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Genetic factors associated with patient-specific warfarin dose in ethnic Indonesians

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Abstract

Background: *CYP2C9* and *VKORC1* are two major genetic factors associated with inter-individual variability in warfarin dose. Additionally, genes in the warfarin metabolism pathway have also been associated with dose variance. We analyzed Single Nucleotide Polymorphisms (SNPs) in these genes to identify genetic factors that might confer warfarin sensitivity in Indonesian patients.

Methods: Direct sequencing method was used to identify SNPs in *CYP2C9, VKORC1, CYP4F2, EPHX1, PROC* and *GGCX* genes in warfarin-treated patients. Multiple linear regressions were performed to model the relationship warfarin daily dose requirement with genetic and non-genetic variables measured and used to develop a novel algorithm for warfarin dosing.

Results: From the 40 SNPs analyzed, *CYP2C9* rs17847036 and *VKORC1* rs9923231 showed significant association with warfarin sensitivity. In our study population, no significant correlation could be detected between *CYP2C9*3, CYP2C9C-65* (rs9332127), *CYP4F2* rs2108622, *GGCX* rs12714145, *EPHX1* rs4653436 and *PROC* rs1799809 with warfarin sensitivity.

Conclusions: *VKORC1* rs9923231 AA and *CYP2C9* rs17847036 GG genotypes were associated with low dosage requirements of most patients (2.05 ± 0.77 mg/day and 2.09 ± 0.70 mg/day, respectively). *CYP2C9* and *VKORC1* genetic variants as well as non-genetic factors such as age, body weight and body height account for 15.4% of variance in warfarin dose among our study population. Additional analysis of this combination could allow for personalized warfarin treatment in ethnic Indonesians.

Keywords: Warfarin, SNP, *CYP2C9*, *VKORC1*, Indonesia

Background

Warfarin is the most widely used oral anticoagulant in the world. It is usually prescribed for treatment of atrial fibrillation, heart valve prosthesis, recurrent stroke, deep vein thrombosis and pulmonary embolism [1]. Although warfarin is indispensable for treatment of thromboembolism and for prophylaxis of stroke, due to the large inter-individual variation in the requirement for this drug the appropriate dose to each patient is not easily adjustable. An insufficient dose will result in failure to prevent thrombosis, while overdose increases the risk of unexpected bleeding. Pharmacogenetic differences are believed to cause the variation in individual response to warfarin [1,2].

Warfarin is primarily metabolized to the 7-hydroxylated form in humans, principally by cytochrome P450 *2C9*. So far, more than 30 variant alleles in the *CYP2C9* gene have been described (http://www.cypalleles.ki.se/cyp2c9.htm). Two common allelic variants *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910) are among the most well characterized of the *CYP2C9* alleles; both alleles have been associated with reduced enzymatic activity, and thus with reduced warfarin metabolism. Individuals bearing variant alleles *CYP2C9*2* and *3 are reported to require a lower maintenance dose of warfarin and a longer time to achieve stable dosing. These individuals are also reported to have a higher proportion of prothrombin-time measurements above therapeutic

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