Researchers identify potential genetic regulators of the heartbeat

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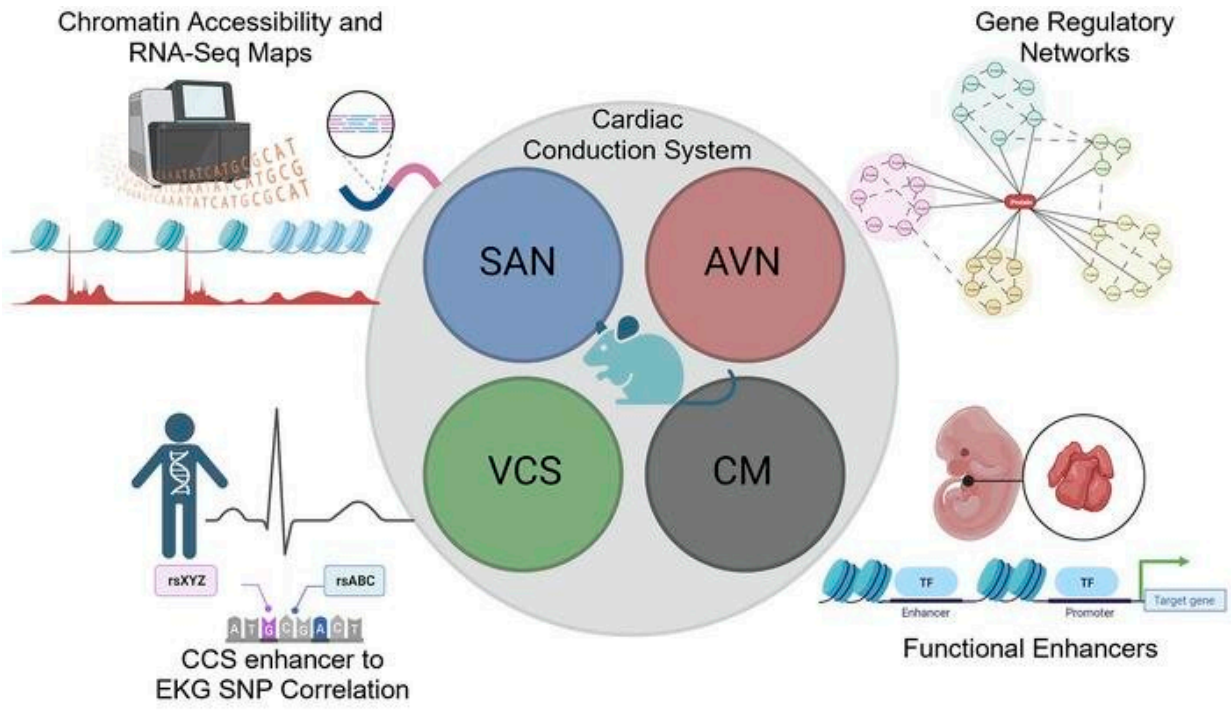

Credit: *Journal of Clinical Investigation* (2022). DOI: 10.1172/JCI153635

UT Southwestern Medical Center researchers have mapped gene control elements in specialized cardiac cells responsible for coordinating heartbeats. The findings of the genome exploration study, published in *The Journal of Clinical Investigation*, provide insight into how heartbeats are regulated and could impact diagnosis and risk prediction for a variety

of common arrhythmias.

"Our study provides the first road map for all the gene-control elements in the specialized population of cardiomyocytes responsible for cardiac rhythm," said corresponding author Nikhil Munshi, M.D., Ph.D., Associate Professor of Internal Medicine, Molecular Biology, in the Eugene McDermott Center for Human Growth and Development, and Assistant Director of the Division of Cardiology's Physician Scientist Training Program. "Among other things, we showed that this information enables us to better understand how certain noncoding, genomic variants in the human population influence a given individual's unique heart properties."

The cardiac conduction system, which comprises about 1%-5% of the heart cell population, coordinates a series of electrical impulses to ensure efficient heartbeat and blood circulation. Failure of this system to work properly can result in arrhythmias such as atrial fibrillation, sinus bradycardia, atrioventricular block, and ventricular tachycardia. Despite this vital function, little is known about the genetics and molecular makeup of this small group of heart cells.

Dr. Munshi and his team of UT Southwestern researchers sought to determine the control components of the cardiac conduction system. Using a technique previously developed by the Munshi lab (PAN-INTACT) and published in *PLOS ONE*, the team isolated nuclei—which contain the cells' genetic material—from mouse cardiac conduction system cells. Using a second method called ATAC-Seq, they identified parts of the genome that control gene expression, known as cis-regulatory elements (CREs).

The researchers gathered their results to establish a CRE database that can be used to better understand the functions of these cells and how they're regulated and help to interpret human variants associated with

arrhythmias.

The study has two immediate clinical implications, Dr. Munshi said. It will facilitate easier interpretation of clinical whole genome sequencing results in patients with familial arrhythmias, and it will enable future risk evaluation for common arrhythmias. Moreover, these results will help formulate hypotheses about how certain arrhythmias arise and potentially how they can be treated in the future.

Other UT Southwestern researchers who contributed to this work include Samadrita Bhattacharyya, Rahul K. Kollipara, Ralf Kittler, Gabriela Orquera-Tornakian, Sean Goetsch, Minzhe Zhang, Cameron Perry, Boxun Li, John M. Shelton, Minoti Bhakta, Jialei Duan, Yang Xie, Guanghua Xiao, Bret M. Evers, and Gary C. Hon.

More information: Samadrita Bhattacharyya et al, Global chromatin landscapes identify candidate noncoding modifiers of cardiac rhythm, *Journal of Clinical Investigation* (2022). DOI: 10.1172/JCI153635

Samadrita Bhattacharyya et al, PAN-INTACT enables direct isolation of lineage-specific nuclei from fibrous tissues, *PLOS ONE* (2019). DOI: 10.1371/journal.pone.0214677

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