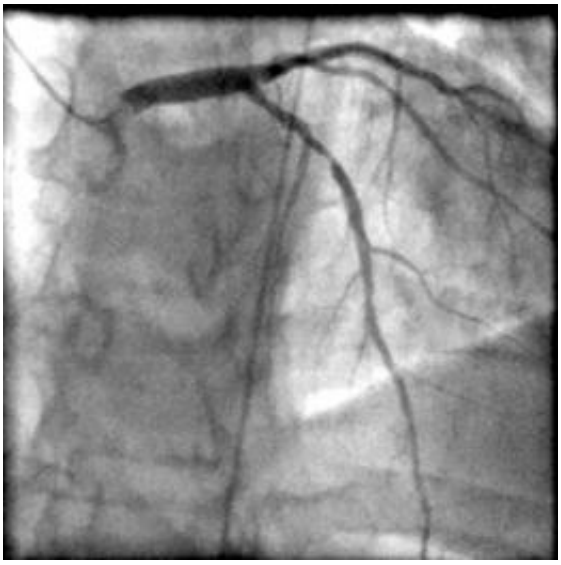
Genetic variant linked to blocked heart arteries in patients with diabetes

September 28 2011, By Julia Evangelou Strait



An example of a coronary angiogram, the imaging method used to assess the severity of coronary artery disease in patients enrolled in the BARI 2D clinical trial. Credit: RICHARD BACH AND SHARON CRESCI

(Medical Xpress) -- Researchers at Washington University School of Medicine in St. Louis have identified the first genetic variant associated with severity of coronary artery disease in patients with type 2 diabetes.

Though this variant is not likely the cause of more severe coronary disease, the researchers say, it implicates a gene that could be. Such a gene has promise as a future target for treating coronary artery disease in

diabetic patients.

“There is a knowledge gap in our understanding of diabetes and how it promotes both coronary artery disease and worse outcomes for patients who have diabetes,” says cardiologist Richard G. Bach, MD, associate professor of medicine. “Any insights into what might be causing this may benefit patients in the future.”

This genetic variant is a change in only one or two letters of a person’s DNA sequence and is located in a gene called TLL1 that is known to be involved with inflammation and calcification of blood vessels. Implicating the TLL1 gene may help guide future research into understanding the mechanisms behind aggressive coronary artery disease in diabetic patients.

“TLL1 and the genes downstream of it have not been on anyone’s radar when investigating diabetes or coronary artery disease,” says cardiologist Sharon Cresci, MD, assistant professor of medicine and first author on the paper published in the Sept. 27 issue of the journal *Circulation*.

Of DNA’s four-letter “alphabet,” A, C, G and T, the most common sequence for this portion of the TLL1 gene is TT. On average, patients with CT in that portion of the sequence had 22 percent more coronary lesions blocking arteries that supply blood to the heart than those with the TT sequence. And those with CC had 37 percent more lesions than those with TT.

On an individual level, the researchers calculated how these variants change the number of lesions for the average patient in the study: a 63 year-old white male with a body mass index of 30 (borderline between overweight and obese).

With the TT sequence, that average patient would have 4.43 lesions. But

if that same patient happened to have the CT sequence, the number of lesions increases to 5.02. And if the sequence is CC, the number increases to 5.46.

“The change in the absolute number of lesions in one person might be small,” Cresci says. “However, this is one variant in the grand scheme of everything else – the rest of the person’s genome and all of the environmental factors. For one variant, it has a remarkably strong correlation to the severity of coronary disease.”

Indeed, the variant predicted the extent of the patient’s coronary artery disease better than the familiar clinical factors typically used to assess risk of blocked arteries, such as age, smoking status, body mass index and blood pressure.

The patients in this study were participants in a worldwide clinical trial called BARI 2D, which stands for Bypass Angioplasty Revascularization Investigation 2 Diabetes. Between 2001-08, this multi-center trial, led by the University of Pittsburgh, investigated treatment strategies for patients with both type 2 diabetes and cardiovascular disease. Bach helped lead the portion of the study conducted at Washington University Medical Center, along with Ronald J. Krone, MD, professor of medicine, and Janet B. McGill, MD, professor of medicine and a co-author of the paper.

All patients in the study had both type 2 diabetes and established coronary artery disease. But their arteries were not so congested that they required immediate bypass surgery. A subset of patients in BARI 2D agreed to participate in the genetic portion of the study and have their DNA sequenced.

After identifying the TLL1 variant associated with more blocked arteries in these patients, the researchers verified their results in two independent

populations of diabetic patients – those in the TRIUMPH study (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status), whose coronary disease was assessed with an angiogram (like BARI 2D) and those in the Family Heart Study, whose disease was evaluated with a coronary CT scan.

"We feel this is a strength of our study," Cresci says. "We looked at the extent of coronary artery disease with two different imaging methods in three independent patient populations and got the same results."

In comparing their findings to the TRIUMPH and Family Heart Study results, they also included participants who did not have diabetes. In those individuals, the same genetic variant did not significantly correlate with the extent of coronary disease. Such findings support the idea that coronary artery disease in diabetic patients is inherently different from the disease in the rest of the population.

"The progression and behavior of coronary artery disease appears uniquely aggressive in patients with diabetes," Bach says. "The disease appears to progress more rapidly and be much more widespread than in patients who do not have diabetes."

The researchers also note that they were able to see this association only in white patients. BARI 2D included African-American participants, but the smaller sample size meant no conclusions could be drawn about whether the association holds true in this group.

Ultimately, a major goal is to treat patients based on their specific genetics.

"In an ideal situation, you would select drug treatment based on the individual's DNA sequence," Cresci says. "Maybe the people with the TT genotype would get one medication, but the ones with CC would get

different therapeutics. Obviously, we're a long way from that, but that's where we would like to be. And that is where work like this is going."

More information: Cresci S, et al., BARI 2D Study Group. Peroxisom proliferator-activated receptor pathway gene polymorphism associated with extent of coronary artery disease in patients with type 2 diabetes in the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial. *Circulation*. Online Sept. 12, 2011.

Provided by Washington University School of Medicine in St. Louis