

Short Communication

COMPT (CATHECOL O-METHYL TRANSFERASE) GENE AS GENETIC RISK FACTOR FOR JAVANESE SCHIZOPHRENIA

EM SUTRISNA¹, RATNA YULIANI²

¹Faculty of Medicine of Universitas Muhammadiyah Surakarta, ²Faculty of Pharmacy of Universitas Muhammadiyah Surakarta
Email: Em.Sutrisna@ums.ac.id, em_sutrisna@yahoo.com

Received: 30 Dec 2015 Revised and Accepted: 11 Feb 2016

ABSTRACT

Objective: Several genes were suspected as a genetic marker of schizophrenia disease. This research was done to investigate the influence of Cathecol O-methyl transferase (COMPT) gene polymorphism toward incidence of schizophrenia on Javanese people.

Methods: There were two groups. The first group was Javanese schizophrenia patients, and the second group was not schizophrenia patients (control group). Each group contains 25 patients. The sample was taken from blood vein patients. Deoxyribonucleic acid (DNA) isolation was done using DNA isolation kit (Qiagen®). The method of genotyping was carried out by restriction fragment length polymorphism polymerase chain reaction (RFLP PCR) followed by digestion by Hin1 II enzyme.

Results: The results of this study showed that 64 % HH allele and 36 % LH allele of COMPT gene (G21881A) were found on Javanese schizophrenia while 76 % HH and 24 % LH allele were found on the control group. Odd ratio (OR) LH allele was 1,781 and OR HH allele was 0,561

Conclusion: The presence of LH allele of COMPT gene A1625G increases the risk of schizophrenia on Javanese people. The COMPT gene (G21881A) is a genetic risk factor for Schizophrenia disease on Javanese people.

Keywords: Schizophrenia, Javanese, COMPT gene

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Cathecol O-methyl transferase is an enzyme that catalyzes the transfer of methyl group of S-methionine-adenosil (AdoMet). This enzyme was coded by COMPT gene. This gene is located on chromosome 22q11.2 [1]. The COMPT was distributed in many tissues. The higher activity of COMPT was detected in brain, kidney and liver [2, 3]. There are two COMPT were coded by COMPT gene namely: membrane-bound COMT (MB-COMT) and soluble COMT (S-COMT). S-COMT contains 221 amino acids while MB-COMT has additional amino terminal 50 amino acids [4-6]. The polymorphism of COMPT gene decreases the activity of COMPT enzyme. This polymorphism was suspected as a risk factor of several diseases including schizophrenia [7, 8].

This research was done to find the influence of COMPT gene polymorphism to schizophrenia in Javanese people.

This cross-sectional study included 25 Javanese schizophrenia patient and 25 Javanese non schizophrenia patients as a control. The research protocol was approved by Health research ethics committee of Faculty of Medicine of Universitas Muhammadiyah Surakarta with no: 081/B.1/KEPK-FKUMS/V/2015.

The materials used in this research were DNA isolation kit (Qiagen®), blood of Javanese Schizophrenia and control, 2 % agarose, ethidium bromide, Hin1 II enzyme.

The DNA isolation was done using Qiagen kit. The Polymerase chain reaction (PCR) was done by RFLP-PCR. The procedure test followed: A total 12,5 ml master mix, 6,5 ml dH₂O, 2 ml forward: 5'-CGAGGCTCATCACCATCGAGATC-3', 2ml reverse 5'-CTGACAACGGGT CAGGAATGCA-3' and 2 ml was run by PCR. The thermocycling condition referred to research by Zaki *et al.* [9], with modification: 94 ° C for 5 min, followed by 32 cycles 94 ° C for 30 seconds, 54 ° C for 30 seconds and 10 seconds on 72 ° C. The final extension for 5 min at 72 ° C. PCR products were digested by Hin1 II enzyme. The procedure was followed: 10 ml PCR product add 2ml PCR buffer (10x buffer) and 1ml of an enzyme of Hin1 II (10U/ml) and 7ml dH₂O (total 20 ml) over 37 ° C for 15-20 min followed inactivation 80 ° C for 5 min. The digestion products were analyzed by 2 % agarose gel and DNA band were detected by ethidium bromide (50 mg/ml). After polymerase chain reaction by restriction fragment of polymorphism (RFLP), the PCR

product was digested by Hin1II. The result of digestion can be seen in fig. 1.

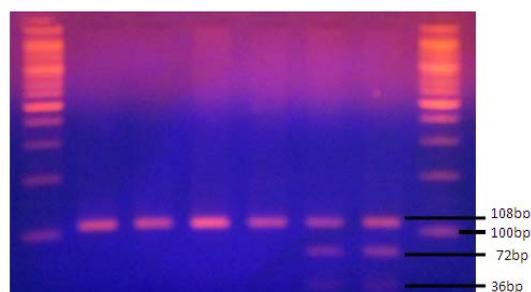


Fig. 1: The agarose electrophoretogram of (COMPT G21881A) gene polymorphism was digested by Hin1II of PCR product

From fig. 1, it can be seen that single band (108bp) show homozygous genotype (with high activity allele, HH), Heterozygous LH (characteristic by 3 fragments, 108 bp, 72bp and 36bp). There is no found homozygous allele with low activity of allele (2 fragments, 72bp& 36bp). From 50 samples of the schizophrenia and control groups, we get the result as described in table 1.

