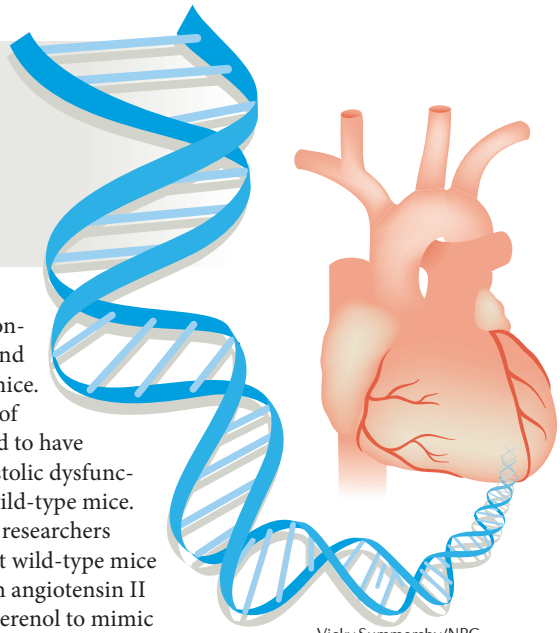
Nature Reviews Cardiology | Published online 17 Dec 2015; doi:10.1038/nrcardio.2015.195

PHARMACOGENETICS

HCRTR2 gene is associated with response to HF therapy



Vicky Summersby/NPG

"The current study by Perez *et al.* used GWAS [genome-wide association study] to identify a new gene variant candidate that is strongly associated with altering the response to conventional HF [heart failure] therapy, which could lead to novel drug treatments," explain Walter J. Koch and Alessandro Cannavo in an editorial that accompanies a new study published in *JACC*.

"Some patients dramatically respond to HF therapy with large increases in ejection fraction (EF) associated with positive remodelling of the left ventricle, whereas others deteriorate," the investigators observe in their report. The researchers studied response to therapy in 866 patients with clinically diagnosed HF. The responses were categorized, and 'dramatic responders' — patients at the extreme of the distribution of dynamic change — were genotyped to inform the design of a customized microarray to identify single nucleotide variants associated with response to HF therapy. A further 798 patients were recruited for an independent replication study to validate results.

Genotyping with the custom array identified a genomic variant in the regulatory region of *HCRTR2* which affects left ventricular function. This variant results in reduced expression of the hypocretin receptor and was found in patients with low functional responses to treatment, whereas patients without this mutation generally responded to therapy with a ≥20% improvement in EF.

HCRTR2 encodes a receptor that binds orexin (also known as hypocretin) A and B. These neuropeptides are expressed in the hypothalamus and other tissues such as the gut and adrenal glands, and are known to regulate sleep and appetite. The investigators also found a consistent increase in total cardiac hypocretin receptor levels in patients with ischaemic or dilated cardiomyopathy compared with controls.

To investigate a causal role of this neuropeptide receptor, the researchers then tested heart function in *Hcrtr2* transcription-disrupted and knockout mice. Both types of mice tended to have greater diastolic dysfunction than wild-type mice. Finally, the researchers showed that wild-type mice treated with angiotensin II and isoproterenol to mimic human HF and receiving orexin A had better systolic function than mice receiving placebo.

"We used a systems approach to identify a promising therapeutic target, *HCRTR2*, for the treatment of HF," the investigators conclude. "Further studies are needed to better elucidate the novel role of this neurohormonal pathway in regulating heart function."

Clarissa Oeser

ORIGINAL ARTICLE Perez, M. V. *et al.* Systems genomics identifies a key role for hypocretin/orexin receptor-2 in human heart failure. *J. Am. Coll. Cardiol.* **66**, 2522–2533 (2015)

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