New genetic cause of cardiac failure discovered

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Over the course of a lifetime, the heart pumps some 250 million liters of blood through the body. In the order to do this, the muscle fibers of the heart have to be extremely durable. The research group headed by Dr. Wolfgang Rottbauer, vice chair of the Department of Medicine III at Heidelberg University Hospital (Germany), has discovered a protein that is responsible for the stability of the smallest muscular unit, the sarcomere.

In cooperation with other researchers within the National Genome Research Network they proved that mutations of this protein are the cause of a new type of heart failure. The results have been published in the November issue of *Nature Medicine*.

Primary heart muscle disease with decreased cardiac pump function leading to enlargement of the heart chambers (dilated cardiomyopathy) is one of the most frequent causes of chronic heart failure. Six new cases per 100,000 people occur each year; 20 percent of these cases are genetic. The heart disease weakens cardiac cells and the heart can no longer pump efficiently which leads to dilation of the cardiac chambers.

Muscle activity takes place in the smallest unit of muscle fiber, the sarcomere. In the presence of an appropriate stimulus, actin and myosin filaments interact and contract the muscle. These movable elements are anchored in what are known as Z-disks. With every heartbeat, enormous forces act on the Z-disks.

Torn Z disks weaken the heart

"In our studies of zebrafish, we discovered a protein that is needed to stabilize the Z-disk. If this protein (nexilin) is mutated, the movable muscle elements are no longer anchored firmly enough. The muscles then lose strength and the heart is weakened," explains Dr. Tillman Dahme, resident and co-author of the study. The researchers examined the genetic material of affected patients and verified a mutated Z-disk protein in 9 of 1000 participants. They showed that in these patients, the defective nexilin was the major cause of heart disease. "The nexilin dilated cardiomyopathy allowed us for the first time to describe a new form of heart muscle dilatation and define the mechanism causing it, namely destabilization of the Z-disk," says Dahme.

The studies also showed that the extent of the damage to the Z-disk is directly related to the workload. This insight has an influence on clinical therapy. "Patients with a nexilin mutation might benefit from early treatment with medications that reduce cardiac stress. This could lower the mechanical stress on the Z-disks and prevent progressive damage to the heart," said Dr. Rottbauer.

More information: Nexilin mutations destabilize cardiac Z-disks and lead to dilated cardiomyopathy. David Hassel, Tillman Dahme, Jeanette Erdmann, Benjamin Meder, Andreas Huge, Monika Stoll, Steffen Just, Alexander Hess, Philipp Ehlermann, Dieter Weichenhan, Matthias Grimmler, Henrike Liptau, Roland Hetzer, Vera Regitz-Zagrosek, Christine Fischer, Peter Nürnberg, Heribert Schunkert, Hugo A Katus & Wolfgang Rottbauer, Nature Medicine 15, 1281 - 1288 (2009), published online 1 Nov 2009, DOI: 10.1038/nm.2037

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