NEW GENE FOR DILATED CARDIOMYOPATHY

Three novel variants in the ankyrin repeat domain 1 (*ANKRD1*) gene, which encodes cardiac ankyrin repeat protein (CARP), have been identified in patients with dilated cardiomyopathy. Most of the ~20 genes that are known to be causative of dilated cardiomyopathy disrupt sarcomeric signalling pathways. “We selected *ANKRD1* as a candidate due to its role in the Z-disk [in the sarcomere],” explains lead investigator Jeffrey Towbin. “Finding mutations, we developed a cellular model to define the mechanisms responsible.” Notably, CARP is upregulated in the cardiomyocytes of patients with hypertrophy and those with heart failure.

The international team of researchers screened 160 patients from the UK and 80 patients from Japan. Heterozygous, missense sequence mutations in *ANKRD1*—resulting in P105S, V107L, and M184I mutations in CARP—were found in four (1.9%) of those tested, all of whom were male and from the UK. None of these mutations was found in a control sample of 180 healthy individuals. The patient with the V107L variant and one of the individuals with a P105S mutation had no family history of dilated cardiomyopathy. The carrier of the M184I variant had a sibling with left ventricular dilation, raising the possibility of autosomal-dominant inheritance.

In yeast 2-hybrid assays, both the M184I and P105S variants were associated with a loss of CARP–Talin 1 binding, which could indicate disruption of stretch-signalling in the cardiomyocyte. Transfection of P105S and V107L variants into H9C2 rat embryonic myocardial cells led to altered regulation of several factors that contribute to apoptosis, cell-cycle control, and cell signalling. Towbin and colleagues plan to take their work forward by “creating a mouse model of dilated cardiomyopathy ... to study the mechanisms” and “evaluating new patients for possible mutations.”

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Original article Moulik, M. *et al.* *ANKRD1*, the gene encoding cardiac ankyrin repeat protein, is a novel dilated cardiomyopathy gene. *J. Am. Coll. Cardiol.* **54**, 325–333 (2009).