40. Detection of COMTVal158Met

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Detection of COMT^{Val}158^{Met} Gene Polymorphism in Chronic Schizophrenic Patients at Psychiatric Unit of DR. Soetomo Hospital Surabaya, East Java, Indonesia

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Keywords: COMT ^{Val}158^{Mc}Polymorphism ^{t}, PANSS Scores, Schizophrenia.

Abstract: Schizophrenia is a complex and severe mental disorder which influences 0.5-1% of the global population. It is highly heritable and considered as a major health problem worldwide, including in Indonesia. The COMT ^{Val}158^{Met} polymorphism is allegedly related to the schizophrenia predisposition. However, previous studies related to the COMT ^{Val}158^{Met}polymorphism among schizophrenic patients in different geographical areas have given different results. This research used cross-sectional study design. It applied a descriptive observational method which was aimed to detect the ^{Val}158^{Met} COMT gene polymorphism in chronic schizophrenic patients. This study was conducted at the Psychiatric Unit of Dr. Soetomo Hospital Surabaya. The examination on COMT ^{Val}158^{Met} polymorphism was conducted by PCR and followed by sequencing. The number of male chronic schizophrenic patients was higher than female (56.7 % over 43.3%) and the average age of male schizophrenic patients (38.53 ± 10.32 years old) was higher than female (41.08 ± 7.44 years old). Moreover, the number of schizophrenic patients with family history of schizophrenia reached 53.3%, which was higher than those without it, 46.7%. The PANNS total score of male schizophrenic patients reached 40.71 ± 16.07, which was higher than female, 40.31 ± 11.42. Furthermore, the sequencing analysis showed that the frequency of COMT ^{Val}158^{Met}polymorphism was 6.7% (2/30), the heterozygote allele was recorded at 21946 for 40% (12/30), and nucleotide substitution variant of T into A at 21971 was recorded at 3.3% (1/30) among chronic schizophrenic patients in the Psychiatric Unit of Dr. Soetomo Hospital Surabaya. There were quite large numbers of the COMT^{Val}158^{Met} polymorphism (6.7%), heterozygote allele at 21946 (40%), and nucleotide variant of T substitution into A at 21971 (3.3%) in chronic schizophrenic patients at the Psychiatric Unit of Dr. Soetomo Hospital Surabaya.

1 INTRODUCTION

Schizophrenia is a complex and severe psychiatric disorder which is still considered as a major health problem worldwide (1,2), including in Indonesia (3). Based on the Diagnostic & Statistical Manual of Mental Disorders 4th ed. Text Revision (DSM-IV-TR), the annual incidence of schizophrenia is influenced by various ethnicities and geographical areas (2). In Indonesia, schizophrenia prevalence is approximately 0.3-1 percent and commonly found in age 18-45 (4).

The fundamental mechanism and etiology of schizophrenia remain unclear. However, it is presumably related to multifactors and multigenics (5). The etiology, which is considered as playing a central role on the predisposition of schizophrenia, is a combination between genetic and environmental factors (2). The genetic variants which are suspected as a predispositional factor of schizophrenia, are Single Nucleotide Polymorphisms (SNPs). A polymorphism can be analyzed by a reference sequence (rs) and gene data from the National Center of Biotechnology Information (NCBI). The polymorphism, which is strongly suspected as the

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cause of schizophrenia and is being examined in various countries, is in the $^{Val}158^{Met}$ COMT polymorphism gene (6-11). Based on the previous research, there were different datas for the percentage of polymorphism from various population, which was 25% in Caucasian (12) and 3-9% in Asian population (13). Moreover, the frequency of Met allele was recorded as 50% in Caucasian, 20 to 30% in East Asian, and 6% in Ghanaian (14). A polymorphism can be detected by using the Polymerase Chain Reaction (PCR) technique, followed by Restriction Fragment Length Polymorphism (RFLP)(7,10,11,15) or by sequencing (16,17).

