R, Pandya D, Elston RC, Ferlini C. Defining "mutation" and "polymorphism" in the era of personal genomics. BMC Med Genomics. 2015;8:37. https://doi.org/10.1186/s12920-015-0115-z
PMid:26173390
20. Hu D, Ziv E. Confounding in genetic association studies and its solution. Pharmacogenomics Drug Discov Dev. 2008;448:31-9.
PMid:18370229
21. Orgogozo V, Morizot B, Martin A. The differential view of genotype-phenotype relationships. Front Genet. 2015;6:179. https://doi.org/10.3389/fgene.2015.00179
PMid:26042146
22. Liao PY, Lee KH. From SNPs to functional polymorphism: The insight into biotechnology application. Biochem Eng J. 2010;49(2):149-58.
23. Peferoen L, Kipp M, van der Valk P, van Noort JM, Amor S. Oligodendrocyte-microglia cross-talk in the central nervous system. Immunology. 2014;141(3):302-13. https://doi.org/10.1111/imm.12163
PMid:23981039
24. Muller N, Weidinger E, Leitner B, Schwarz MJ. The role of inflammation and the immune system in schizophrenia. Neurobiol Schizophr. 2016; Front neurosci. 2015;9:372. https://doi.org/10.3389/fnins.2015.00372
PMid:26539073
25. Kim YS, Joh TH. Microglia, major player in the brain inflammation: Their roles in the pathogenesis of Parkinson's disease. Exp Mol Med. 2006;38(4):333-47. https://doi.org/10.1038/emm.2006.40
PMid:16953112
26. Laskaris LE, Di Biase MA, Everall I, Chana G, Christopoulos A, Skafidas E, *et al*. Microglial activation and progressive brain changes in schizophrenia. Br J Pharmacol. 2016;173(4):666-80. https://doi.org/10.1111/bph.13364
PMid:26455353