Schizophrenia is a mental disorder that characterized by more than two of the symptoms as follows: delusion, hallucinations, speech disorder (disorganization speech), catatonic behavior and the presence of negative symptoms [10]. Prevalence of this disease in Indonesia is 0.3-1 %. This disease usually attacks people within 18-45 y old [11].

Several genes were suspected as genetic markers of this disease. COMT (Cathecol O-methyl transferase) gene was suspected as risk factor of several diseases. Polymorphism of COMPT gene which causes substitution of valin to methionine (COMPT G21881A) increases risk of schizophrenia disease [8]. DTNBP1 (dystrobrevin binding protein 1) gene is a gene located in chromosome 6p22.3.

This gene was also allegeted as a risk factor of schizophrenia. There is low level of dysbindin in schizophrenia people [12]. The polymorphism of DTNBP1gene A1625G influences schizophrenia

incidence [13]. This polymorphism was detected by PCR-RFLP Method causes substitution of valine to methionine (Val 158 met) [14].

Table 1: The number of allele of (COMPT G21881A) polymorphism (n=25) and odds ratio (OR)

Allele	Schizophrenia	Control	Odds ratio
HH allele	16 (64 %)	19 (76 %)	0.561
LH allele	9 (36 %)	6 (24 %)	1.781
LL allele	0 (0 %)	0 (0 %)	

From table 1, it can be seen that the number LH allele on schizophrenia more than control (36 %vs 24 %) with OR 1.781.

Polymorphism of COMPT gene alters the activity of COMPT. The HH allele is the high activity of COMPT gene allele. Meanwhile LL allele is low activity COMPT gene allele [8]. Low allele of COMPT (LL) has methionine/methionine genotype. High allele (HH) is valine/valine genotype [15]. The catechol O-methyl transferase is an enzyme that involved in clearance of dopamine. This gene was suspected as a candidate gene for schizophrenia [16]. The low activity of this allele would be associated with schizophrenia [17]. This research found that heterozygous LH allele of COMPT gene of Javanese schizophrenia people was more than the control group (36 % vs 24 %).

The presence of LH allele of COMPT gene A1625G increases risk of schizophrenia on Javanese people

ACKNOWLEDGMENT

We thank Directorate general of higher education of Indonesia for funding this research

CONFLICT OF INTERESTS

Declared none

REFERENCES

- Grossman MH, Emanuel BS, Budarf ML. Chromosomal Mapping of The Human catechol-O-methyltransferase gene to 22q11.1-q11.2. *Genomics* 1992;12:822-5
- Axelrod J. O-methylation of epinephrine and other catechols *in vitro* and *in vivo*. *Science* 1957;26:400-1
- Guldberg HC, Marsden CA. Catechol-O-methyl transferase: pharmacological aspects and physiological role. *Pharmacol Rev* 1975;27:135-206
- Bertocci B, Miggiano V, Da Prada M, Dembic Z, Lahm HW, Malherbe P. Human catechol-O-methyltransferase: cloning and expression of the membrane-associated form. *Proc Natl Acad Sci U S A*.1991;88:1416-20.
- Lundström K, Salminen M, Jalanko A, Savolainen R, Ulmanen I. Cloning and Characterization of Human Placental Catechol-O-Methyltransferase cDNA. *DNA Cell Biol* 1991;10:181-9
- Mannisto PT, Kaakkola S. Catechol-O-methyltransferase (COMT): Biochemistry, Molecular Biology, Pharmacology, and

- Clinical Efficacy of The New Selective COMT Inhibitors. *Pharmacol Rev* 1999;51:593-628
- Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinsilboum RM. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics* 1996;6:243-50.
- Lotta T, Vidgren J, Tilgmann C, Ulmanen I, Melen K, Julkunen I *et al.*, Kinetics of Human Soluble and Membrane-Bound Catechol OMethyltransferase: A Revised Mechanism and Description of The Thermolabile Variant of The Enzyme. *Biochemistry* 1995;34:4202-10
- Zaki ME, El-Salam MA, Hassan NAM, Mohamed SK, Zaher MM, Ibraheim RAM *et al.* Association of adiponectin gene polymorphisms 276g>t with obesity and biochemical parameters in adolescents. *Int J Pharm Pharm Sci* 2014;6:226-9.
- Sinaga BR. Skizofrenia dan diagnosis banding. Medical Faculty Press; 2007. p. 14-15, 70.
- Arif IS. Skizofrenia, Memahami Dinamika Keluarga Pasien. PT Refika Aditama. Bandung; 2006. p. 1-47.
- Weickert CS, Straub RE, McClintock BW. Human dysbindin (DTNBP1) gene expression in normal brain and in schizophrenic prefrontal cortex and midbrain. *Arch Gen Psychiatry* 2004;61:544-55.
- Galehdari H, Ajam T, Pooryasin A, Foroughmand AM, Kazeminejad SR. Combined effect of polymorphic sites in theDTNBP1 and GRIN1 genes on schizophrenia. *Med J Islamic Republic Iran* 2010;24:5-10.
- Lajin B, Alachkar A, Detection of catechol-O-methyltransferase (COMT) Val158 met polymorphism by a new optimized PCR-RFLP method. *Am J Biomed Sci* 2011;3:170-5.
- Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, *et al.* Catechol-O-methyl-transferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci USA* 2003;100:6186-91.
- Axelrod J, Tomchick R. Enzymatic O-methylation of epinephrine and other catechols. *J Biol Chem* 1958;233:702-5.
- Williams HJ, Owen MJ, O'Donovan MC. Is COMT a susceptibility gene for schizophrenia. *Schizophrenia Bull* 2007;33:635-41.