DRD2 Gene Polymorphisms in Schizophrenia

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DRD2 Gene Polymorphisms in Schizophrenia Patients

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Abstract: Schizophrenia is one of the most common mental health issues worldwide, affecting millions of people. Schizophrenia is a multifactorial condition with many risk factors, including genetics. Recent studies on the genetic factors underlying schizophrenia have focused on the genes such as the DRD2 gene that regulate dopamine function. The dopaminergic system plays a pivotal role as a modulator of affective and cognitive functions. Dopamine is a catecholamine that acts on the central nervous system and is inhibitory or excitatory, depending on the dopamine receptors activated. DRD2 is the main presynaptic receptor of the dopaminergic system. Polymorphisms of the DRD2 gene are known as risk factors for the occurrence of schizophrenia. Some of the known DRD2 gene polymorphisms that play a pivotal role in the incidence of schizophrenia are the Taq1A, -141C Ins/Del, and C957T polymorphisms. We summarize the effects of these polymorphisms on the risk of schizophrenia in different populations.

1 INTRODUCTION

Schizophrenia is a major global health problem. In 2017, 1.1 million people worldwide were affected by schizophrenia. About 70% of the cases occur in individuals within the age group of 25-55 years (James et al., 2018). Globally, the prevalence of schizophrenia is estimated at 0.28% of the population (Charlson et al., 2018). The prevalence of schizophrenia in Indonesia has reached 1.7 incidents per 1,000 individuals according to Penelitian and Pengembangan (2013).

Polymorphisms of the dopamine receptor DRD2 gene have been identified as a risk factor for schizophrenia. Single nucleotide polymorphisms (SNPs) at this receptor can also play a role in the effectiveness of antipsychotics and influence their side effects (Ye et al., 2019). These SNPs are determining factors for clinical symptoms as well (Vijayan et al., 2007).

Dopamine (DA) is a catecholamine that acts on the central nervous system, and is inhibitory or excitatory, depending on the activated dopamine receptors (Pradnyawati, 2017). DRD2 is the main presynaptic receptor of the dopaminergic system. The DRD2 gene in humans resides on chromosome 11q22-23 and is 270 kb in size. Several DRD2 polymorphisms related to schizophrenia have been identified (He et al., 2013). The Taq1A polymorphism causes a decrease in the ability to inhibit behavior and impairs the activation of the brain's frontal lobe. The -141C Ins/Del polymorphism and the C957T mutation are also considered as risk

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factors for schizophrenia (Wang et al., 2016; Lawford et al., 2005).

2 DOPAMINE RECEPTOR D2

Dopamine (3-hydroxytryptamine) is a catecholamine neurotransmitter that functions as a precursor for the synthesis of the neurotransmitter norepinephrine. DA is synthesized from tyrosine in a dual-step process, wherein tyrosine hydroxylase acts as a rate-limiting enzyme (Speed, 2010).

The dopamine receptor is a transmembrane (TM)-7 member of the G protein-coupled receptor (GPCR) family, and consists of five subtypes (DRD1-DRD5) divided into two major groups, namely the D1-like receptors and D2-like receptors. Analysis of the dopamine receptor structure reveals similarities and differences between the D1-like receptor and D2-like receptor groups. The D1-like receptors have a -COOH terminal end that is seven times longer than that of the D2-like receptors and a third intracellular loop that is larger than that observed in the D2-like receptors. DRD1 and DRD5 exhibit 80% similarity in their TM domains, while DRD2 and DRD3 exhibit 75% similarity, and DRD2 and DRD4 exhibit 53% similarity in this domain. DRD1 and DRD5 have two glycosylation sites (N-glycosylation), while DRD2 has four, DRD3 has three, and DRD4 has one such site (Missale et al., 1998).

DRD2 exhibits negative feedback such that it causes the release of neurotransmitters when activated. α -2 receptors are also present on platelets, and function as mediators in platelet aggregation by influencing the concentration of the enzyme platelet adenylosuccinase. In the CNS, post-synaptic stimulation of α-2 using drugs such as clonidine or dexmedetomidine increases conduction and membrane hyperpolarization, which reduces the need for anesthetics. The TM signal system consists of the following three parts: (a) the recognition side, (b) the effector or catalytic side, and (c) the protein transducing or coupling side. The role of dopamine as a neuromodulator that promotes psychosis is shown by the administration of psychostimulant agents that result in dopamine release. These psychostimulants can cause psychosis, which can be overcome by administration of dopamine-blocking agents. Neuroimaging studies confirm that schizophrenic patients possess increased dopamine synthesis (Stoelting, 2005).

