When the heart gets out of step

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Atrial fibrillation is a cardiac arrhythmia -- a chronic irregularity of heartbeat -- which affects an estimated 1 million people in Germany. Although the condition is not acutely life-threatening, it does increase the risk of developing more serious illnesses, such as cardiac insufficiency, stroke and dementia.

In the third of a series of genomewide asssociation studies, an international team of researchers, led by LMU physician PD Dr. Stefan Kääb, now reports the identification of a new gene locus that has a significant influence on risk for atrial fibrillation. The product of this gene is a so-called potassium channel, which plays a role in coordinating the electrical impulses that control heartbeat.

"The discovery of this functional link will enable us to develop new and more specific drugs for the treatment of atrial fibrillation", explains Kääb. The discovery is the result of a meta-analysis of data from ten large-scale epidemiological studies, and emerged from a comparison between the genomes of 1335 patients with atrial fibrillation and those of 12844 healthy control subjects. The analysis was carried out in close collaboration with scientists at the Technical University of Munich and the Helmholtz Center Munich, with contributions from over 50 other international research institutions. (*Nature Genetics* online, 21 February 2010)

In order to transport blood efficiently through the vascular system and ensure that all vital organs receive an adequate supply, the heart must function in a highly coordinated fashion. Contractions of the atrium and

the ventricles must occur in the correct sequence and in the right temporal relationship to each other. This process is controlled by the coordinate generation and conduction of electrical signals, which are initiated by the sinus node and can be recorded on electrocardiograms. Cardiac arrhythmias arise when the sinus node is unable to perform this task adequately. Atrial fibrillation is a milder form of arrhythmia than ventricular fibrillation and does not pose an acute threat. But as LMU's PD Dr. Stefan Kääb points out, "Atrial fibrillation can give rise to more serious conditions - principally as a result of the fact that the blood is not completely expelled from the heart, and this facilitates the formation of thromboses. These, in turn, can precipitate strokes or an embolism - the complete obstruction of a blood vessel. Atrial fibrillation also increases the risk of cardiac insufficiency, which may result in reduction of brain function and, ultimately, dementia."

Atrial fibrillation is also a disease of great socioeconomic importance. In Germany alone, up to 1 million people are thought to suffer from the condition, and the number of cases worldwide is estimated to be around the 600 million mark. An international team led by Dr. Kääb has therefore taken on the task of uncovering the genetic factors that contribute to the still mysterious underlying functional disturbance that results in atrial fibrillation. In two studies published earlier, the group showed that variants at several gene loci have a significant influence on risk for atrial fibrillation One of these genes lies on chromosome 16 and is responsible for the synthesis of a protein that is involved in directing cardiac development. They also pinpointed a total of nine genes that affect the duration of the PR interval (a particular segment of the contraction cycle that can be measured on an electrocardiograph) and also modulate risk for atrial fibrillation.

In their latest study, which was carried out in the context of the German National Genome Research Network (NGFN) and in cooperation with Patrick T. Ellinor, a cardiologist at Massachusetts General Hospital in

Boston, USA, the team performed a meta-analysis on data collected in the course of five extensive genomewide association studies. They focused on a particular subset of patients - the 1335 subjects who showed a specific form of the condition, known as lone atrial fibrillation. This form is unusual because it becomes clinically manifest before the age of 65 and is not associated with any obvious changes in heart structure. "The homogeneous nature of this group of patients allowed us to identify a gene called KCNN3, which markedly influences risk for atrial fibrillation", says Kääb. "Interestingly, it turns out that this gene is required for the synthesis of a potassium channel, a protein that regulates the flow of potassium ions across cell membranes. The protein participates in the conduction of electrical impulses in the heart, and therefore represents a promising new drug target."

Thus, in future studies it may be possible to develop and test new agents that specifically bind to this potassium channel and so help to regularize the coordination of cardiac activity. "Our results improve our understanding of the pathophysiological mechanisms that contribute to the manifestation of atrial fibrillation", says Kääb. "We also hope that in the longer term, they will allow us to predict individual levels of risk".

More information: "Common variants in KCNN3 are associated with lone atrial fibrillation"; Patrick T. Ellinor et al.; *Nature Genetics* Online, 21 Februar 2010

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