Out of sync: How genetic variation can disrupt the heart's rhythm

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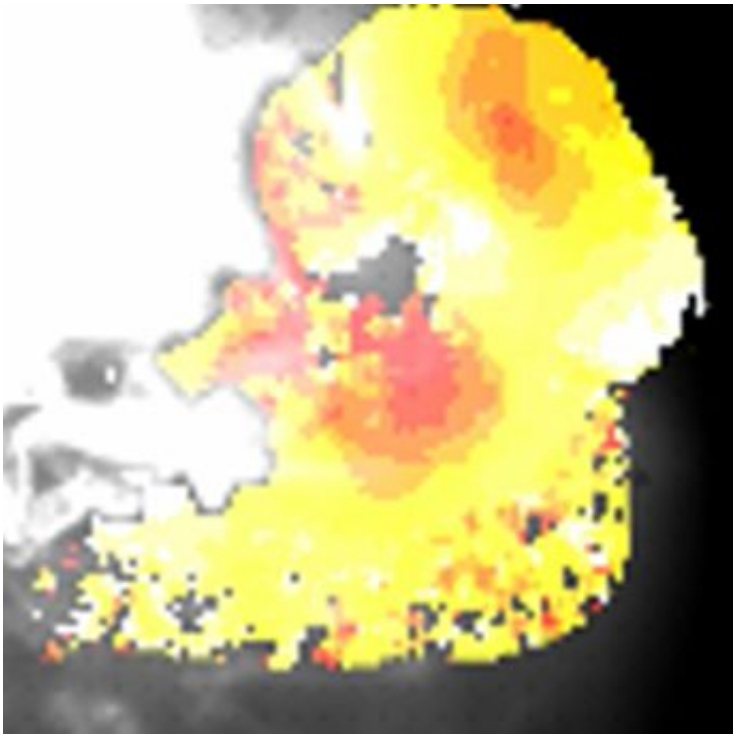

In the August 31 issue of *Science Translational Medicine*, new research from the University of Chicago shows how deficits in a specific pathway of genes can lead to the development of atrial fibrillation, a common irregular heartbeat, which poses a significant health risk.

Researchers describe a complex system of checks and balances,

including the intersection of two opposing regulatory methods that work to maintain normal cardiac rhythm, and offer insights that could lead to individualized treatment in humans.

"We hope that this and similar studies contribute to a mechanistic understanding underlying the genetic basis of heart arrhythmias" said study author Ivan Moskowitz, MD, PhD, associate professor in the Department of Pediatrics, Pathology, and Human Genetics at the University of Chicago. "Such studies will allow clinicians to stratify patients based on their likely natural history of disease and potentially their response to specific therapeutics."

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the world. It affects more than 2.7 million Americans, according to the American Heart Association. AF occurs when the normal rhythm of the heart goes awry, causing a rapid, irregular heartbeat. When blood is not properly ejected from the heart, blood clots can form, leading to high risk of stroke.

Patients with other forms of heart disease, such as congestive heart failure or hypertension, have an increased risk of AF. For decades this observation caused doctors to believe that AF was just a side effect of other heart-related issues. However, some patients with AF have no other cardiac issues and not all patients with congestive heart failure have AF. Having a family member with AF is associated with a greatly increased risk for the arrhythmia, suggesting a genetic component.

One of the regions in the genome implicated in AF is near a gene named Tbx5. Although its role in AF was not understood, Tbx5 is known to control other genes and to be important in both the structure and the rhythm of the heart.

It was long thought that a mouse heart could not develop primary AF,

but when first author Rangarajan Nadadur and others in Moskowitz's team knocked out the Tbx5 gene from adult mice, they found that the mice developed spontaneous AF. Using this model system the researchers investigated what role Tbx5 played by looking for the genes it controlled. About 30 genes have been linked to AF in humans. The researchers found that half of those genes were decreased in the absence of Tbx5 and that Tbx5 directly targeted some of those genes.

Pitx2, a gene controlled by Tbx5, is the most commonly identified gene in genome wide association studies for AF. This finding prompted the researchers to reach out to James Martin's research group at Baylor College of Medicine, collaborators on a Leducq Foundation grant to study AF, who were studying Pitx2.

"Both Tbx5 or Pitx2 directly control important rhythm genes in the heart , but in opposite directions" said Moskowitz. "Removing either causes a susceptibility to AF."

"The clinical application of this model is that we may be able to provide more precisely targeted treatments to AF patients depending on whether their cardiac rhythm network is up- or down-regulated," said Moskowitz. For example, if an important calcium channel is too active and causing AF, blocking it with medication would be helpful. However, if that calcium channel is not active enough and contributing to AF, prescribing a calcium channel blocker may be ineffective or even harmful. "We believe that a better understanding of the mechanisms underlying the genetic risk of the disease will ultimately have a significant impact on treatment."

More information: "Pitx2 modulates a Tbx5-dependent gene regulatory network to maintain atrial rhythm," *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aaf4891