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Three Gene Variants Exert Major Genetic Influences on Therapeutic Warfarin Dose

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March 24, 2009 — A genomewide association study (GWAS) of variants associated with clinical response to warfarin dose is the first with adequate sample size to identify single nucleotide polymorphisms (SNPs) with moderate effects. The study identified 2 genes already known to determine more than 40% of variation in warfarin response, as well as a third gene — cytochrome P450, family 4, subfamily F, polypeptide 2 (*CYP4F2*) — that causes approximately 1% to 2% of dose variability.

Results of the multicenter study were reported March 20 in *PLoS Genetics* by Ralph E. McGinnis, PhD, statistical geneticist at Wellcome Trust Sanger Institute, Hinxton, United Kingdom, and colleagues at Sanger Institute and several Swedish institutions.

Warfarin is an anticoagulant commonly used to protect at-risk patients from myocardial infarction, stroke, and thrombosis. However, the effective dose varies as much as 20-fold within white populations. The anticoagulant response is quantified as international normalized ratio (INR) — a "ratio of the time required for a patient's blood to coagulate relative to that of a reference sample." The therapeutic goal of warfarin administration is an INR value between 2.0 and 3.0.

The present study enrolled Swedish patients (n = 1053) and tested more than 325,000 SNPs for their association with warfarin dose. The quantitative measure of the GWAS was the mean warfarin dose (milligrams/week) a patient was receiving during 3 or more consecutive INR readings between 2.0 and 3.0.

The strongest associations were found for SNPs near the vitamin K epoxide reductase complex, subunit 1 gene (*VKORC1*; $P < 10^{-78}$) and the cytochrome P450, family 2, subfamily C, polypeptide 9 gene (*CYP2C9*; $P < 10^{-31}$). These genes were already considered responsible for 30% and 12%, respectively, of variation in warfarin dose. "[T]he widely replicated warfarin dose associations with *VKORC1* and *CYP2C9* represent one of the most successful applications of pharmacogenetics to date," the authors observed.

After adjusting for factors known to influence warfarin dose (the preceding 2 genes, age, and sex) the investigators identified 1 additional SNP in *CYP4F2* ($P < 8.3 \times 10^{-10}$). These findings, presented at the American Society of Human Genetics annual meeting in November 2008, were previously reported by *Medscape Pathology & Lab Medicine*.

CYP4F2 association with warfarin dose was further validated by this group in a replication test of Swedish warfarin patients (n = 588), as well as discovery in an independent study of transporter and warfarin-metabolizing genes. Results of the replication combined with GWAS results yielded an overall $P < 3.3 \times 10^{-10}$. Investigators detected no additional strong warfarin associations in this population for haplotypes, copy number variations, or imputed SNPs.

The authors point out that their GWAS and statistical analysis imply that "additional common SNP variants that influence [warfarin] dose may not exist in Caucasian populations." However, "Caucasians might carry common variants with effects smaller than *CYP4F2* or rare variants whose effects are substantially larger than the ~1% of dose variance explained by *CYP4F2*." It is likely that other genes, yet unidentified, may be associated with warfarin dose in Asian or African populations and should be investigated, the authors note.

"[A]dditional major genetic predictors may not exist in Caucasians or may not emerge in the near-term," the investigators write. They conclude that "large-scale trials of patient benefit from dose forecasting based on *VKORC1* and *CYP2C9* (with possible inclusion of *CYP4F2* as a minor predictor) are likely to provide state-of-the-art clinical benchmarks for warfarin use during the foreseeable future."

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