Black individuals with a genetic mutation found to have increased risk of developing atrial fibrillation, heart failure

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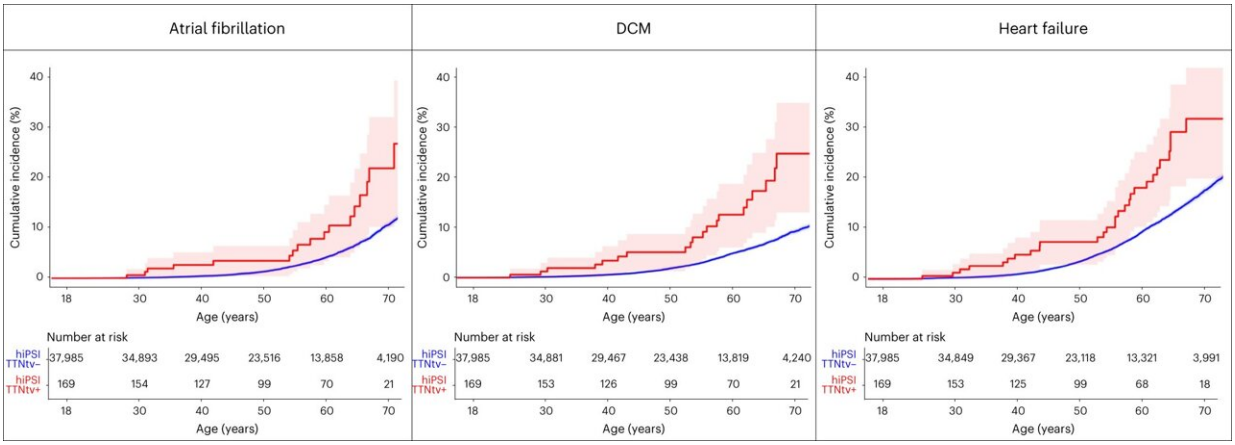


This figure depicts the cumulative incidence of the study outcomes stratified by the hiPSI TTNtv carrier status in individuals of African ancestry. The study outcomes include atrial fibrillation, DCM and heart failure. TTNtv carriers and noncarriers have been depicted in red and blue, respectively. Credit: *Nature Cardiovascular Research* (2024). DOI: 10.1038/s44161-023-00417-5

Physician–scientists from the University of Alabama at Birmingham Marnix E. Heersink School of Medicine led a nationwide genetic study

examining the role of genetic mutations in the Titin, TTN, gene in Black individuals. In their study, published in *Nature Cardiovascular Research* they found that Black individuals carrying these genetic variants were at a high risk of developing atrial fibrillation and heart failure.

"Titin is an essential protein that is required for the contraction and relaxation of the heart," said Naman S. Shetty, M.D., a research fellow in the UAB Division of Cardiovascular Disease and first author.

Shetty explains the TTN gene, encoding the Titin protein, is one of the largest genes in humans.

"The sheer size of the gene makes it prone to genetic mutations," Shetty said. "However, not all mutations in the Titin gene cause disease. A specific subset of mutations known as high-proportion splice-in (hiPSI) Titin truncating variants (TTNtvs) have been found to increase the risk of diseases such as atrial fibrillation and heart failure. These hiPSI TTNtvs variants are a unique set of mutations that expressed at least 9 out of 10 times in the Titin protein and disrupt the structure of the protein."

