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Sanger Researchers, Collaborators Uncover Warfarin Response Genes in Large GWAS

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PHILADELPHIA (GenomeWeb News) – In a genome-wide association study of more than 1,500 Swedish individuals, researchers from the Wellcome Trust Sanger Institute and elsewhere have uncovered three SNPs associated with warfarin dose response.

Based on their GWAS study of 1,523 individuals in the Warfarin Genetics cohort, the team identified two SNPs in well-known warfarin response genes — VKORC1 and CYP2C9 — as well as a SNP that changed the coding sequence of a third gene, CYP4F2, Sanger statistical geneticist Ralph McGinnis told reporters today at the American Society of Human Genetics meeting here.

Others have implicated CYP4F2 as having a role in warfarin metabolism, McGinnis said, but it has not been previously detected in large-scale dose response studies.

The researchers verified these results in a smaller study of nearly 600 Swedes.

Because there is such a wide variation in the warfarin dose required to achieve a targeted amount of blood thinning, researchers are using GWAS in an effort to find genetic variants influencing dose response. This is not the first such study, but, McGinnis said it is the largest to date.

McGinnis and his team concluded that variations in VKORC1, CYP2C9, and CYP4F2 can predict 29 percent, 11 percent, and 1.5 percent of the warfarin response, respectively. Together with factors such as age and gender, which account for roughly 15 percent of the variation in warfarin response, the team noted that it is now possible to predict about half of the warfarin response variation observed in treated individuals.

The researchers also made predictions about the sorts of genetic variations that may have evaded their detection. For instance, McGinnis noted that SNPs commonly found in the general population may influence two to three percent of the variation in warfarin response. On the other hand, he added, there may be low-frequency SNPs — carried by fewer than ten percent of individuals — that influence around five percent of the variation.

In addition, McGinnis said, the researchers may have missed other genetic variants such as copy number variations and inversions.

Down the road, the researchers hope to gain even more insight into the genetics of warfarin response. For example, McGinnis noted that they are interested in finding genetic variants that can help predict adverse warfarin response events, such as a sometimes-fatal severe bleeding condition that affects a small percentage of those taking the drug. These variants may not necessarily be the same as those influencing dose response, he added.

While McGinnis stressed that he is a research scientist and not a clinician, he expressed optimism that such genetic approaches will improve warfarin treatment, decreasing over- and under-dosing and adverse events. “This is potentially an important advance,” he said. “Our GWAS lays out what the genetic landscape looks like.”