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Current warfarin pharmacogenomics research for personalized medicine: status and perspectives

Evaluation of: Cooper GM, Johnson JA, Langaee TY *et al.*: A genome-wide scan for common genetic variants with a large influence on warfarin maintenance dose. *Blood* 112, 1022–1027 (2008).

Safe and effective warfarin therapy is a challenge to clinicians, since warfarin has a very narrow therapeutic range and shows wide interindividual variations in optimum therapeutic doses. Traditionally, individual warfarin dosing has been affected by the biological factors such as age, gender and weight, and environmental factors including co-administration of other drugs and diet. Around the beginning of the 21st century, the genetic polymorphisms of *CYP2C9* have been published for their association with the clinical responses of warfarin [1]. More recently, the warfarin target protein was cloned as vitamin K epoxide reductase complex subunit 1 (*VKORC1*) in 2004, and genetic variants were reported to correlate with warfarin doses required to be within therapeutic international normalized ratio (INR) [2]. Since then, at least three prospective clinical trials, as well as many cross-sectional clinical trials, have proven the genetic contribution of these two genes in the explanation of warfarin dosing, to reveal that approximately 30% of interindividual variation of warfarin dosing is attributed to *CYP2C9* and *VKORC1* genetic polymorphisms. If the genetic and the other non-genetic factors are combined, 45–55% of interindividual variation of warfarin doses appears to be explained from the multiple regression analyses. Recognizing the clinical utility of the genetic information, the US FDA relabeled warfarin in August

2007 and has also approved at least four *in vitro* diagnostics for the genetic tests. The successful pharmacogenetic studies of *CYP2C9* and *VKORC1* have provoked succeeding genetic studies extending the list of candidate genes. Wadelius *et al.* evaluated 29 candidate genes known to involve the warfarin pathway for their possible association with individual warfarin dose, and revealed a marginal contribution of other genetic variants in *PROC*, *EPHX1*, *GGCX* and *ORM1–2* genes [3]. Caldwell *et al.* also screened the genetic polymorphisms of most of the known drug-metabolizing enzymes using microarray analysis, and identified *CYP4F2* as another candidate gene explaining warfarin dose variance, but the effect of the *CYP4F2* variants seems to be very minor (i.e. ~1–2% of total variance) [4]. Since these candidate gene approaches were considered to be limited to evaluate the possible association of known genetic variants that were selected from our current knowledge (hypothesis-driven), several groups are undergoing genome-wide studies for warfarin pharmacogenomics in order to explore any novel candidate genes associated with warfarin dose. In June of 2008, Cooper *et al.* published the study results of a retrospective genome-wide association study on warfarin dosing using Illumina 550K array in 181 white patients and two replication studies in a total of 379 white patients [5]. Interestingly, from the initial genome-wide scan, only *VKORC1* was selected as the only significant gene to determine stable warfarin doses from the statistically significant cut-off level after Bonferroni correction. Thus, 355 SNPs that showed relatively low p-values in univariate analysis, and approximately 30 SNPs of previously known candidate genes, were further evaluated in the

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replication studies. From the replication, both *VKORC1* and *CYP2C9* variants were confirmed to show the strong association with warfarin dose at p-values of 4.7×10^{-34} and 6.2×10^{-12} , respectively, and no additional genetic variants were identified to have such strong association. Although one intronic SNP in *CACNA1C*, a membrane calcium-channel gene, was associated with warfarin doses in both genome-wide scan and replication studies, it did not reach the significance cut-off level. The report by Cooper *et al.* seems to provide an apparent message in warfarin pharmacogenomics research. No common genetic variants except *VKORC1* and *CYP2C9* appear to have such large effects on warfarin dose variation. This may support the current idea that a pharmacogenetic test for warfarin dose prediction based on *VKORC1* and *CYP2C9* genotypes is scientifically reasonable and adequate for clinical application into personalized pharmacotherapy of warfarin dosing. However, the limitation of the study of Cooper *et al.* should be considered to confirm this issue. Since they studied only 'common' genetic variants, the possibility that warfarin doses may be affected by rare functional alleles identified in different ethnicities cannot be ruled out, as some genetic profiles are different among ethnic populations. For example, the list of functional genetic variants of *CYP2C9* has been continuously updated by CYP nomenclature system, and many of the variants are found in subsets of the specific ethnic populations. Therefore, in order to predict warfarin doses more precisely, it may be necessary to include those rare functional variants to warfarin genetic tests.

Since the direct interaction between genetic and nongenetic factors can influence the individual warfarin dose, quite different nongenetic factors, such as diet or herbal medicine among different ethnic populations, may be further considered in the following genome-wide study for warfarin pharmacogenomics. At present, the global warfarin pharmacogenomics consortium is ongoing, conducting a genome-wide association study in different ethnic populations that reside in different regions of the world. This may add more information on warfarin pharmacogenomics to

predict personalized pharmacotherapy of this very complicated therapeutic drug in global populations.

Although it may be too early to say, according to current published pharmacogenomics data on warfarin, the identification of new strong predictive genetic markers for personalized warfarin dosage through candidate-gene or genome-wide approaches appears to be very difficult. We still need more continuous efforts to identify additional contributing biomarkers, regardless of their relative extent of contribution to warfarin dose variation, and to develop a better predictive algorithm for personalized warfarin therapy through global/local pharmacogenomics research including genetic and nongenetic factors as the possible covariates of the drug responses.

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