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Genetic factors contribute to patient-specific warfarin dose for Han Chinese

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ABSTRACT

Background: Warfarin is a commonly prescribed anticoagulant drug for the prevention of thromboses. To address the association of genetic factors and warfarin dosage for ethnic Han Chinese, we genotyped six candidate genes involved in the warfarin interactive pathway with focus on SNPs with reported association with warfarin dose.

Methods: We recruited a study population consisted of 318 patients receiving warfarin treatment and 995 healthy controls. PCR and direct sequencing were used to identify the sequence polymorphisms.

Results: In our study population, SNP rs1799853 of *CYP2C9*, rs1687390 of *ORM1-2*, and rs2069919 of *PROC* showed no variation. SNPs rs12714145 of *GGCX* and rs1799809 of *PROC* showed no significant correlation with warfarin dose. The associations of SNPs rs9934438 and rs9923231 of *VKORC1*, the *3 (rs1057910) and C₋₆₅ (rs9332127) alleles of *CYP2C9*, and SNP rs4653436 of *EPHX1* with the dose of warfarin were significant.

Conclusion: A multiple regression model based on the genetic polymorphisms of *VKORC1*, *CYP2C9*, *EPHX1* and the non-genetic factors of age and body weight can explain 40.2% of the variance in warfarin dose in Han Chinese patients. Translation of this knowledge into clinical guidelines for warfarin prescription may improve the safety and efficacy of warfarin treatment among Han Chinese.

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1. Introduction

Warfarin is one of the most widely used coumarin anticoagulants for the treatment of atrial fibrillation, heart valve prosthesis, recurrent stroke, deep vein thrombosis and pulmonary embolism [1]. Due to its narrow therapeutic range and large inter-individual variation, risk of bleeding frequently complicates warfarin therapy and occurs at a rate of 7.6–16.5 per 100 patients per year in the UK and many other countries [2,3]. It is insufficient to predict warfarin dose based on non-genetic factors including age, gender, bodyweight and other environmental factors. Recent progress in elucidating the pharmacogenetic variables associated with warfarin dose made it feasible to use genetic polymorphism information to assist warfarin dose prediction [4,5].

The molecular basis of warfarin pharmacokinetics has been elucidated [6]. Warfarin acts through its interference with the recycling of vitamin K, which leads to the secretion of inactive vitamin K-dependent protein and inhibits the γ -carboxylation of vitamin K-dependent clotting factors II, VII, IX, and X [7,8]. Vitamin K epoxide reductase complex subunit 1 (*VKORC1*) gene encodes vitamin K epoxide reductase involved in liver vitamin K cycle [9,10]. Several common variations in *VKORC1* were identified as important genetic factors determining warfarin dose [4,11–13]. Cytochrome *P*₄₅₀ 2C9 (*CYP2C9*) is the major isoform of human liver cytochromes *P*₄₅₀ that modulates the physiological effect of warfarin [14,15]. Genes coding for *VKORC1* and *CYP2C9* have been associated with warfarin dose variance [16–18]. Patients with *CYP2C9* variant (<http://www.imm.ki.se/CYPaleles/>), such as *CYP2C9* variant alleles *2 (rs1799853, Arg144/Cys) and *3 (rs1057910, Ile359/Leu), require lower mean daily warfarin doses than the carriers for homozygous *1 wild type allele do, and may have a greater risk of bleeding complication, especially during the induction of therapy [6,19,20]. A novel genotypic polymorphism C₋₆₅ of *CYP2C9* affecting warfarin dose was reported in Taiwan Chinese [21]. Moreover, recently study demonstrated that genetic variation of cytochrome *P*₄₅₀ 4F2 (*CYP4F2*) was also associated with a clinically relevant effect on warfarin dose requirement [22]. A DNA variant

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