Genome-wide Approach vs Candidate Gene Approach in Personalizing Warfarin Therapy

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Warfarin is a anticoagulant used for the prophylaxis of thrombosis and embolism. Warfarin therapy shows a wide inter-individual variation among patients in its required dosage. This variation is in part due to the well known environmental or demographic factors including age, weight, co-administered drugs, etc. In an effort to assess genetic contribution to individual variation to warfarin therapy, a number of candidate gene approaches have been carried out and several candidate genes have been identified. Genetic variations in warfarin metabolizing enzyme, cytochrome P450 2C9, and in Vitamin K epoxide reductase complex subunit 1 have been repeatedly associated with altered therapeutic dose of warfarin and are now regarded as valid genetic markers for personalized warfarin therapy. Genetic variations of these two enzymes help to explain more than 30% of the variability of warfarin dose. When genetic factors are combined with the demographic factors, the extent of predictability can be increased upto 65%. In order to discover the additional relevant genetic variations to affect warfarin therapy, two different approaches may be adopted according to the study design; genome-wide and candidate gene approaches. During last several years of candidate gene approaches have identified several additional genes including mEH, ApoE, GGCX, CALU, etc. but the results are not conclusive. One of the reasons for the controversial results of the candidate gene approache may be the fact that only limited number of genetic variants is investigated in this approach. To overcome this problem, genome-wide approach with the DNA arrays has been tested. In this presentation, two genetic approaches are introduced and compared with regard to variability of warfarin dose. And, a recent trend of global collaboration for warfarin pharmacogenomics will be addressed.

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