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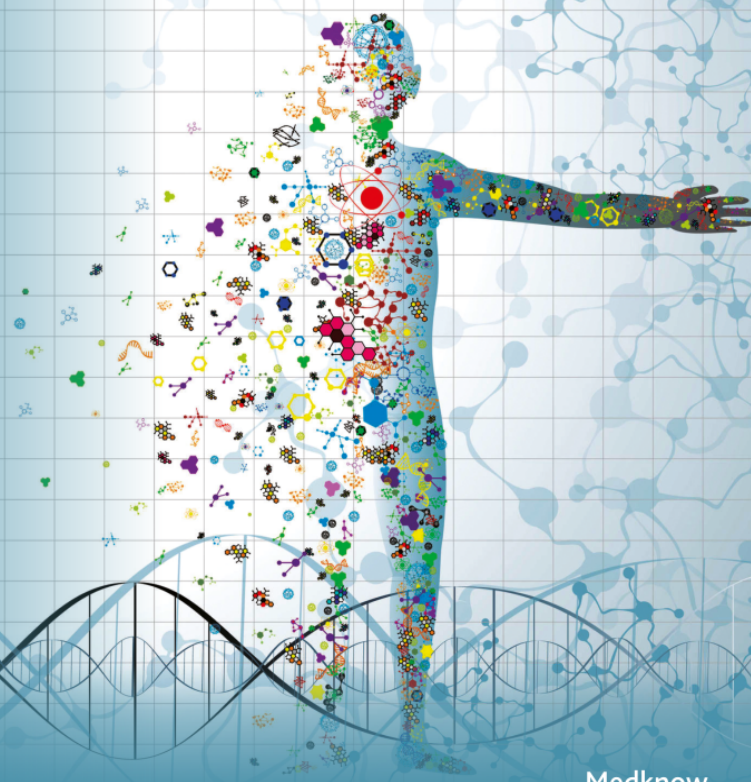
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DRD2 Gene-141C Insertion/Deletion Polymorphism among Schizophrenia Patients: The First Investigation in Palembang, Indonesia

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Abstract

Introduction: Schizophrenia remains one of the most common mental health disorders, affecting people worldwide. Its causes comprise environmental risk factors to genetic risk factors. One of the candidate genes for schizophrenia is the dopamine D2 receptor (DRD2) gene. There are several single-nucleotide polymorphisms found in the gene, with-141 C insertion/deletion polymorphism as one of the most commonly investigated polymorphisms. This study is the first to investigate the DRD2 gene-141 C insertion/deletion polymorphism among schizophrenia patients in Palembang, Indonesia. **Materials and Methods:** Eighty schizophrenia patients from the only national reference mental hospital in the South Sumatra area, Eraldi Bahar Mental Hospital, participated in this cross-sectional study. DRD2 gene-141C insertion/deletion polymorphism (DD, DI and II) was detected using restriction fragment length polymorphism analysis. **Results:** The-141 C insertion or DD genotype was less frequent ($n = 4$; 5%) compared to the II genotype ($n = 25$; 31.25%) and-141 C deletion or DI ($n = 51$; 63.75%) as the most frequent genotype found. **Conclusion:** This study is one of the few studies in the Indonesian population investigating the DRD2 gene-141 C insertion/deletion polymorphism. With a small sample size in consideration, our findings suggest that this polymorphism is prevalent in the Indonesian population.

Keywords: Dopamine D2 receptor gene polymorphism, Indonesian population, schizophrenia

INTRODUCTION

Schizophrenia is a condition one would not fail to mention when talking about mental health due to its peculiar characteristics, such as distortion in cognition, perception, emotion and behaviour.^[1] It is also one of the most common mental health disorders, affecting around 20 million people worldwide.^[2] In Indonesia, the prevalence is 7% in 1000 households. While in South Sumatra, where this study was conducted, it reached 8.05%.^[3] Schizophrenia is associated with considerable disabilities, and it may affect the lives of not only the patients but also families and the community. With that many cases and impacts, it deserves proper attention and concern.

Despite its common prevalence, its aetiology is still elusive. It is believed as a complex multifactorial psychiatric disorder.^[1] Some studies suggest the involvement of several neurotransmitters, whereas some point out the role of genetics and environmental factors in its development. Among varied

proposed risk factors, genetic factors were the least identified risk factors in the Indonesian population.

The dopamine hypothesis has long been regarded as one of the main explaining theories for the origins of schizophrenia.^[1,4-6] Dopamine D2 receptor (DRD2) gene is considered one of the most important candidate genes for schizophrenia development due to its role in dopamine signalling.^[6-8] However, there has been limited genetic identification and association study conducted on Indonesian schizophrenia patients. One


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of the most interesting investigated polymorphisms of the DRD2 gene is a cytosine (c) insertion/deletion in nucleotide position-141 of the 5' promoter region.^[9-15] This polymorphism alters gene expression *in vitro*, reduces transcription and affects transcriptional activity and D2 receptor density.^[10,11] As mentioned before, there were limited studies regarding this polymorphism in Indonesia. There have been only two studies, in Makassar and North Sumatera, with different results, regarding the most commonly found genotype.^[16,17] Thus, this study wished to investigate the DRD2 gene 141C insertion/deletion polymorphism among schizophrenia patients in Palembang, Indonesia.