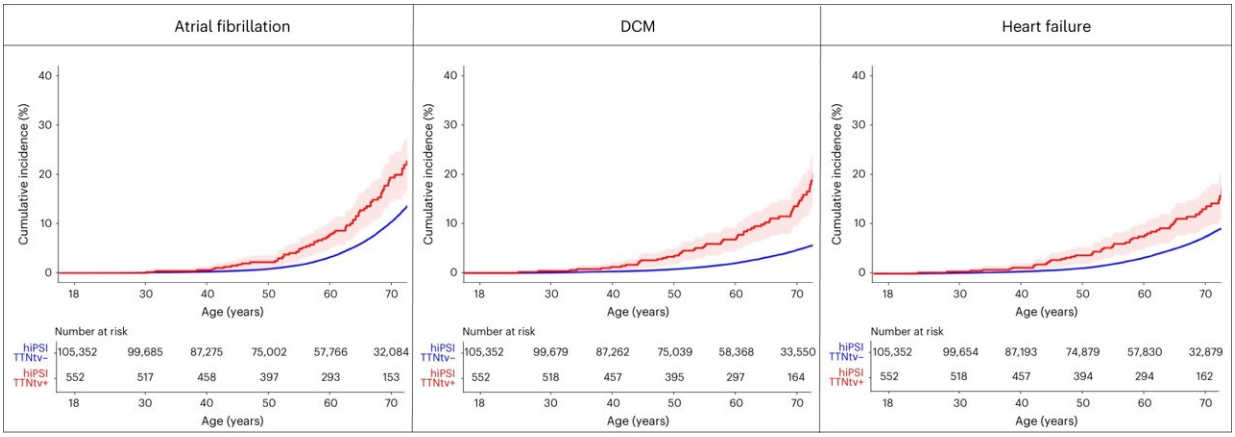
Prior studies showed that these variants increase the risk of atrial fibrillation, heart failure and dilated cardiomyopathy in white individuals.

"DCM is a rare type of heart disease where the chambers of the heart enlarge in size, which prevents the heart from effectively pumping blood to the rest of the body," Shetty said. "Due to the underrepresentation of Black individuals in genetic studies, the role of hiPSI TTNtvs in the development of atrial fibrillation, heart failure and DCM could not be established in Black individuals."

Shetty and his team leveraged data from the All of Us Research Program to examine if hiPSI TTNtvs were associated with adverse cardiovascular events in Black individuals. The All of Us Research Program is a program that aims to recruit a diverse group of individuals from across the United States and promote precision medicine research by providing researchers with access to genetic and phenotypic data.

"Since race is predominantly considered as a social construct, we used the genetic data to ascertain the genetic ancestry in each individual," Shetty said. "Using genetic ancestry, we conducted our analysis in individuals of African ancestry. We found that individuals of African ancestry carrying a hiPSI TTNtv were at a twofold higher risk of developing atrial fibrillation, DCM and heart failure."

This study generated comparative data in individuals with European ancestry.



This figure depicts the cumulative incidence of the study outcomes stratified by the hiPSI TTNtv carrier status in individuals of European ancestry. The study outcomes include atrial fibrillation, DCM and heart failure. TTNtv carriers and noncarriers have been depicted in red and blue, respectively. Credit: *Nature Cardiovascular Research* (2024). DOI: 10.1038/s44161-023-00417-5

"Similar to the prior studies, we found that carriers of a hiPSI TTNtv had a high risk of developing atrial fibrillation, DCM and heart failure," said Pankaj Arora, M.D., senior author and an associate professor in the UAB Division of Cardiovascular Disease. "Notably, the increase in risk of atrial fibrillation, DCM and heart failure among carriers were similar in individuals of African and European ancestry."

Arora directs the UAB Cardiogenomics Clinic and is regularly involved in the care of patients with DCM and says the study was born out of the observation at the clinic, where they noticed that a large proportion of patients with DCM carried mutations in the Titin gene, irrespective of their race. However, corroborative evidence in literature was lacking.

"Our study highlights that hiPSI TTNtvs are equally pathogenic across ancestry groups," Arora said. "The All of Us Research Program provides us with access to a large group of individuals from diverse ethnic backgrounds, which allowed us to examine the role of hiPSI TTNtvs in causing cardiovascular disease across two ancestry groups."

"Our findings support the role of genetic screening for hiPSI TTNtvs in both European and African ancestry," Arora said. "Identification of these individuals may allow regular monitoring and preventive measures to delay the onset of disease. Furthermore, identification of carriers may also prompt cascade screening wherein first-degree relatives of the carrier undergo genetic screening as they have a likelihood of carrying the same genetic variant."

Arora emphasizes the need to increase awareness of the role of hiPSI TTNtvs in causing DCM and to develop and implement a population screening for hiPSI TTNtvs.

More information: Naman S. Shetty et al, High-proportion spliced-in titin truncating variants in African and European ancestry in the All of Us Research Program, *Nature Cardiovascular Research* (2024). DOI: 10.1038/s44161-023-00417-5

Provided by University of Alabama at Birmingham