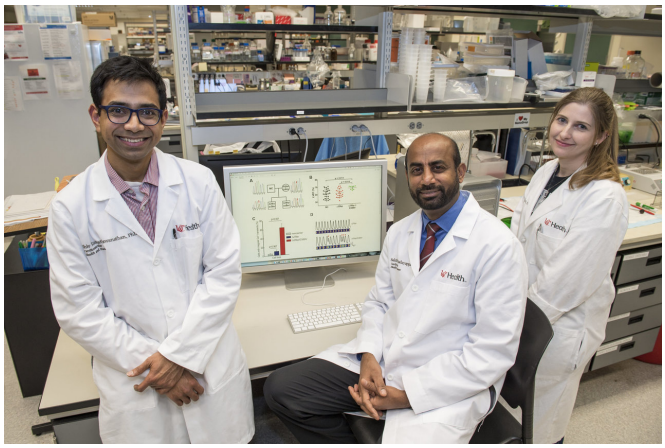
Genetic variant might be a better marker for heart disease

11 April 2018



Shiv Kumar Viswanathan, Ph.D., Sakthivel Sadayappan, Ph.D., and Jennifer A. Schwanekamp, Ph.D., shown in a laboratory in the University of Cincinnati College of Medicine. Credit: University of Cincinnati College of Medicine

Researchers at the University of Cincinnati (UC) College of Medicine have found that a newly identified subset of a known genetic variant found primarily in individuals of South Asian descent may be a better marker for carriers of heart dysfunction in this population and that individuals with this genetic variant are more likely to develop early signs of hypertrophic cardiomyopathy.

The findings are published in the April 11, 2018 edition of the journal *JAMA Cardiology*. The article is titled "Association of Cardiomyopathy with MYBPC3 D389V and MYBPC3?25bp Intronic Deletion in South Asian Descendants."

The variant is known as myosin binding protein C, cardiac 25-base pair deletion (MYBPC3?25bp) and the subset variation as D389V. This variant and subset have not been found in populations outside of individuals with South Asian ancestry.

"What we are seeing is the genetic variant is probably marking a population and within this group there can be a subpopulation that is even more at risk of cardiomyopathy," says Shiv Kumar Viswanathan, PhD, post-doctoral fellow in the UC Division of Cardiovascular Health and Disease, and the study's lead author. "We have previously shown that some of the people with no other mutation than just 25-base pair deletion, went on to have cardiomyopathy.

"If we can predict in that population those who are at higher risk then we can hone in and focus on them and get them to a physician's care faster," he says.

Hypertrophic cardiomyopathy occurs when heart muscle cells enlarge and cause the walls of the ventricles to thicken. The ventricle size often remains normal, but the thickening may block blood flow out of the ventricle and cause the heart to work harder. Hypertrophic cardiomyopathy, also commonly referred to as enlarged heart, can lead to sudden cardiac arrest.

Myosin binding protein C, cardiac 25-base pair deletion (MYBPC3?25bp) is prevalent in 4 to 6 percent of individuals of South Asian descent and while associated with a greater risk of various forms of cardiomyopathies and heart failure, it is not the only factor that may indicate whether someone develops heart dysfunction, says Sakthivel Sadayappan, PhD, professor in the UC Division of Cardiovascular Health and Disease and the study's corresponding author.

For the study, researchers screened 2,401 South Asians living in the U.S. for MYBPC3?25bp and found that 6 percent, or 144 individuals, carried the genetic variant. Of that population, 9.6 percent or 13 individuals also carried the novel MYBPC3 variant D389V on the same single allele. Researchers think the prevalence of both the variant and subset occurring in the population of

people of South Asian descent to be 1 in 200 individuals.

"We checked 174 genes by next generation DNA sequencing that are known to be in the heart and possible mutations in these genes that could cause cardiomyopathies, and we found this particular subset variation stood out uniquely from the rest of the modest changes," says Sadayappan.

Electrocardiograms along with blood and DNA samples were taken from study participants, who were divided into three groups: non-carriers of the genetic variant, individuals with only the genetic variant MYBPC3?25bp and individuals who have MYBPC3?25bp along with the new subset D389V. Researchers found that D389V did not occur without MYBPC3?25bp and that individuals carrying the variant and its subset had significant increases in their left ventricular ejection fraction (LVEF).

An ejection fraction indicates how much blood the left ventricle pumps out with each contraction. A number surpassing 75 may indicate pre-hypertrophic cardiomyopathy, says Sadayappan.

Viswanathan says the hearts of the 13 individuals in the study carrying the genetic variant and the new subset were on a pathway to hypertrophy.

"For these subjects, their heart is in an over-pumping phase," says Viswanathan. "The heart goes through phases before it approaches hypertrophy. It becomes thick before it gets to a phase where it is pumping like crazy. The heart can't sustain that force so it becomes thicker and then the thickness isn't compensating so it loses the force and becomes like a floppy balloon.

"Everyone who had the myosin binding protein C, cardiac 25-base pair deletion and the D389V subset were heading toward hypertrophy. All of them had this super contraction phase. We took the blood cells from them and made them into heart cells in the laboratory. The difference between those with 25-base deletion and those with the added subset is stark. The heart cells from the genetic variant subset are thicker, bigger and they are performing poorer than other samples."

Sadayappan, research director in the UC Heart, Lung and Vascular Institute, says more study is needed to determine how environmental factors such as diet, stress and sedentary lifestyles impact the heart health of individuals carrying the genetic variant alone and those with the variant and new found subset. He says the study was done in the United States and needs to be replicated in South Asia.

Provided by University of Cincinnati Academic Health Center