MATERIALS AND METHODS

Subjects

Eighty schizophrenia outpatients from the Ernaldi Bahar Mental Hospital of South Sumatera Province in Palembang, Indonesia, who were able to comprehend and give informed consent, participated in the study. Schizophrenia patients with a history of organic mental disorder and suicidal thoughts were excluded from the study. The study was approved by the Ethical Board of Faculty of Medicine, Universitas Sriwijaya No. 147-2020. The team also investigated the history of having family members (nuclear and extended) affected with schizophrenia.

Genotyping

DNA was extracted from whole blood by standard protocol before it was then genotyped using polymerase chain reaction (PCR)-restriction fragment length polymorphism. The primers originally described by He *et al.*^[17] were used along with 6 µl DNA, 8 µl ddH₂O and 10 µl GoTag green to amplify a 304 bp region. The PCR profile was as follows: initial denaturation for 5 min at 94°C, followed by 30 cycles of denaturation for 30 s at 94°C, annealing for 30 s at 60.4°C, extension for 40 s at 72°C and final extension at 72°C for 10 min. The amplicon was digested with 0.5 µl of BstNI enzyme and incubated at 37°C. Digestion products were separated on a 2.2% agarose stained with 0.5 µg/ml ethidium bromide. The products were then observed under ultraviolet light. Undigested 304 bp PCR product is II genotype/deletion allele/-141C deletion. While the DD genotype/insertion allele/-141C insertion will have two fragments of 160 bp and 144 bp. The wild-type genotype (DI genotype) itself will have three fragments of 303 bp, 144 bp and 160 bp.

RESULTS

The results are shown in Table 1. More than half of the schizophrenia patients in this study are men (62.5%), with a wild-type genotype, DI (63.75%). Among the two mutant genotypes, the II/deletion allele was more common (31.25%) than the DD/insertion allele (5%). The investigation also revealed that half of the schizophrenia patients had family members affected with schizophrenia as well (58.8%). Some had nuclear family members affected, like fathers and siblings.

Table 1: Sample characteristics

Variable	Subjects (n=80), n (%)
Sex	
Male	50 (62.5)
Female	30 (37.5)
Family history	
Yes	47 (58.8)
No	33 (41.3)
Genotype	
DD	4 (5)
DI	51 (63.75)
II	25 (31.25)

At the same time, some had second-degree relatives affected, namely uncles, aunts and grandfathers.

DISCUSSION

Half of the subjects in this study were male ($n = 50$; 62.5%), consistent with past epidemiology finding where males were found to have a higher rate of schizophrenia than females.^[18] However, as more studies are conducted, schizophrenia is now known as a non-sex-specific condition with no consistent pattern of its incidence rate in men and women.^[19,20] With that being said, many facets of schizophrenia are affected by gender differences. The most common example of gender difference in schizophrenia is the higher age at onset.^[20]

Genetic factors as one of the causes of schizophrenia had come to attention when the modern twin and adoption studies provided pivotal evidence contradicting the psychological theories of schizophrenia causation.^[21] As more and more genome-wide studies emerged, many associated DNA variants are revealed, with the single-nucleotide polymorphisms (SNPs) of the DRD2 gene-141C insertion/deletion polymorphism being the prominent one. This SNP is located on the 5' promoter region of the DRD2 gene, causing the increment of transcription modulation activity and the increment of D2 receptor density as well.^[22] Studies by Arinami *et al.* and Xiao *et al.* further discovered that the deletion allele serves as a protective factor against schizophrenia, whereas the insertion allele serves as the genetic risk factor.^[11,23] Breen *et al.* and Lafuente *et al.*, on the other hand, stated that the deletion allele was a genetic risk factor for schizophrenia.^[13,24]

Most genetic studies of schizophrenia have been performed in European samples, with relatively few studies in other populations, including the Indonesian. The distinct finding of the -141 C insertion/deletion polymorphism is that it increases the risk of developing schizophrenia in the Asian population.^[25] However, studies exploring the prevalence of this polymorphism in the Indonesian population were limited. The only known Indonesian studies focusing on this polymorphism were one in Batak, North Sumatra population, and one in Makassar, South Sulawesi population. Despite only two studies, the results were slightly contradictory, with one

prominent similarity. One study in Makassar on schizophrenia patients showed II genotype or the deletion allele as the most commonly found genotype among the patients, followed by DD or the insertion allele, and the wild-type allele as the least allele found.^[17] Meanwhile, another study in the Batak population displayed different results, where the wild-type allele was the most commonly found one, followed by the deletion and insertion allele.^[16] Findings in the Batak population resemble those in the current study. One of the possible causes for this similarity is the shared root of ethnicity, which is Malay ethnicity. Other possible explanations include the inclusion and exclusion criteria of the study. However, one thing in common is that the deletion allele is consistently more common than the insertion allele in these three studies. Despite its resemblance in results to the study in the Batak population, this study has its limitation where it did not involve non-schizophrenic people as the control group. Its finding suggested an even more need for a control group since the wild-type allele was the most commonly found allele among schizophrenic patients.

CONCLUSION

This study remains one of the few studies investigating the DRD2 gene-141 C insertion/deletion polymorphism in the Indonesian schizophrenia population. Given the small sample size and findings from two other similar studies, this polymorphism appears to be relatively common in Indonesians, with possible different prominent genotypes due to ethnicity or other factors. The deletion allele is consistently more common than the insertion allele, implying clinical or pharmacological implications. Further research into different variants of DRD2 gene polymorphism in the Indonesian population is recommended, as is research into the association between-141 C insertion/deletion polymorphism and clinical or pharmacological aspects, to elucidate the causes and prevent its occurrence in the future.

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Conflicts of interest

There are no conflicts of interest.

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