

Warfarin pharmacogenetics: How close are we to clinical practice?

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The past decade has seen substantial advances in our understanding of the genetic factors influencing response to a variety of drugs including warfarin. Though there has been an increase in the clinical use of pharmacogenetic information to individualize treatment regimens, yet there generally has not been broad acceptance of pharmacogenetic testing.

Warfarin remains the mainstay therapy for oral anticoagulation; it also remains one of the most challenging medications to manage despite over 60 years of experience with the drug. It is one of the top 10 drugs related to adverse drug events and hospitalization. Clinical management of warfarin therapy mainly is complicated by a narrow therapeutic index and high inter- and intra-individual variability in drug disposition and response. Supratherapeutic international normalized ratio (INRs) can lead to fatal hemorrhage while subtherapeutic INRs can lead to thrombosis.

Growing evidence indicates that up to 60% of the individual pharmacological response to warfarin might be due to genetic variables and affected by polymorphisms in the genes mainly, vitamin K epoxide reductase complex subunit 1 (VKORC1), the target enzyme of warfarin and cytochrome P450 2C9 (CYP2C9), the main enzyme involved in warfarin metabolism.

Although the genotypes of VKORC1 and CYP2C9 are clearly the most important genetic factors for warfarin response, genetic variations in other genes for instance, CYP4F2 and GGCX also show significant association with warfarin response. Non-genetic factors such as age (elderly patients), diet (vitamin K rich diet), disease states (thyroid activity, liver or renal dysfunction, fever), other drugs (e.g., amiodarone, propafenone, metronidazole, tamoxifen, etc.), life-style (alcohol intake, smoking, exercise) can also substantially modulate the response to warfarin.

VKORC1 polymorphisms have been reported to be more potent modifiers of warfarin response than the CYP2C9 polymorphisms. Recent work by Rieder *et al.*^[1] has also shown that individuals with VKORC1 A haplotype (H1 and H2) require low warfarin dose as a result of a decreased expression of messenger ribonucleic acid when compared to individuals with VKORC1 B haplotype (H7, H8 and H9).

In the present issue of the journal, Kumar *et al.*^[2] have studied genotype, allele and haplotype frequencies of VKORC1 and CYP4F2 in South Indian population. The authors have used 5 VKORC1 single nucleotide polymorphisms (SNPs) (similar to the report by Rieder *et al.*) to draw the VKORC1 haplotypes and the haplotype frequency has been compared with that of other populations. Except two SNPs, a strong LD pattern ($D' > 0.8$) has been observed in this study for all the remaining studied SNPs in VKORC1 gene. In addition, the genotype frequencies of CYP4F2 were also found to be distinct in Indian population when compared to the rest of the populations. Thus, the study further

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confirms the earlier finding that Indian population is distinct from the rest of the world population and requires high warfarin dosing.^[3,4]

Many of the studies have earlier shown that, around 75-80% of the Indian population carries VKORC1-1639GG (rs9923231) genotype, which is associated with high dose requirement.^[4-6] The current study clearly shows that VKORC1-1639G > A (rs9923231) SNP is in strong linkage disequilibrium with other SNPs. Thus, adding other SNPs or replacing VKORC1-1639G > A (rs9923231) with other VKORC1 SNPs will not increase the dosage predicting power. It can also be assumed that haplotype analysis does not add more information than the single SNP VKORC1-1639G > A (rs9923231) analysis in Indian population. Other authors have also shown that VKORC1-1639G > A (rs9923231) SNP is good predictor to distinguish high and low dose requirement group over the VKORC1 haplotype.^[7,8]

Although translation of warfarin pharmacogenetics into clinical practice has been slow, yet it is slowly emerging. Introduction of alternative anticoagulants such as Dabigatran, Rivaroxaban and Apixaban is changing the landscape of anticoagulation therapy, but warfarin anticoagulation therapy is likely to remain as the major anticoagulant therapy for many more years.

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