CYP4F2 polymorphism as a genetic risk factor for major hemorrhagic complications in Chinese patients on warfarin therapy

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To the editor

Warfarin is a commonly used anticoagulant with a narrow therapeutic range and risk of hemorrhagic complications.^[1] After *CYP2C9* and *VKORC1*, *CYP4F2* was confirmed as the third principle genetic determinant of warfarin dose variability.^[2,3] *CYP4F2* functions as a vitamin K₁ (VK₁) oxidase, a counterpart to vitamin K oxidize reductase (encoded by *VKORC1*) in limiting excessive accumulation of VK₁ in vitamin K cycle.^[4] Genotypes of *CYP2C9* and *VKORC1* are associate with increased risk of over anticoagulation or bleeding events during warfarin therapy.^[5-10] However, little is known about the influence of *CYP4F2*. Herein we present the association of *CYP4F2* polymorphism and risk of major hemorrhage in Chinese patients on warfarin. HapMap Data (Phase III/Rel#2, Feb09, on NCBI B36 assembly, dbSNP b126) covering 50 kb length centered on *CYP4F2* for Chinese was downloaded (<http://hapmap.ncbi.nlm.nih.gov/>). Haplotype blocks were constructed using Haploview version 4.2 software. The tag SNPs were selected with an LOD score cutoff of 3.0 and r^2 threshold of 0.80. We genotyped eight tag SNPs (rs7251296, rs4808394, rs12610962, rs3093168, rs2074901, rs2018454, rs1558139 and rs3093200) in *CYP4F2* using the multiplexed PCR-based SNaPshot system (Applied Biosystems) in 312 Han Chinese patients on warfarin. Three genetic determinants of warfarin dose, *CYP2C9**3, *VKORC1* -1639 G>A, and *CYP4F2* V433M were also genotyped. Among the genotyped 312 patients (mean age, 56.6 ± 16.0 years; 50.6% men) on warfarin with

the target international normalized ratio (INR) from 1.6 to 3.0, a total of 11 major and 69 minor hemorrhagic complications occurred over 147.25 person-years. The incidence for major hemorrhagic complications in this cohort (7.5 per 100 patients-years) was similar to those reported previously.^[1,6,10] All participants were recruited consecutively from the Chinese PLA General Hospital. The protocol for this study was approved by the ethical review committee, and all subjects provided written informed consent. The association of the tag SNPs and the risk of major hemorrhagic complications (including serious, life-threatening and fatal bleeding episodes as defined by Fihn *et al.*^[11]) was evaluated using Cox proportional hazard regression with adjustment for potentially confounding variables.

Of all the tested *CYP4F2* polymorphisms, only the SNP rs3093168 was statistically associated with major hemorrhagic complications. The incidence rate of major hemorrhagic complications was significantly higher among patients with CC alleles than those with the CG and GG alleles (17.1 vs. 4.5 per 100 patient-years), resulting in an adjusted hazard ratio (HR) of 7.61 (95%CI: 1.26–45.83) (Table 1). No other tag SNPs of *CYP4F2* including V433M allele were statistically associated. All the major hemorrhagic complications in the patients with rs3093168 CC genotype occurred after the stabilization of warfarin anticoagulation.

The SNP rs3093168 located in intron 9 of *CYP4F2* has never been studied. The genotype frequencies of CC in the Han Chinese (Beijing, China), Japanese (Tokyo, Japan), Caucasian (Utah, USA) and African (Ibadan, Nigeria) HapMap populations were 30%, 13%, 47% and 43%, respectively. Thus, a substantial portion of the populations harbor this genotype and might at higher risk for major hemorrhage when treated with warfarin. Validation of the association between *CYP4F2* rs3093168 and major hemorrhage complications in larger ethnic diverse cohort, and functional analysis of the linked SNPs might confirm the contribution of *CYP4F2* to the risk of haemorrhage complications in patients on warfarin.

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Table 1. Hazard ratios and 95%CI for the association of variant CYP4F2 rs3093168 with major hemorrhage.

Genotypes	Patients, n(%)	Follow-up, (person –years)	Major hemorrhage, n (per 100 patient-years)	Unadjusted Hazard ratio (95%CI)	P value	Adjusted hazard ratio (95%CI)	P value
CC	77 (24.7)	35.17	6 (17.1)				
CT+TT	235 (75.3)	112.08	5 (4.5)	4.56 (1.29–16.20)	0.019	7.61 (1.26–45.83)	0.027
Total	312 (100.0)	147.25	11 (7.5)				

Hazard ratios were adjusted for age, sex, body surface area, initial and stable warfarin dose, target International Normalized Ratio, alcohol intake, number of comorbid conditions (including hypertension, hyperlipidemia, diabete mellitus, liver cirrhosis, stroke, nephritis, and malignant tumors), genotypes of CYP2C9*3 and VKORC1 -1639 G>A, and use of amiodarone.

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