As the main presynaptic autoreceptor of the dopaminergic system, DRD2 is expressed throughout the DA region of the brain. DRD3, another member of the same receptor family, inhibits the production of is cyclic adenosine mono phosphate (cAMP). The diversity of dopamine receptors expressed at the given synapses can help determine the response of the neurons when DA is absent. Furthermore, the response depends not only on the identity of the receptors present at the synapse, but also on the number of receptors (Speed, 2010).

3 THE DRD2 GENE

The human gene DRD2 resides on the 11q22-23 chromosome. It is divided into eight exons, spanning at least 270 kilobases. Some studies have shown that D2 antagonists interfere with attributions of value to rewards and cause decrease in productivity, according to self-reported responses. Several polymorphisms have been identified in this gene in the last few decades, including Taq1A, rs6277, and -141C Ins/Del. One such polymorphism in this gene is Taq1A at the locus rs1800497 where cytosine (A2-allele) is replaced with thymine (A1-allele). Several studies have explored the association of this polymorphism with Major Depressive Disorder (MDD); however, the results are elusive. Other polymorphisms of the DRD2 gene that have been studied include -141C Ins/Del (rs1799732) and C957T (rs6277). Neither SNP displays a connection to MDD. However, carriers of the SNP C957T variant with T/T showed more depressive symptoms in the MDD patients than carriers of other SNPs. Some potential causes for this disparity could be limited sample size, ethnic variation, associations with other mood disorders, and biases in reporting. The association of the three DRD2 gene polymorphisms with major depressive disorder in the Chinese population is inadequately understood (He et al., 2013).

DRD2 performs specific functions within the limbic and caudal regions of the brain. Thus, it is a common target for antipsychotic drugs (Gejman et al., 2010). The pathophysiology of schizophrenia is also associated with alterations in dopamine production and receptor activation (Murray et al., 2008). Therefore, the DRD2 gene is widely considered as a causative factor in schizophrenia (Bulayeva et al., 2007).

The specificity of numerous antipsychotic drugs such as dopamine receptor antagonists is related to their capacity to suppress DRD2 activity. Many antipsychotic drugs, including aripiprazole and risperidone, strongly block post-synaptic DRD2 activity in the central nervous system, particularly in

the mesolimbic and striatal-frontal systems (Sadock, 2008; Katzung, 2018).

4 DRD2 GENE POLYMORPHISM

The two single nucleotide polymorphisms (SNPs) of the DRD2 gene, Taq1A and -141C Ins/Del polymorphisms, may be linked to schizophrenia susceptibility. Several studies have explored the link between Taq1A polymorphisms and the risk of developing schizophrenia. However, the outcomes of these reports are conflicting. Some studies have shown that the Taq1A polymorphism increases the risk of developing schizophrenia. Similarly, the -141C Ins/Del (rs1799732) polymorphism was deemed to be related to the risk of schizophrenia as well. However, these findings are inconsistent.

Several similar case-control studies were conducted to determine the potential role of the DRD2 gene polymorphisms in the incidence of schizophrenia. For example, Arinami et al. (1997) identified a positive correlation for -141C Ins/Del with susceptibility for schizophrenia. The results of studies reported by Betcheva et al. (2009) in the Bulgarian community are consistent with the positive correlations observed in different Caucasian populations between the C957T (rs6277) polymorphism and schizophrenia.

Two variants of G allele, which coincides with the C allele in both the database and the literature for the single nucleotide polymorphism, was defined as a risk allele. After an initial study by Lawford et al. (2005), which recorded a relationship between rs6277 and schizophrenia in an Australian (Caucasian) population, three other studies documented markedly higher frequencies of C alleles and C/C genes in schizophrenic patients of European origin (natural populations of Finland, Spain, and Russia). However, case-control studies using Indian subjects did not confirm a positive correlation with schizophrenia. (Kukreti et al., 2006).

Moreover, the findings of two meta-analyses using data from five studies or a Caucasian population revealed a relationship between the C allele and the C/C genotype with a combined odd ratio of 1.42 (95% confidence interval (CI): 1.26-1.61) and 1.45 (95% CI: 1.21–1.73), and the OR estimates for the genotype were 1%. Since all positive associations are found in European ancestral populations, the effects of ancestry must be understood and the genetic effects of this variant should be tested across populations with different ancestral descent (Betcheva et al., 2009).

5 CONCLUSIONS

Various studies suggest that Taq1A, -141C Ins/Del, and C957T polymorphisms in the DRD2 gene play a major role in the incidence of schizophrenia. They can affect the pathophysiology and the degree of severity of clinical symptoms experienced by patients. Therefore, further studies on the polymorphisms of the DRD2 gene at Taq1A, -141C Ins/Del, and C957T are necessary.