The COMT enzyme as the product of COMT gene expression (located at the chromosome 22q11.2) is a crucial enzyme which has an important role in the inactivation of catecholamine neurotransmitter, particularly dopamine (9,18). The COMT enzyme has two forms: 1) a soluble form (S-COMT), which is often found in the peripheral network; and 2) a membrane bound form (MB-COMT), which is abundantly found in the brain network (18). Genetically, a COMT enzyme activity can differ (genetically polymorphic) in different people's networks (10). Dopamine dose at the Prefrontal Cortex (PFC) area has some influence on disorders of the cognitive function and the working memory of schizophrenics (6,9). COMT genetic variants at codon 158 (mutant type homozygote Met/Met) can alter the activities of COMT enzyme and enhance the dopamine concentration at the PFC synapse area, thus influencing its neurocognitive functions (14,19). A frequent polymorphism found in the COMT gene is $^{Val}158^{Met}$ (rs4680) at exon 4 (14). The mutant-type of COMT enzyme at the codon of COMT 158 gene with an amino acid substitution of valine into methionine has a four-time decrease of catalytic activity compared to the wild-type of COMT Val/Val homozygote enzyme, while the COMT Val/Met heterozygote enzyme has an intermediate catalytic activity. To date, a schizophrenia diagnosis is only based on phenotypic symptoms. Therefore, the identification of predisposition genes which lead to schizophrenia is a valuable biological biomarker to understand the etiopathogenesis of the disease and therapy development, as well as to investigate hereditary genes within the patient's family (9,20,21).

To date, research on the genetic predisposition causing schizophrenia and geographical variations of the disease related to the COMT gene polymorphism has been rarely conducted in Indonesia. Hence, the aim of this study was to detect the COMT$^{Val}158^{Met}$ gene polymorphism in chronic schizophrenic patients at the Psychiatric Unit of Dr. Soetomo Hospital Surabaya.

2 RESEARCH METHODS

This study was an observational research to detect the COMT $^{Val}158^{Met}$ gene polymorphism in chronic schizophrenic patients at the Psychiatric Unit of Dr. Soetomo Hospital Surabaya. Its research design was cross-sectional.

The diagnosis of schizophrenia based on psychiatric history and mental checkup was conducted under the Guidance of Mental Disorder Categorization and Diagnosis in Indonesia III (PPDGJ 3rd edition) (22) and the criteria of Positive and Negative Symptom Scale (PANSS) (23).

Subjects in this study were schizophrenic patients enrolled from the Psychiatric Unit of Dr. Soetomo Hospital Surabaya. They had to meet various inclusion criterias: age of ≥ 18 years old, Javanese, male and female schizophrenic patients, being diagnosed with schizophrenia, and having persistent symptoms for at least six months.

Blood sampling was conducted after obtaining an ethical clearance from the research ethics committee of Dr. Soetomo Hospital Surabaya. Prior to the research, the families of schizophrenic patients were given an explanation about the research and asked to sign an Informed Consent statement.

The blood samples were collected from schizophrenic patients and put inside 5mL venoject tubes with EDTA anticoagulant. Then, in accordance with the procedure, the peripheral Blood Mononuclear Cells (PBMCs) were separated from the samples using a Ficoll solution. Genomic Deoxyribonucleic Acids (DNA) extraction was conducted on the PBMCs. DNA isolation was performed by using DNA Isolation Kit for Blood/Bone Marrow (cat no. 2 032 805). Both Peripheral Blood Mononuclear Cells and DNA were enclosed in Eppendorf tubes and stored at -80^{0}C at the Institute of Tropical Disease of Airlangga University until the laboratory examination was conducted. For Polymerase Chain Reaction (PCR) the following primer pairs were used: 5'-TCG TGG ACG CCG TGA TTC AGG -3' (forward) and 5'-AGG TCT GAC AAC GGG TCA GGC -3' (reverse) (7). The PCR products were then electrophoresed. A sequencing process was conducted by ABI 310 sequencer for PCR products, which gave positive result in the form of DNA

fragment at the length of 217bp. The results were then analyzed by using clone manager 9 program.

