Sanger-Led Team Publishes Results of Warfarin GWAS

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NEW YORK (GenomeWeb News) – Researchers from the Wellcome Trust Sanger Institute and elsewhere have published data on a large genome-wide association study aimed at detecting polymorphisms related to warfarin dose. The work appeared online today in *PLoS Genetics*.

The published paper follows a presentation of the results of the study presented last November at the American Society of Human Genetics meeting.

The researchers sequenced more than 1,000 Swedish individuals at nearly 326,000 SNPs to look for genetic variants influencing warfarin dose requirements. Along with polymorphisms in two known warfarin-related genes, *VKORC1* and *CYP2C9*, they found a third variant in a gene called *CYP4F2* that also contributes to warfarin dose variability — an association that the team validated in almost 600 other Swedish patients.

"We are quite confident that in terms of common variants ... this approach has identified what is there," senior author Panos Deloukas, a senior investigator in human genetics at the Sanger Institute, told *GenomeWeb Daily News*. "What we cannot exclude is that there are more rare variants."

Variants in the genes for two enzymes — vitamin K epoxide reductase complex subunit 1 gene, or *VKORC1*, and cytochrome P450 2C9, or *CYP2C9* — have been linked to warfarin dose response. And in 2007, the US Food and Drug Administration updated the warfarin guidelines to encourage testing for polymorphisms in these genes. Still, the SNPs identified so far only explain some of the observed variability in warfarin dose, which can differ by up to 20-fold in individuals of European descent.

In an effort to identify additional warfarin dose-related polymorphisms, the team genotyped 1,053 Swedish individuals at 325,997 SNPs using the Illumina HumanCNV370 BeadChip array and two additional *VKORC1* and *CYP2C9* SNPs from the Applied Biosystems' TaqMan assay. The subjects were enrolled through the Warfarin Genetics study, a multi-center study of warfarin-related bleeding complications and treatment response.

As expected from previous studies, the GWAS turned up three SNPs: one in *VKORC1* and two in *CYP2C9*. The researchers also found an association between warfarin dose and a SNP in the cytochrome P450 4F2 gene, which they subsequently validated in an independent cohort consisting of another 588 Swedish individuals.

CYP4F2 was also implicated as a factor in warfarin dose by another group, Deloukas noted — work that was published while he and his colleagues were writing up their results.

Overall, the team concluded that *VKORC1* explains roughly 30 percent of the variance in warfarin dose

response while *CYP2C9* and *CYP4F2* explain about 12 percent and 1.5 percent, respectively.

The researchers' search for copy number variations influencing warfarin dose, also using the Human CNV370 array, was less fruitful. They speculated that this may be because the array they used doesn't have sufficient power to detect common CNVs across the entire genome.

"The current chip doesn't have the right content for CNV analysis," Deloukas explained, noting that other chips, such as the one used to evaluate Wellcome Trust Case Control Consortium samples, may be more useful for evaluating CNVs.

In the future, the researchers plan to look at larger sample sizes and may start directly comparing the genetics of individuals who experience bleeding events while taking warfarin with those who don't, Deloukas said. He also emphasized the need for research to assess warfarin-related genetics in individuals from non-European populations.

And with the roster of warfarin-related common variants apparently nearing completion, researchers are starting to turn their attention to rare variants. Deloukas predicts that in the "not too distant future" genome sequencing will help uncover some of the rare variants influencing warfarin dose. "New sequencing technologies will allow us to tackle [rare variants] in a more efficient way because we can really search the entire genome," he explained.

Based on their results so far, the researchers suggest that "clinical trials assessing patient benefit from individualized dose forecasting based on a patient's genetic makeup at *VKORC1*, *CYP2C9*, and possibly *CYP4F2* could provide state-of-the-art clinical benchmarks for warfarin use during the foreseeable future."

Indeed, other groups have started assessing the usefulness and cost effectiveness of using genetic variants to guide warfarin dosing. For example, a study published in the *New England Journal of Medicine* last month suggested that genetic testing for *CYP2C9* and *VKORC1* polymorphisms improves warfarin dose predictions for those who need relatively high or low doses of the drug.

Meanwhile, a study published in the *Annals of Internal Medicine* this January indicated that warfarin genetic testing is only cost effective for dosing individuals at high risk of hemorrhaging. Even so, Deloukas believes warfarin genetic testing holds great potential benefit for patients.

"I still believe that there is a very good value for the patient that is treated," he said.