REFERENCES

Arinami, T., Gao, M., Hamaguchi, H., & Toru, M., 1997. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. *Human Molecular Genetics*, [online] 6, pp. 577–582.

Betcheva, E. T., Mushiroda, T., Takahashi, A., Kubo, M., Karachanak, S. K., Zaharieva, I. T., …& Nakamura, Y., 2009. Case-control association study of 59 candidate genes reveals the DRD2 SNP rs6277 (C957T) as the only susceptibility factor for schizophrenia in the Bulgarian population. *Journal of Human Genetics*, [online]54, pp. 98-107.

Bulayeva, K. B., Glatt, S. J., Bulayev, O. A., Pavlova, T. A., Tsuang, M. T., 2007. Genome-wide linkage scan of schizophrenia: A crossisolate study. *Genomics*, , [online] 89(2), pp. 167-177.

Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., ... & Whiteford, H. A. et al., 2018. Global epidemiology and burden of schizophrenia : findings from the global burden of disease study 2016. *Schizophrenia Bulletin*, [online] 44(6), pp. 1195-1203.

Gejman, P. V., Sanders, A., & Duan, J., 2010. The role of genetics in the etiology of schizophrenia. Psychiatric Clinics, [online] 33(1), pp. 35–66.

He, M., Yan, H., Duan, Z. X., Qu, W., Gong, H. Y., Fan, Z. L., Kang, J. Y., Li, B. C., & Wang, J. M., 2013. Genetic distribution and association analysis of DRD2 gene polymorphisms with major depressive disorder in the Chinese Han population. *International Journal of Clinical and Experimental Pathology*, [online] 6(6), pp. 1142.

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., ... & Abdollahpour, I., 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990 – 2017 : a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, [online] 392(10159), pp. 1789-1858.

Katzung, B. G., 2018. Basic & clinical pharmacology: Antipsychotic agents & lithium. McGraw Hill, New York, 4th edition.

Kukreti, R., Tripathia, S., Bhatnagara, P., Guptab, S., Chauhan, C. S., Kubendran, S., et al… & Brahmachari, S. K., 2006. Association of DRD2 gene variant with schizophrenia. *Neuroscience Letters*, [online] 392(1-2), pp. 68-71.

Lawford, B. R., Young, R. M., Swagell, C. D., Barnes, M., Burton, S. C., Ward, W. K., & Morris, C. P., 2005. The C/C genotype of the C957T polymorphism of the dopamine D2 receptor is associated with schizophrenia. *Schizophrenia Research*, [online] 73(1), pp. 31-37.

Missale, C., Nash, S. R., Robinson, S. W., Jaber, M., & Caron, M. G., 1998. Dopamine receptors: From structure to function. *Physiological Reviews*, [online] 78, pp. 189-225.

Murray, R. M., Lappin, J., & Di Forti, M., 2008. Schizophrenia: From developmental deviance to dopamine dysregulation. *European Neuropsychopharmacology*, [online] 18(3), pp. S129-134.

Penelitian, B., & Pengembangan, D. A. N., 2013. Riset Kesehatan Dasar 2013. Ris Kesehat Dasar 2013.

Pradnyawati NPW., 2017. Neurofisiologi. Fakultas Kedokteran Universitas Udayana. Denpasar: Udayana University Press.

Sadock, V. A., 2008. Kaplan & Sadock's concise textbook of clinical psychiatry: Schizophrenia. Lippincott Williams & Wilkins, Philadelphia, 3rd edition.

Speed, N. K., 2010. The role of insulin signaling on dopamine transporter trafficking. (Doctoral Dissertation, Vanderbilt University).

Stoelting, R. K., 2005. Pharmacology and physiology in anesthetic practice: Autonomic nervous system. Lippincott Williams & Wilkins, Philadelphia, 4th edition.

Vijayan, N. N., Bhaskaran, S., Koshy, L. V., Natarajan, C., Srinivas, L., Nair, C. M., … & Banerjee, M., 2007. Association of dopamine receptor polymorphisms with schizophrenia and antipsychotic response in a South Indian population. *Behavioral and Brain Functions,* [online] 3(1), pp. 34.

Wang, Y., Liu, L., Xin, L., Fan, D., Ding, N., Hu, Y., …& Yang, X., 2016. The -141C Ins/Del and Taq1A polymorphism in the dopamine D2 receptor gene may confer susceptibility to schizophrenia in Asian populations. *Journal of Clinical Neuroscience*, [online] 30, pp. 1-7.

Ye, J., Ji, F., Jiang, D., Lin, X., Chen, G., Zhang, W., ... & Zhuo, C., 2019. Polymorphisms in dopaminergic genes in schizophrenia and their implications in motor deficits and antipsychotic treatment. *Frontiers in Neuroscience*, [online] 13, pp. 355.

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