3 RESULTS AND DISCUSSIONS

From the 30 studied patients, male schizophrenic patients were more prevalent (56.7%) than female (43.4%). Furthermore, the average age of the male schizophrenic patients was younger (38.53 ± 10.32 years old) than female (41.08 ± 7.44 years old). This is likely caused by the influence of estrogen hormone which has a protective effect against schizophrenia. Thus, the schizophrenic manifestation in males tends to occur at younger age compared to females (2,24). In female schizophrenic patients, a fluctuation of psychotic symptom was found during the menstruation cycle. Furthermore, it was stated that the estrogen hormone had a pleiotropic effect on the variation of brain development process in adults (24). The characteristics of chronic schizophrenic patients at the Psychiatric Unit of Dr. Soetomo Hospital, Surabaya are illustrated in Table 1 below.

Table 1: Characteristics of chronic schizophrenic patients.

	Number of Patients		Average Age ± SD	Family History of Schizophrenia			
				Yes		No	
	N	%	Years old	N	%	N	%
Male	17	56.7	38.53 ±10.32 [25 – 62]	6	20	11	36.7
Fe-male	13	43.3	41.08 ±7.44 [31 – 58]	10	33.3	3	10
Total	30	100	39.63 ±9.13 [25 – 62]	16	53.3	14	46.7

All schizophrenic patients in this research were Javanese, which was assumed as due to the sampling location taking place in the Psychiatric Unit of Dr. Soetomo Hospital, a referral hospital of Eastern Java, thus the Javanese ethnic was predominant. Data from Riset Kesehatan Dasar (RISKESDAS) Indonesia in 2013 showed that the prevalence of severe mental disorder in East Java was 0.22%, while the highest prevalence was in Yogyakarta (0.27%), and its total prevalence in Indonesia was 0.17%.

The number of schizophrenic patients with family history of schizophrenia in this research was higher than those without it. This study has shown that genetic factor plays a significant role as a predisposition factor of schizophrenia. This result is in line with McGuffin et al. (1995) stating that schizophrenia is highly prone to be genetically passed down (nearly 80 percent) (25). Other previous research has mentioned that the genetic polymorphism which is susceptible to the onset of schizophrenia and influences the dopamine regulation within PFC, is the COMT $^{Val}158^{Met}$ (rs4680) SNP gene (8). The genetic predisposition and the pre-existing environmental factors (such as family-related stress) are stated as complex factors which cause schizophrenia (26).

In this research, the PANSS scores were calculated to evaluate the clinical symptoms of schizophrenic patients. The PANSS scores of schizophrenic patients at the Psychiatric Unit of Dr. Soetomo Hospital Surabaya are displayed in Table 2.

Table 2: PANSS scores of chronic schizophrenic patients at Psychiatric Unit of Dr. Soetomo Hospital Surabaya.

Gender	PANNS Scores			
	Positive Average	Negative Average	General Average	Total Average
Male	10.71 ± 4.98 [7 – 20]	9.88 ± 5.18 [7 – 28]	20.12 ± 8.24 [16 – 49]	40.71 ± 16.02 [28 – 87]
Female	9.62 ± 2.87 [7 – 15]	10.62 ± 6.74 [7 – 28]	20.08 ± 3.90 [16 – 28]	40.31 ± 11.42 [30 – 68]
Average	10.23 ± 4.17 [7 – 20]	10.20 ± 5.81 [7 – 28]	20.10 ± 6.61 [16 – 49]	40.53 ± 14.02 [28 – 87]

Table 2 shows that the average score of positive symptoms was 10.71 ± 4.98, the general average score was 20.12 ± 8.24, and the total average score was 40.71 ± 16.02. Overall, the average score for male patients was higher than those of female patients (9.62 ± 2.87, 20.08 ± 3.90, 40.31 ± 11.42), while the average score for negative symptoms (9.88 ± 5.18) of the male patients was lower than those of the female. In this research, the male average scores for positive symptom, general, and total, were higher than those of the female. By contrast, the female average negative score was higher than those of the males. Different clinical symptoms observed between male and female schizophrenic patients were allegedly related to the protective nature of estrogen hormone (24).

