Researchers find sleep gene linked to heart failure

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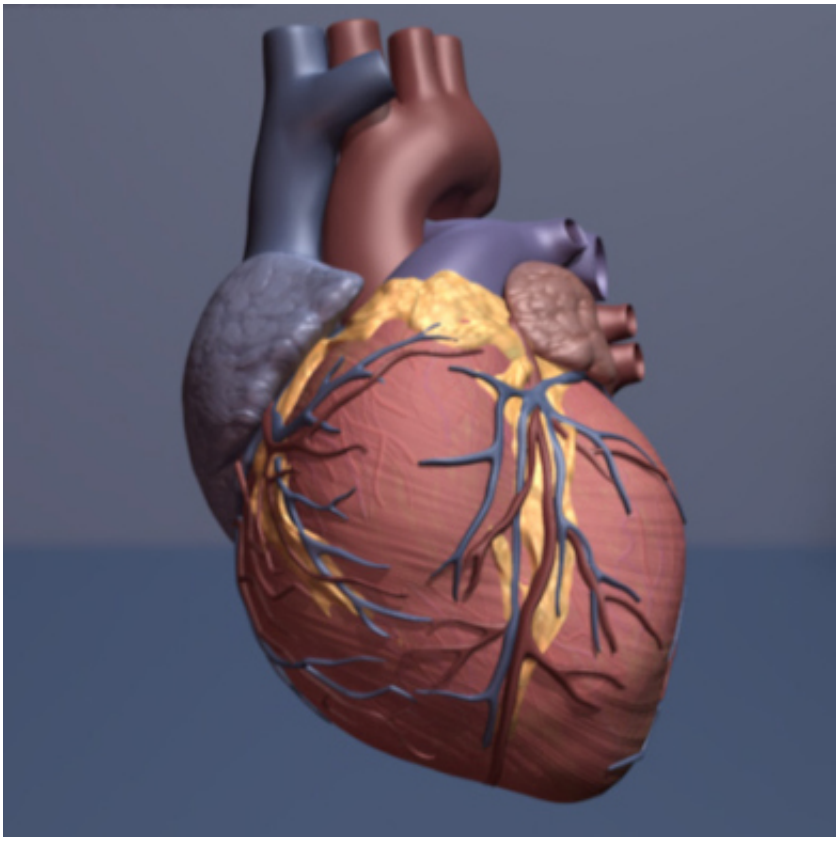

Human heart. Credit: copyright American Heart Association

Researchers at the Stanford University School of Medicine have identified a gene that, when working properly, appears to reduce the risk of heart failure and improve treatment outcomes, highlighting a possible target for the development of new drugs.

The gene codes for a protein that was first identified when a mutated form was shown to cause narcolepsy.

Caring for patients with heart failure costs the United States $40 billion a year, according to Euan Ashley, MRCP, DPhil, associate professor of cardiovascular medicine at Stanford. Despite the condition's enormous impact, few new treatments have been developed, and those that exist produce varied responses among patients. One major challenge to the development of new treatments has been the lack of genes that can be confidently associated with heart failure. Ashley is hopeful that the new finding will open doors to evaluating possible treatments.

The research is described in a paper to be published online Nov. 30 in the *Journal of the American College of Cardiology*. Ashley is the senior author. The lead author is Marco Perez, MD, assistant professor of cardiovascular medicine, who said the study was motivated by the observation that individual patients with heart failure often respond differently to the same types of medical interventions.

"We have noticed some patients with heart failure who get medical therapy respond really nicely," Perez said. "Their heart function improves dramatically with medications. Whereas other patients, despite medical therapy, continue to worsen and require transplant."

Perez wondered if there were genetic reasons for the discrepancies in treatment outcomes observed in the study. He suspected genetic variation in the study's patient group might point toward a link.

From men to mice

The team genotyped heart-failure patients at the extremes of responses—those who had the best and worst responses to therapy. They combined these results with gene expression data from human cardiac

tissue available from a large, publicly accessible data set. By combining a variety of approaches including network modeling, which looks at the relationship between genes, the team searched for genetic variants associated with heart health.

Intrigued that their analyses spotlighted a gene near the region coding for the orexin receptor protein, which is known to be involved in the control of sleep, appetite and blood pressure, the team investigated further. Through a series of experiments, the researchers concluded that the gene likely regulates how much of the receptor is made in a cell. They then looked for evidence that the orexin receptor could be involved in heart function and found that its expression was increased in diseased human heart tissue. The researchers wondered whether this could mean that the receptor and its binding partner, orexin, have a protective function in the heart.

"We found this new receptor that looked very promising," said Ashley. "But what I'm most proud of is that the team didn't stop there; they went on to validate it in another data set, explore its mechanism in cellular models and then test the effect in several different mouse models."

Using a mouse model that mimics heart failure through artificially elevated levels of adrenaline, the researchers examined the role of the receptor and orexin. They found that if they gave orexin to the mice with failing hearts, those mice showed better systolic heart function—relating to the contraction phase of a heartbeat—than did mice that did not receive orexin.

Ultrasounds of the hearts in a different group of mice, which were missing the orexin receptor, showed that these mice had greater diastolic heart dysfunction—relating to the relaxation phase of a heartbeat—another hint suggesting that the receptor is important for healthy hearts.

"The exciting thing is that this gene is in a completely different neurohormonal axis—a completely different pathway than what has been looked at previously," Perez said. "Nobody had ever studied heart function in relation to this gene."

The project was selected to receive funding from Stanford's SPARK program, a drug and diagnostic development program that supports promising research with the potential to move from the laboratory to the bedside.

Perez, whose work won him recognition as a finalist for the 2013 American Heart Association Young Investigator's Award, said he is optimistic that exploring the role of this receptor in the heart could inform new research, possibly leading to the development of novel therapies.

Sleep and hearts

The orexin receptor's link to narcolepsy was identified in 2000 by a research group that included Emmanuel Mignot, MD, PhD, professor of psychiatry and behavioral sciences, but the new study marks the first time the gene and receptor have been associated with heart failure. Perez, Ashley and their team are eager to do further studies to explore this link.

"The connection between sleep and the heart is fascinating," said Ashley, who has recently been spending more time interacting with his sleep-expert colleagues in an effort to explore possible associations.

In fact, the finding has raised the question of whether insomnia medications that work by blocking the function of the orexin receptor could harm the heart, although this has not yet been studied, Perez said.

"We already know that sleep apnea is bad for the heart," said Ashley. "One of the things we are now hoping to do is look at heart function in patients with narcolepsy."

Provided by Stanford University Medical Center

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