European Heart Journal: CNIC scientists report the first use of CRISPR activation to treat a cardiac disease in mice

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The results, published in the European Heart Journal and presented at the European Society of Cardiology Congress, opens the way to new therapies for patients with genetic heart diseases

An international multidisciplinary team led by scientists at the Centro Nacional de Investigaciones Cardiovasculares (CNIC), with participation from scientists at Hospital Universitario Puerta de Hierro and the University of California San Diego, has demonstrated for the first time that CRISPR-based gene activation (CRISPRa) can be used to treat genetic heart disease *in vivo*. The study, published in the *European Heart Journal* and presented at the European Society of Cardiology Congress in Madrid, paves the way for novel targeted therapies for patients with genetic cardiac disorders. This approach could be especially useful for patients with conditions caused by mutations in genes too large to be targeted with conventional gene therapy.

The team made this discovery in a new animal model they developed that carries a truncating mutation in the filamin C gene (FLNC). Truncating variants in FLNC (FLNCtv) reduce the amount of Filamin C protein produced and are a frequent cause of genetic dilated cardiomyopathy and left ventricular non-dilated cardiomyopathy. Both diseases predispose patients to severe arrhythmias and increase the risk of sudden cardiac death. There are currently no specific therapies available for this type of mutation, and clinical options are limited to general heart failure treatments and implantable defibrillator devices.

The researchers developed a mouse model carrying a truncating FLNC mutation that reproduces the electrical abnormalities observed in patients, including increased vulnerability to drug-induced arrhythmias.

To restore gene function, the team designed a CRISPRa-based gene-therapy system packaged in a cardiotropic adeno-associated virus (AAVMYO). “This system does not cut DNA,” explains study first author Dr. Rodrigo Cañas Álvaro, “but instead uses a nuclease-inactive CRISPR protein fused to a transcriptional activator to switch on the FLNC promoter, thereby increasing Filamin production in the heart.”

After administration of the vector to adult mutant mice, the researchers observed normalization of FLNC RNA and protein expression to the levels found in healthy animals. Electrocardiogram recordings showed recovery of QRS amplitude and, most importantly, the complete disappearance of flecainide-induced arrhythmias.

“This study demonstrates for the first time that CRISPRa gene activation can reverse manifestations of a hereditary cardiomyopathy in an animal model,” says Dr. Enrique Lara-Pezzi, a CNIC and CIBERCV investigator and the lead author on the study. “Our results suggest that even after the disease has developed, it is possible to restore the heart’s electrical function through a targeted approach.”

Study collaborator Dr. Pablo Garcia-Pavía—head of the Inherited Cardiac Diseases Unit at *Hospital Universitario Puerta de Hierro*, CNIC and CIBERCV investigator—stresses the significance of the findings. “This research establishes the basis for the development of CRISPRa-AAV therapies not only for FLNC mutations but also for other cardiac disorders caused by insufficient production of essential proteins that cannot be targeted by conventional gene therapy.”

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- *Cañas-Alvaro R, Lalaguna L, Rubio B, Ausiello A, López-Olañeta M, Serrano-Blanco RF, Ochoa JP, de la Pompa JL, Chavez A, García-Pavía P, Lara-Pezzi E.* ***CRISPR activation to repair ECG abnormalities caused by a FLNC truncating variant in mice.*** *Eur Heart J. 2025 Aug 31:ehaf703.* doi: 10.1093/eurheartj/ehaf703

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