Medscape Medical News

ASHG 2008: Genomewide Association Study Finds Genetic Predictors of Warfarin Required Dose CME/CMLE

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Disclosures

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From the American Society of Human Genetics 58th Annual Meeting

November 17, 2008 (Philadelphia, Pennsylvania) — Genomewide association studies have identified another gene variant that influences individual variations in response to warfarin dosage. Warfarin, described as the 11th most widely prescribed drug worldwide, is an effective anticoagulant used in patients with stroke, myocardial infarction, and pulmonary embolism. However, among whites, the required dosage varies 10- to 20-fold between individuals. A dose that creates bleeding problems in some patients may fail to protect others against clotting disorders.

In the November 14 presentation here at the American Society of Human Genetics 58th Annual Meeting, and a subsequent press briefing, Ralph E. McGinnis, PhD, a statistical geneticist at the Wellcome Trust Sanger Institute, Cambridge, United Kingdom, described a genomewide association study (GWAS) focused on genetic predictors of required warfarin dose.

The clinical index of appropriate warfarin dose is a coagulation level known as the prothrombin time international normalized ratio (INR). The INR for a healthy person is 1.0, but for patients taking warfarin to reduce clotting, the target INR is 2.0 to 3.0. Lacking predictive information about genetic and nongenetic factors influencing a patient's warfarin response, physicians determine doses empirically and initially may err in either direction.

Dr. McGinnis and colleagues were among the first to demonstrate that polymorphisms in *VKORC1*, the drug target of warfarin, may alter gene expression and explain approximately 30% of variation in warfarin response. Variants in *CYP2C9*, a gene coding for a liver enzyme that metabolizes warfarin, account for about 12% of the dose variation. Factors such as age and sex explain another 15% of the variation. A study in press, involving 1523 Swedish patients, assessed patient benefits of forecasting the required warfarin dose.

The current GWAS genotyped 1053 Swedish patients in the Warfarin Genetics (WARG) cohort and determined the mean warfarin dosage required to establish an INR of 2.0 to 3.0 in each subject. Doses ranged from 5.0 to 107.0 mg/week. Univariate regression analysis

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Learning Objectives
Upon completion of this activity, participants will be able to:

1. Inform clinicians of the latest medical information on genetic factors affecting the variability in the therapeutic dose of warfarin, as presented at the American Society of Human Genetics 58th Annual Meeting.
2. Describe the relevance of the findings on genetic variation in warfarin response in different patients to clinicians in the care of their patients who require warfarin treatment.

Authors and Disclosures

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found *VKORC1* and *CYP2C9*, previously identified, and multiple regression analysis identified a third gene associated with response to warfarin: *CYP4F2* (P = 8.3 x 10^{-10}). The single-nucleotide polymorphism (SNP) alters the coding sequence for the gene product.

"This new gene [*CYP4F2*] that we found only explains about 1.5%, actually, of the variation in dose. The rest of our study involves calculations of what might have evaded detection, flown under the radar so to speak, in this scan technology that we use," said Dr. McGinnis in the press briefing.

"[T]here may be other common SNPs out there ... that we weren't able to detect. They probably only account for 2% to 3% of the variation in dose. ... Also possibly there are low frequency SNPs that are carried by less than 10% of individuals, that we missed, that might individually contribute a lot of the variation in dose — maybe up to 5%," Dr. McGinnis suggested. The investigators concluded that the GWAS had greater than 80% power to detect SNPs that explained 1.5% of the dosage variance, but 40% or less power for SNPs explaining variance below 1%. The statistical techniques were considered critically important for successful detection of genetic predictors.

Clinical trials are currently underway to determine whether genetic prediction of dose benefits patients, and there is evidence that it does. The FDA recommends, but does not mandate, that genetic information should be considered in deciding the warfarin dose. "Our GWAS, at this point, lays out what the genetic landscape looks like, and gives more impetus to conducting trials showing that *CYP2C9*, *VKORC1*, [and] *CYP4F2* are the major genetic predictors," said Dr. McGinnis. "There may be some other ones that we will find ... It's not perfect, but it's a lot better than doing it empirically, adjusting by trial and error."

Medscape Pathology & Lab Medicine asked Dr. McGinnis if identifying additional dose-associated genes would yield significant benefits. "My expectation is that the clinical trials taking place now will be evaluated for success, and I think there will be more work on warfarin to try to detect other genes, other variants ... that may contribute sizeable amounts — they may contribute 5% or 3% or 4%. Those are the sizes contributed by the polymorphism of lesser effect that changes the coding sequence of the warfarin metabolizing gene *CYP2C9*," he said.

"I think that we've probably found the really big effects, the drug target, but there may still be polymorphisms that individually explain 3% to 5% of the variance which, when you put them together, might account for quite a bit... Another possibility is that we may not find that much more. It's really an empirical question," concluded Dr. McGinnis.

Medscape Pathology & Lab Medicine also discussed the study with comoderator Joel N. Hirschhorn, MD, PhD, professor of genetics and pediatrics, Children's Hospital, Harvard Medical School, and coordinator of the Metabolism Initiative, Broad Institute of Harvard and MIT, Boston, Massachusetts. "If you're trying to use [the SNPs] just for a predictive algorithm, they've got a fair bit of the variability explained already," said Dr. Hirschhorn. "If they could explain a substantial chunk more of the variability, that might be more useful. But this study would indicate that you'd need a very much larger sample size or a different approach to get at most of the rest of the variability. And I think it remains to be seen how clinically useful the current amount of information is."

Dr. McGinnis and Dr. Hirschhorn disclosed no relevant financial relationships.

American Society of Human Genetics 58th Annual Meeting. Abstract #163. Presentation and press briefing. Presented on November 14, 2008.

Pearls for Practice

- Genetic coding in the genes *VKORC1*, *CYP2C9*, and *CYP4F2* explain 30%, 12%, and 1.5%, respectively, of the variance in the warfarin dose required to achieve an INR of 2.0 to 3.0, while other genes may account for 3% to 5% more of the variance.
- The other factors that account for about 15% of the variation in warfarin dosage to achieve an INR of 2.0 to 3.0, which can be a dosage that ranges from 5.0 - 107.0 mg/week, include age and sex.

CME / CE Test

Questions answered incorrectly will be highlighted.

Which of the following genes explains the smallest amount of variance in accounting for the warfarin dose required to achieve an INR of 2.0 to 3.0?

to change based on topic selection and article length.

AAFP Accreditation Questions

American Society for Clinical Pathology

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