Researchers show genetic variant common among Black Americans contributes to large cardiovascular disease burden

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Researchers at Brigham and Women's Hospital and Duke University showed that a genetic variant, present in 3-4% of self-identified Black individuals in the U.S., increases the risk for both heart failure and death and contributes to significant decreases in longevity at the population

level

A genetic variant carried by 3-4 percent of self-identified Black Americans increases the risk for heart failure and death, contributing to a significant decrease in longevity at the population level, according to a new study led by researchers at Brigham and Women's Hospital, a founding member of the Mass General Brigham health care system, and Duke University School of Medicine. The new research shows that individuals who carry the V142I transthyretin variant are at significantly increased risk for heart failure beginning in their 60s, with an increased risk for death beginning in their 70s. Further, the researchers showed that carriers on average died 2 to 2.5 years earlier than expected. With nearly half a million Black Americans carriers over age 50, the researchers estimate that approximately a million years of life will be lost due to this variant among currently living Black individuals who are in mid-to-late life. Results are published in *JAMA*.

"We believe these data will inform clinicians and patients regarding risk when these genetic findings are known, either through family screening, medical, or even commercial genetic testing," said senior author Scott D. Solomon, MD, the Edward D. Frohlich Distinguished Chair, Professor of Medicine at Brigham and Women's Hospital and Harvard Medical School. "There are now several potential new therapies for cardiac amyloidosis, and understanding the magnitude of this risk, at the individual and societal level, will help determine which patients might be best suited for novel therapies."

The V142I variant causes transthyretin, a protein in the blood, to misfold leading to deposits of abnormal amyloid protein in the heart and other parts of the body. In the heart, these deposits cause the muscle to become thick and stiffened, a condition known as cardiac amyloidosis, which can ultimately lead to heart failure. Recently, several therapies have been developed to treat cardiac amyloidosis, including therapies

that: prevent the protein from misfolding, reduce the amount of protein, remove the protein, and even a gene-editing therapy that is currently undergoing clinical trials. A better understanding of the epidemiology of V142I and cardiac amyloidosis would help physicians connect patients with the appropriate treatment at the appropriate age, the researchers say.

Although the association between the V142I variant and heart failure has been previously described, precise estimates of how the variant increases risk were unclear until now. Considering approximately 48 million Americans self-identify as Black, 1.5 million across the lifespan are estimated to carry this variant. However, since effects of the variant aren't typically seen until after age 50, the researchers focused on the risk among Black Americans in mid-to-late life.

To uncover these details, the researchers pooled data from self-reported Black participants in four NIH-funded studies in the United States (ARIC, MESA, REGARDS and Women's Health Initiative). Altogether, the team examined data from 23,338 self-reported Black individuals, 754 (3.23 percent) of whom carried the V142I genetic variant.

They showed that V142I increased the risk for heart failure hospitalization by age 63 and the risk of death by age 72. The variant's contribution to heart failure risk increased substantially with age but was not itself increased by other known risk factors such as diabetes and hypertension. The team also showed that female and male carriers of the variant were equally at risk, contrary to some previous studies showing that men were more affected. This suggests that women are likely underdiagnosed with the condition. The researchers estimated that individual carriers with the V142I variant live 2-2.5 years less than expected.

"Since 3-4 percent of self-identified Black individuals in the United

States carry this variant, a significant number are at elevated risk for developing cardiac amyloidosis, being hospitalized for heart failure, and dying several years earlier than expected," said first author Senthil Selvaraj, MD, an advanced heart failure physician-scientist at Duke University School of Medicine. "With our improved understanding of the risks with the variant, future efforts to increase disease awareness and ultimately connect carriers with the disease to effective therapies will be important."

In future studies, the researchers plan to investigate why some, but not all, carriers of the V142I variant develop cardiac amyloidosis. They are also actively involved in developing and testing therapies for the disease, including the gene therapy mentioned above.

"One of the areas that will be really important going forward will be whether we can actually prevent the onset of the disease if we identify these patients earlier," said Solomon.

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More information: Selvaraj, S et al. Cardiovascular Burden of the V1421 Transthyretin Variant, *JAMA* (2024). DOI: 10.1001/jama.2024.4467

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