Mayo Clinic spearheads research to discover unsuspected gene for atrial fibrillation

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Mayo Clinic researchers have found a gene mutation linked to one family's hereditary form of atrial fibrillation. Researchers hope this discovery will lead to better understanding of the disease and, eventually, better ways to predict, prevent and treat the heart rhythm problem.

The study was based on a large family with an inherited form of atrial fibrillation in 11 relatives. Investigators discovered the defective gene by scanning the entire human genome, comprised of more than 30,000 genes. By mapping the gene's location to a specific chromosome region, the search was narrowed to eight candidate genes. Ultimately, a mutation — a flaw in the DNA sequence — was discovered in one of these genes among family members with the arrhythmia. Collaborators at the University of Iowa confirmed in an animal model the mutation's role in altering the electrical properties of the heart. The study results appear July 10 in the online version of the *New England Journal of Medicine*.

Atrial fibrillation is the most common irregular heartbeat seen by physicians and affects more than two million Americans. Most individuals with atrial fibrillation have identifiable risk factors, such as high blood pressure or structural heart disease, and tend to be elderly. But studies indicate that genetics also has a role, says Timothy Olson, M.D., a pediatric cardiologist at Mayo Clinic and senior author of the study.

"We know that some patients develop atrial fibrillation at a younger age without an apparent underlying cause, suggesting a hereditary basis for

their disease and prompting research to identify gene mutations," Dr. Olson says. "The family history may provide an additional clue. Atrial fibrillation can be caused by genetic defects that patients are born with, yet it typically takes years or decades for the heart to become electrically unstable and for symptoms of arrhythmia to develop."

Dr. Olson led a team of investigators that gathered and analyzed clinical and genetic data from 11 affected and five unaffected family members. The researchers were surprised to find that the 11 family members who had atrial fibrillation shared a mutation in the gene that codes for atrial natriuretic peptide (ANP). The ANP hormone circulates in the blood stream and normally serves a beneficial role in regulating body water, sodium and vascular tone. The mutation, however, resulted in a faulty hormone with a detrimental effect on the heart's electrical properties, according to researchers. Mayo Clinic co-investigators John Burnett, M.D. and Denise Heublein determined that these 11 family members had blood levels of mutated peptide in much higher concentrations than the normal peptide.

Previous research has discovered relatively few genes for atrial fibrillation, and most are genes for ion channels that regulate movement of potassium and sodium in heart cells, Dr. Olson says.

"While the family members with atrial fibrillation have a rare mutation, the study findings provide insight into pathways that may be applicable to people in the general population with atrial fibrillation," says the study's first author, Denice Hodgson-Zingman, M.D., an electrophysiologist at the University of Iowa. "It is intriguing that a defective circulating hormone can cause atrial fibrillation. It gives us a potential new target for developing treatments."

Dr. Hodgson-Zingman and co-author Leonid Zingman, M.D., also of the University of Iowa, used an animal model to establish that mutated ANP

changes the heart's electrical function and promotes atrial fibrillation, thus providing crucial evidence that the mutated ANP is not a neutral or incidental finding.

In atrial fibrillation, the heart's two upper chambers beat irregularly and out of coordination with the two lower chambers. The resulting irregular and often rapid heart rate can lead to poor blood flow to the body. A person can experience shortness of breath, heart palpitations and weakness and is at an increased risk of stroke. Treatment focuses on preventing stroke through the use of aspirin or other blood thinners and controlling symptoms with medications or invasive procedures.

"This research helps us see a potential window of opportunity for early diagnosis and treatment of at-risk individuals before the development of clinically overt disease," Dr. Olson says.

This research continues ongoing work at Mayo Clinic. Dr. Olson's team is trying to identify patients with familial forms of atrial fibrillation where single, yet unidentified, genetic mutations are the primary cause for their disease. To date, the researchers have recruited nearly 50 families with the hereditary condition, constructed detailed family trees and collected DNA samples for genetic analyses.

"This work has laid the foundation for human genome mapping studies to pinpoint and discover the defective genes," Dr. Olson says. "Instead of treating the symptoms of advanced heart disease, targeted therapies could be developed that would reverse or compensate for the principal defect, potentially preventing the disease altogether. That is our long-term goal."

Source: Mayo Clinic