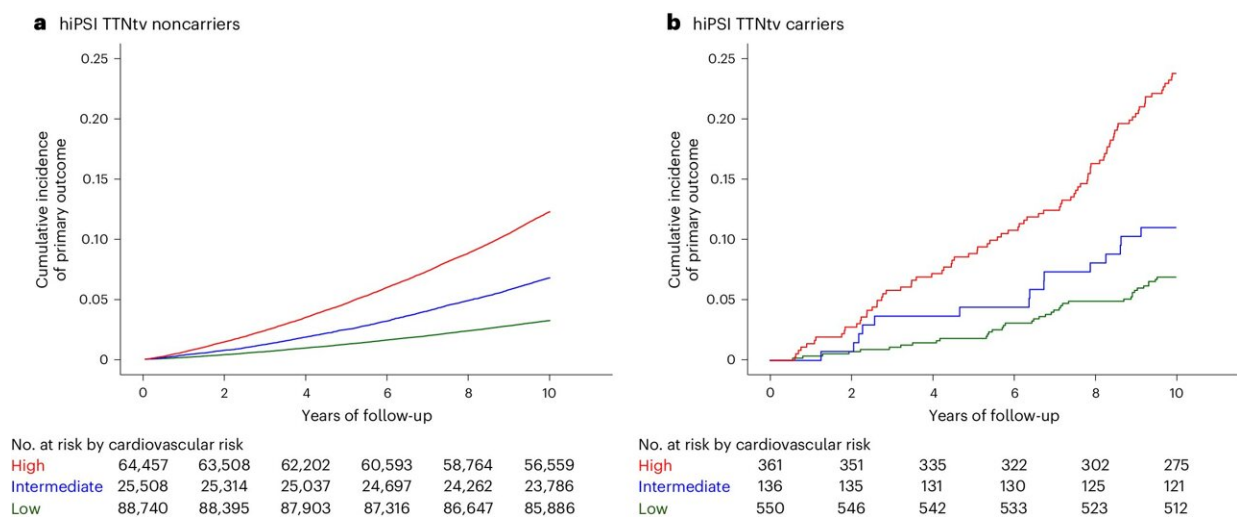


Study unveils impact of cardiovascular risk factors on genetic predisposition to heart disease

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Cumulative incidence of primary outcome stratified by hiPSI TTNtv carrier status and cardiovascular risk. Credit: *Nature Cardiovascular Research* (2024). DOI: 10.1038/s44161-024-00511-2

Physician-scientists from the University of Alabama at Birmingham Marnix E. Heersink School of Medicine have unveiled critical insights into the influence of high-proportion spliced-in titin truncating variants, or hiPSI TTNtv, on cardiovascular disease risk.

The [study](#), recently published in *Nature Cardiovascular Research*,

examines how these genetic variants can substantially elevate the risk of [heart disease](#), especially when combined with other cardiovascular risk factors such as hypertension, diabetes and hypercholesterolemia.

The titin gene produces a protein that is crucial for the structure and function of muscle cells, especially in the heart. When the gene is spliced in, parts of the gene are combined in a specific way to make the final protein. Truncating variants refer to a shorter, incomplete version of the protein. These mutations cause the production of an incomplete titin protein, and they are frequently included in the gene's final version. These changes can impact muscle function, particularly in the heart. They often cause enlargement and weakness of heart muscle.

The study, led by Pankaj Arora, M.D., and Naman Shetty, M.D., analyzed data from 179,752 participants in the UK Biobank to explore how these genetic variants, in combination with traditional cardiovascular risk factors such as hypertension, diabetes and hypercholesterolemia, impact the risk of heart disease.

Key findings from the study include:

- **Elevated risk in hiPSI TTNtv carriers:** Individuals carrying the hiPSI TTNtv genetic [variant](#) were found to have a significantly higher risk of developing heart disease when also possessing high cardiovascular risk factors.
- **Risk stratification:** Participants were categorized based on their cardiovascular risk levels such as low, intermediate or high. Those with low cardiovascular risk but carrying the hiPSI TTNtv variant exhibited nearly double the risk of serious heart complications compared to non-carriers. In contrast, carriers with high cardiovascular risk had an over eightfold increase in risk.
- **Increased incidence of heart events:** Among hiPSI TTNtv carriers, there were 14.03 heart-related events per 1,000 people,

compared to 7.19 events for non-carriers. Additionally, the study identified a significant increase in the incidence of atrial fibrillation and heart failure among those with the hiPSI TTNtv variant.

"Our findings highlight the necessity of personalized health care," Shetty said. "By comprehending both genetic and lifestyle risk factors, we can more effectively identify high-risk individuals and implement strategies to reduce these risks."

Arora is an expert in treating inherited cardiovascular diseases and a cardiologist at the UAB Cardiovascular Institute.

"Genetics are a crucial element, but maintaining a [healthy lifestyle](#) can significantly mitigate the risk of severe heart issues for individuals with this [genetic variation](#)," Arora said. "The idea for this research was to test whether DNA is destiny in monogenic causes of dilated cardiomyopathy. We leveraged [big data](#) to explore genetic determinism.

"Our research underscores the critical role of [cardiovascular risk factors](#) in influencing genetic risks. By managing these factors, we can potentially reduce the impact of genetic mutations on heart health."

Arora says this research represents a significant advancement in the understanding and prevention of heart disease, emphasizing the integration of genetic and lifestyle factors in personalized health care strategies. This study underscores its pivotal role in advancing our knowledge of cardiovascular health.

More information: Naman S. Shetty et al, Titin truncating variants, cardiovascular risk factors and the risk of atrial fibrillation and heart failure, *Nature Cardiovascular Research* (2024). [DOI: 10.1038/s44161-024-00511-2](#)

Provided by University of Alabama at Birmingham

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