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Media release

For the first time, gene therapy corrects a life-threatening cardiac arrhythmia in an animal model

Researchers at the Inselspital, Bern University Hospital, and the University of Bern, in collaboration with researchers at the Mayo Clinic, Rochester, USA, have developed and tested a novel gene therapy that successfully corrects a life-threatening genetic cardiac arrhythmia in an animal model. The procedure restores the normal function of the affected cardiac ion channel and opens up new perspectives for the future treatment of both rare and common cardiac arrhythmias.

Short QT syndrome type 1 is a rare, potentially lethal genetic heart disorder associated with a high risk of life-threatening cardiac arrhythmias. Affected patients often experience ventricular tachycardia and fibrillation which can lead to sudden cardiac death. These arrhythmias often occur as early as during childhood or early adulthood and often in people who previously appeared completely healthy. The disorder is caused by changes in the *KCNH2* gene, which provides the blueprint for an important channel in the heart through which electrical signals are transmitted. This genetic change causes the electrical excitation of the heart muscle to subside too quickly. The result is a shortened QT interval on the electrocardiogram (ECG) – hence the name “short QT syndrome,” or “SQTS” for short.

Until now, treatment of SQT1 has been limited to symptomatic measures such as the insertion of a defibrillator, which stops arrhythmias as soon as they occur, or the administration of drugs such as hydroquinidine. Both approaches come with significant disadvantages: while a defibrillator can be psychologically stressful for patients and can cause complications such as

inadequate shock delivery, drugs such as hydroquinidine are often associated with pronounced side effects that can lead to the discontinuation of the therapy.

Therapy targets a genetic cause for the first time

Researchers from Prof. Katja Odening's team of the Department of Cardiology at the Inselspital, Bern University Hospital, and the Institute of Physiology at the University of Bern, together with Prof. Michael Ackerman's team at the Mayo Clinic in Rochester, USA, have now succeeded for the first time in testing a new gene therapy in an animal model that directly targets the genetic cause of SQT1. This approach simultaneously suppresses the defective KCNH2 gene and replaces it with a healthy copy. This so-called KCNH2 SupRep dual strategy (discovered and patented by the Mayo Clinic) was able to completely correct the typical disease characteristics in the SQT1 animal model: The shortened QT interval on the ECG was normalized, the electrical recovery of the heart was restored, and the risk of life-threatening arrhythmias was also significantly reduced. Similarly, at the cellular level, the ion currents and the interplay between electrical signals and heartbeat were normalized.

Prof. Katja Odening, Full Professor of Translational Cardiology at the University of Bern, Senior Consultant at the Inselspital Department of Cardiology and the lead author of the study emphasises its uniqueness: «This preclinical study was the first to successfully apply gene therapy in the treatment of short QT syndrome. This approach enables us for the first time to directly target the genetic cause of this disease, which until now could only be treated symptomatically.»

Targeted result in the heart

A key aim of the research group was to design the therapy in such a way that it acts as specifically as possible in the heart without causing undesired effects in other organs. This was achieved by transporting the gene therapy via AAV9 viruses which preferentially infect heart muscle cells. Genetic switches (so-called promoters) also ensured that the introduced gene was only active in heart muscle cells. Finally, the gene therapy was injected directly into the coronary arteries via the aorta, similarly to the procedure used for a cardiac catheterization in a hospital. In this way, it was able to bring about a result directly in the heart. This combination enabled a targeted and efficient implementation of the therapy without systemic side effects.

New prospects for a larger group of patients

Mutations in the KCNH2 gene which was replaced in the gene therapy are not only the genetic substrate for SQT1, but can also cause the so-called long QT syndrome type 2 (LQT2). «This condition is considerably more common and, like SQT1, is associated with a high risk of

sudden cardiac death,» Prof. Odening adds. «So this promising approach could open up new therapeutic prospects not only for a very small number of patients affected with SQT1, but potentially hundreds of families with LQT2. In fact, in collaboration with Mayo Clinic and Solid Biosciences, the pre-human animal trial for LQT2 is already underway.»

Further research is crucial

Around the world, more and more gene therapies are being approved for rare diseases. The current study shows that new avenues are also opening for the treatment of genetically determined cardiac arrhythmias. At the same time, Prof Odening expresses a note of scientific caution: «Only through further preclinical research and clinical studies can the translation from animal models to patient care be achieved.» Before the gene therapy can begin to be used in patients, further studies must confirm its safety, rule out possible side effects in other organ systems, and demonstrate its long-term effectiveness over a period of years – ideally after only a single dose. These are precisely the questions which the research team is now investigating, while at the same time testing the gene therapy in an animal model of LQT2 as well.

Within the framework of a Bern Center of Precision Medicine (BCPM) Lighthouse Project Grant – «PACE – Precision Diagnosis and Therapy in Cardiac Channelopathies», Prof. Katja Odening's research team, together with researchers from Human Genetics (Prof. Christiane Zweier), Anatomy (Prof. Nadia Mercader), the Department for BioMedical Research (DBMR) (Ass. Prof. Marco Osterwalder) and Chemistry (Prof. Jean-Louis Reymond), are currently investigating the extent to which gene therapy approaches can be developed and implemented also for other genetic heart diseases with an increased risk of sudden cardiac death.

Links

Universitätsklinik für Kardiologie – Inselspital Bern

Publication

Nimani S, et al. AAV9-mediated KCNH2 suppression-replacement gene therapy in a transgenic rabbit model of type 1 short QT syndrome. Eur Heart J. 2025 Aug 30:ehaf660. doi: 10.1093/eurheartj/ehaf660. Online ahead of print.

Expert

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