Patients with G/G (Val/Val) genotype polymorphism showed more severe negative symptoms, memory disorders, and executive function disorders in PFC than those with A/A (Met/Met) genotype (16). Bray et al. (2003) has proved that the changes of other variants besides the COMT Val/Met gene play a significant role in human brain development and are highly related to

the susceptibility to schizophrenia (27). Furthermore, a single nucleotide polymorphism of COMT gene can influence the down regulation of COMT gene expression, directly and indirectly (27). SNP of COMT gene with G/G genotype causes the deterioration of COMT gene expression (27).

The COMT gene plays a major role in brain development, particularly on cerebral cortex thickness, and has a high tendency to be passed down (hereditary) to family members (5). It is supported with the results of MRI examination in which the deterioration of cerebral cortex thickness in schizophrenic patients is confirmed (8). The existence of the $^{Val}158^{Met}$ polymorphism influences the starting age of schizophrenia, cognitive function, severity of psychotic symptoms, and brain volume (9).

From a sequencing examination on the samples, the mutant COMT $^{Val}158^{Met}$ (rs4680) SNP homozygote gene was found in two patients. This finding was consistent with Al-Asmary et al., (2006), who stated that there was a significant relationship between the COMT $^{Val}158^{Met}$ gene polymorphism with the cause of schizophrenia. Further, it was also found that male patients were more prone to schizophrenia than the female ones. The Met allele (A) frequency and the $^{Val}158^{Met}$ genotype (G/A) were significantly higher in the schizophrenic patients than in the control group (17).

The PCR product in this research was a DNA fragment with 217bp length. In the electrophoresis examination, it appeared as a band positioned between 200 and 300 band markers when compared to the 100bp DNA ladder band. An example of electrophoresis result of COMT gene PCR products with positive results is displayed in Figure 1.

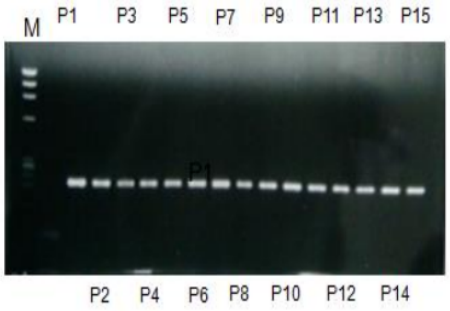

Figure 1: Electrophoresis result of COMT gene polymorphism.

PCR products giving positive results were further sequenced with ABI 310 sequencer and forward (sense) primer. The reference sequence rs4680 was retrieved from NCBI (NC_000022.11) databases. Our sequencing results were then aligned using clone manager 9 by comparing with rs4680. The results of multiple alignment rs4680 from the sequencing of 30 samples are illustrated in Figure 2.

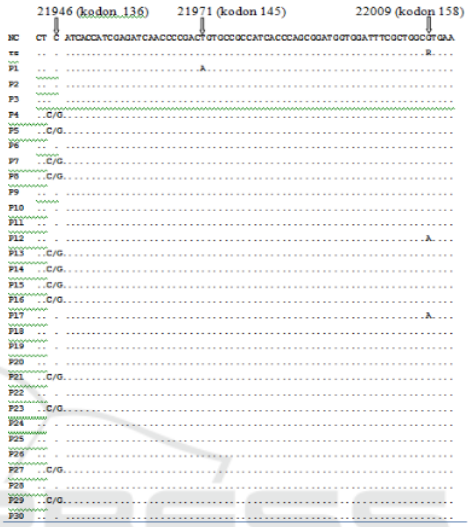

Figure 2: The results of multiple alignment of rs4680 (COMT $^{Val}158^{Met}$ SNP) gene and the sequencing results of 30 samples(R = G or A).
Notes: nucleotide 21946 (heterozygote); 21971 (substitution from T to A), 22009 (R).

