Common gene variant may increase risk for a type of cardiac arrhythmia

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An international research team has identified a common gene variant associated with a form of the irregular heartbeat called atrial fibrillation. In their report in the journal *Nature Genetics*, being published online, the investigators describe finding that variations affecting a protein that may help control the heart's electrical activity appear to increase the risk of what is called lone atrial fibrillation (AF), a type seen in younger individuals with no other form of heart disease.

"The genetic location we have identified could be a new drug target for the treatment of AF," says Patrick Ellinor, MD, PhD, of the Massachusetts General Hospital (MGH) Cardiovascular Research Center and Cardiac Arrhythmia Service, a co-corresponding author of the report. "We also will be investigating whether these variants can help us predict patients' clinical outcomes or their response to the various treatments for AF."

The most common type of irregular heartbeat, atrial fibrillation affects more than 2.2 million people in the U.S. In AF the upper chambers of the heart, called the atria, beat in a rapid and uncoordinated fashion, which can cause blood to pool within the heart. If blood clots form within the heart, they can break loose, travel to the brain and cause a stroke. While AF is most commonly seen in older individuals with hypertension, heart failure or other forms of heart disease, about 10 percent of AF patients begin having symptoms when they are younger and have no other known cardiovascular disease, a condition called lone AF.

Patients with lone AF are more likely to have overt symptoms and to require treatment, which includes the use of blood-thinning drugs to prevent clots and other medications that slow heart rhythm. If AF persists, procedures such as minimally invasive catheter ablation can inactivate the regions of the heart that trigger the arrhythmia.

Family history is known to increase the risk of AF and plays a larger role in lone AF. Several earlier genome-wide association studies (GWAS) linked gene variants on chromosomes 4 and 16 to increased risk for both forms of AF. To search for additional variants associated with the more heritable lone AF, the research team conducted a meta-analysis of five previous GWAS studies involving more than 1,300 individuals with lone AF - defined for this study as those with no other heart disease whose symptoms began before age 65 - and almost 13,000 unaffected participants.

The analysis associated lone AF with several common variants on a segment of chromosome 1. The most significant variants were found in the gene for KCNN3, a potassium channel protein that carries signals across cell membranes in organs including the brain and the heart. While the exact cardiac role of the protein is unknown, it may play a part in resetting the electrical activity of the atria, a process that goes awry in AF. Animal studies have suggested that a related protein, KCNN2, may help control signals originating in the atria and in the pulmonary veins, areas known to be involved in lone AF. The researchers replicated the association of KCNN3 variants with lone AF in data from two additional GWAS studies involving another 1,000 lone AF patients and 3,500 controls.

Ellinor, an assistant professor of Medicine at Harvard Medical School, and his colleagues note that additional study is required to clarify exactly how variations in KCNN3 and associated genes may affect the risk for lone AF, whether these and other gene variants can predict how a

patient's symptoms will progress and to investigate their usefulness as treatment targets. The study was supported by a wide range of public and private funders, including the National Institutes of Health.

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