Team finds genetic variant that could improve warfarin dosing in African-Americans

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In the first genome-wide association study to focus on warfarin dose requirement in African-Americans, a multi-institutional team of researchers has identified a common genetic variation that can help physicians estimate the correct dose of the widely used blood-thinning drug warfarin.

The discovery, reported online first in *The Lancet*, suggests that people of African ancestry who carry this variant—more than 40 percent of the patients enrolled in this study—need significantly less warfarin to obtain optimal benefits compared to those who lack this variant.

"Adding this genetic marker to standard dosing algorithms could improve the predictability of warfarin dosing by 21 percent in these individuals, increasing the safety and effectiveness of this notoriously hard to administer drug," said Julie Johnson, PharmD, a distinguished professor of pharmacy and medicine at the University of Florida and a leader of the International Warfarin Pharmacogenetics Consortium.

Warfarin, used to prevent blood clots after a heart attack, stroke or major surgery, is one of the world's most widely prescribed drugs, accounting for more than 33 million prescriptions in the United States in 2012. It is also a drug for which correct dosing is notoriously difficult.

"It's very important to get warfarin dosing right," said the study's lead

author, Minoli Perera, PharmD, PhD, assistant professor of medicine at the University of Chicago. "People take this drug because they've had a clotting problem. If you give them too little, they could form another clot, possibly causing a stroke or pulmonary embolism. If you give too much, they could bleed."

But dose requirements vary widely, making it difficult to get the quantity right. "Some people need a few milligrams per day and some need 20," Perera said. The average dose for African-Americans generally has been about 30 percent higher than that for Caucasians.

As a consequence, warfarin contributes to a third of hospitalizations for adverse drug reactions in people older than 65 years in the United States. "It is one of the most litigated of drugs," Perera said.

Earlier studies found variations of two genes, VKORC1 and CYP2C9, that can predict about 30 percent of the difference in warfarin response in people of European or Asian ancestry. These genetic markers have proved less useful in determining the proper dose in African-Americans.

To identify additional genetic factors that control warfarin dose requirements in African-Americans, Perera, Johnson and colleagues analyzed health information and DNA samples from 533 African-American adults on stable doses of warfarin from several sites. The majority of patients came from the University of Chicago, the University of Illinois at Chicago, and the University of Alabama at Birmingham.

The researchers found a strong association between one gene variant known as rs12777823 on chromosome 10 and warfarin dose. This finding was corroborated in a second independent cohort of 432 additional African-American patients.

The genome study showed that African-Americans who possess one copy of this genetic variant need to reduce their dose by about 6 mg per week. Those with two copies of this variant may need to reduce their dose by as much as 9 mg per week.

By factoring genetic information into the standard formula for estimating the dose, physicians could improve their starting point for determining the optimal warfarin dose by 21 percent.

"We still don't know every genetic or environmental factor that plays a role in determining the ideal dose," Perera said. "But this improves our starting point. Working from that baseline, we can adjust doses until we have it right. This finding can help us get to the therapeutic dose quicker."

In an accompanying editorial in the journal, stroke specialist Mark Alberts, MD, professor of neurology and neurotherapeutics at the University of Texas Southwestern Medical Center in Dallas, notes that there has long been a need to identify "additional genetic factors that play a role in determining warfarin metabolism … so that the accuracy of various dosing algorithms can be optimized."

"This is particularly true for African-American patients," he wrote, "since prior studies have not enrolled such patients in large numbers, and current genetic markers appear to be less predictive of dosing regimens in this population."

This study is also a triumph for a growing effort to focus more attention on genomic studies of health issues among African-Americans.

"There have been several studies like this one that relied almost entirely on Caucasian populations, and they came up dry," Perera said. "They kept finding the same genes over and over again. It's reassuring to

replicate previous studies, but only when we shifted the focus to African-Americans did we find something new and different."

"The need for more studies such as this in the African-American population is critical," she added. "Not only do they help to make personalized medicine available to everyone, but as our study demonstrates, they can provide clinically important results that could never have been found by looking for them only in Caucasians."

More information: www.thelancet.com/journals/lan … (13)60942-3/abstract

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