The sequencing results of 30 chronic schizophrenic patients showed that the COMT$^{Val}158^{Met}$ SNP was found in samples 12 and 17. The SNP of codon 158 of rs4680 located in exon 4 showed R-code nucleotide (meaning the nucleotide is type G or A, while the COMT gene is from NCBI – NC_000022.11) at the codon position (precisely at nucleotide number 22009). A sample of DNA fragment from the electropherogram result of COMT$^{Val}158^{Met}$ SNP gene sequencing result is displayed in Figure 3.

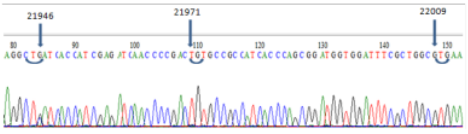

Figure 3: sample of DNA fragment from the electropherogram result of COMT$^{Val}158^{Met}$ SNP gene sequencing results.

Note: The heterozygote Allele is located at the nucleotide number 21946, T substitution into A at 21971, and R at 22009.

In this research, the wild-type of (Val/Val) SNP homozygote genotype and the mutant (Met/Met) homozygote were found. However, the heterozygote genotype was not found. These findings are different from those found in previous research conducted in Asian countries of the Philippines, China, Japan, and Korea which has stated that there are three types of genotypes, namely, the wild type of (Val/Val homozygote, the mutant (Met/Met) homozygote, and the Val/Met heterozygote (11).

Another finding of this research was the existence of the heterozygote allele, specifically at the nucleotide position number 21946 (C/G) on 12 samples (P4, P5, P7, P8, P13, P14, P15, P16, P21, P23, P27, and P29). In such positions, the C nucleotide (codon CTC) or the G (codon CTG) does not cause amino acid code changes (leucin). Thus, it predictably does not influence the COMT enzyme's activities. A nucleotide substitution variant from T to A was found in one sample (P1) at the nucleotide number 21971 (figure is not illustrated). The nucleotide change from T to A causes the change of decoded amino acid cysteine (TGT) to serine (AGT).

In this research, the average PANSS scores of total positive symptoms, total negative symptoms, and total general symptoms for the chronic schizophrenics with the mutant COMT (Met/Met) genotype were lower than those of the wild-type of (Val/Val) genotype. The PANSS scores for mutant genotype and wild-type of COMT ^{Val}158^{Met} SNP gene are shown in Table 3

Table 3: PANSS scores for the mutant-type and the wild-type of the COMT^{Val}158^{Met} SNP gene.

	COMT^{Val}158^{Met}*SNP*Genotype gene		
PANSS score	A/A	A/G	G/G
Positive	7.00	-	10.46
Negative	7.50	-	10.39
General	17.50	-	20.29
T o t a l	32.00	-	41.14

The findings of this research were in accordance with the results of Bilder et al. (2002) and Muskovitz et al. (2015) which stated that there was a relationship between variants of the COMT Met gene and the decreasing risks in the emergence of negative symptoms and cognitive symptoms in schizophrenic patients (6, 28).

However, these findings were not in line with Lindenmayer et al. (2015), who found that there was no significant difference between the PANSS total scores for individuals with the Met/Val, Met/Met, and Val/Val genotype (29). Furthermore, it was also not consistent with the results of research done by Al-Asmary et al. (2006), which mentioned that there was no significant relationship between the COMT^{Val}158^{Met} SNP gene and the negative/positive symptom scores in schizophrenic patients (17).

In conclusion, this research found that the number of male schizophrenic patients at the Psychiatric Unit of Dr. Soetomo Hospital Surabaya was higher than the females. The male schizophrenic patients in average were also younger and having lower total PANSS scores than the females. Furthermore, the COMT^{Val}158^{Met} SNP gene at codon 158 at the nucleotide number 22009 was recorded to reach a quite high percentage (6.7%). Finally, the heterozygote allele in number 21946 reached 40% and the change of nucleotide variant of T to A at number 21971 was 3.3%.

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40. Detection of COMTVal158Met

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