

**Distribusi Frekuensi Alel Gen Penyandi Transporter Carbamazepine :
ABCBI rs1045642 C>T Pada Populasi Perempuan Suku Jawa di
Provinsi Daerah Istimewa Yogyakarta**

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INTISARI

Carbamazepine (CBZ) merupakan obat antiepilepsi (OAE) pilihan utama dan tercantum dalam formularium nasional 2017. Sebagai OAE dengan kisaran terapeutik sempit, kegagalan terapi CBZ akibat resistensi banyak ditemukan pada ranah klinis. Resistensi CBZ dapat terjadi akibat adanya variasi genetik pada transporter utama CBZ yaitu P-glikoprotein, protein yang berperan dalam *efflux* CBZ dari sel endotel kapiler pada sawar darah otak kembali menuju ke luar sel (kembali ke darah), yang disandi oleh gen *ABCBI*. Adanya *Single Nucleotide Polymorphisms* (SNP) *ABCBI* rs1045642 C>T diketahui sebagai penyebab ekspresi berlebih transporter ini, sehingga berkontribusi terhadap resistensi CBZ. Studi frekuensi varian gen *ABCBI* rs1045642 belum pernah dilakukan pada suku Jawa sebelumnya. Nilai *minor allele frequency* (MAF) sebesar 0,3952 menjadi pertimbangan pemilihan rs1045642 sebagai target penelitian ini. Tujuan penelitian ini untuk mengkaji frekuensi varian gen *ABCBI* rs1045642 C>T pada relawan sehat perempuan suku Jawa-Indonesia. Penelitian ini melibatkan 50 relawan sehat perempuan yang memenuhi kriteria inklusi. Isolasi DNA dilakukan dengan metode silika gel menggunakan *Genomic DNA Mini Kit*. Analisis variasi genetik dilakukan dengan metode *Polymerase Chain Reaction-Restriction Fragment Length Polymorphism* (PCR-RFLP) menggunakan primer *forward* 5'-TGCTGGTCCTGAAGTTGATCTGTGAAC-3' dan primer *reverse* 5'-ACATTAGGCAGTGAAGGCA-3'. Kondisi PCR yang digunakan yaitu 1 siklus pre-denaturasi 95°C (2 menit), 35 siklus denaturasi 95°C (30 detik), *annealing* 55°C (30 detik), dan *extension* 72°C (30 detik) secara berurutan, serta 1 siklus *final extension* 72°C (5 menit). Produk PCR yang dihasilkan yaitu 248 bp. Enzim restriksi *MboI* mengenali sekuen |GATC dan memotong *wild-type* (Basa *Cytosine*) pada 189 bp. Hasil penelitian menunjukkan frekuensi alel C (Genotip CC dan CT) dan alel T (Genotip TT dan CT) gen *ABCBI* rs1045642 pada populasi perempuan Jawa-Indonesia yaitu sebesar 49% dan 51%. Hasil ini hampir sama dengan yang ditemukan pada populasi Hungaria dan Jordania. Penelitian lebih lanjut diperlukan untuk menganalisis korelasi antara polimorfisme ini dengan variabilitas profil farmakokinetik maupun kejadian resistensi carbamazepine.

Kata Kunci : Carbamazepine, Transporter *ABCBI*, *Single Nucleotide Polymorphism* (SNP), rs1045642, PCR-RFLP.

**Allele Frequency Distributions of the Drug Transporter Genes
Carbamazepine : *ABCB1* rs1045642 C>T among the Javanese Woman
Population in Special Region of Yogyakarta**

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ABSTRACT

Carbamazepine (CBZ) is a major choice antiepileptic drug (AED) and it is listed in a national formulary 2017. As AED with a narrow therapeutic range, the failure of CBZ therapy due to resistance is found in many clinical care. CBZ resistance may occur due to genetic variation in the main CBZ transporter P-glycoprotein, a protein that plays a role in the CBZ efflux from brain capillary endothelial cells in the blood brain barrier back into the blood, that is encoded by the *ABCB1* gene. The presence of Single Nucleotide Polymorphisms (SNP) *ABCB1* rs1045642 C>T is known to cause excessive expression of these transporters, thus contributing to CBZ resistance. The study of the frequency of *ABCB1* gene variant rs1045642 among Javanese population has never been conducted in other studies. rs1045642 was chosen as the target of this study by considering the minor allele frequency (MAF) of 0.3952. This study aimed to determine the distribution of allele frequencies in *ABCB1* gene rs1045642 C>T among the healthy subjects Javanese-Indonesian women. The study involved 50 healthy female subjects who met the inclusion criteria. DNA isolation was performed by silica gel method using Genomic DNA Mini Kit. Analysis of genetic variation was performed by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) using 5'-TGCTGGTCCTGAAGTTGATCTGTGAAC-3' forward primer and reverse 5'-ACATTAGGCAGTGAAGGCA-3' primer. The PCR conditions used were 1 cycle of pre-denaturation 95°C (2 minutes), 35 cycle of denaturation 95°C (30 seconds), annealing 55°C (30 seconds), and extension 72°C (30 seconds), and 1 cycle of final extension 72°C (5 minute). The result of PCR product is 248 bp. Restriction enzyme *MboI* recognizes |GATC sequences and cuts wild-type (Base Cytosine) at 189 bp. The results showed that the frequencies of C allele (CC and CT genotypes) and T allele (TT and CT genotypes) of *ABCB1* gene rs1045642 in Java-Indonesia female population were 49% and 51%. These results are similar to those found in the Hungarian and Jordanian population. Further studies are needed to analyze the correlation between these polymorphisms with the variability of the pharmacokinetic profile and the occurrence of carbamazepine resistance.

Keywords : Carbamazepine, *ABCB1* transporter, *Single Nucleotide Polymorphism* (SNP), rs1045642, PCR-RFLP.