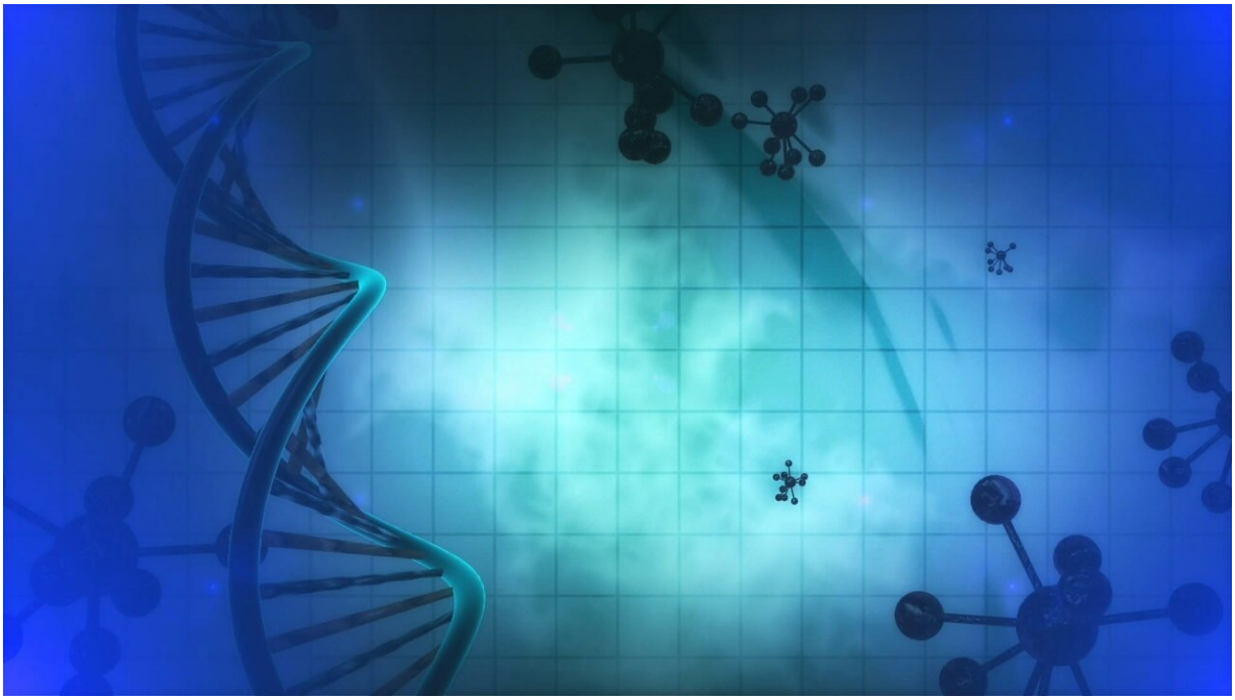
First hybrid gene therapy shows early promise in treating long QT syndrome

January 28 2021



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In a new study published in *Circulation*, Mayo Clinic researchers provide the first preclinical, proof-of-concept study for hybrid gene therapy in long QT syndrome, a potentially lethal heart rhythm condition.

Researchers demonstrated its potential therapeutic efficacy in two in vitro model systems using beating heart cells reengineered from the

blood samples of patients with 1 long QT syndrome. They targeted the whole KCNQ1 gene rather than specific LQT1-causative mutations, making this study applicable to all patients with long QT syndrome 1, regardless of their specific disease-causing variant.

The prevalence of long QT syndrome is about 1 in 2,000. When untreated, high-risk patients have an estimated 10-year mortality of 50%.

Long QT syndrome is a genetic heart rhythm condition that can potentially cause fast, chaotic heartbeats. These rapid heartbeats might trigger people to suddenly faint. Some people with the condition have seizures. In some severe cases, long QT syndrome can cause sudden cardiac death. The most common subtype, type 1 long QT syndrome, or LQT1, is caused by pathogenic variants in the KCNQ1 gene.

"Gene therapy is an emerging area of interest for treating a variety of genetic heart diseases in general and long QT syndrome in particular," says Michael Ackerman, M.D. Ph.D., a Mayo Clinic genetic cardiologist and director of Mayo Clinic's Windland Smith Rice Comprehensive Sudden Cardiac Death Program. "We designed and developed the first suppression and replacement KCNQ1gene therapy approach for the potential treatment of patients with type 1 long QT syndrome." Dr. Ackerman is senior author of this study.

According to Dr. Ackerman, over the past two decades, substantial improvements have been made to manage long QT syndrome, but current therapies, such as beta blockers and defibrillators, a more invasive therapy, still have limitations, risks and an array of unwanted side effects.

Gene therapy is a technique that treats diseases caused by defective genes by altering genes in a patient's cells rather than using drugs or

surgery. Genes contain DNA—the code that controls the body's form and function. Gene therapy replaces faulty genes or adds a new gene to try to treat a disease.

According to Dr. Ackerman in this case, this is the first time that hybrid gene therapy (simultaneous out with the old, in with the new) has been created for any form of genetic heart disease.

"If the therapeutic efficacy of this 'disease-in-the-dish' gene therapy trial with KCNQ1 can be replicated in a nonhuman, animal model of long QT syndrome, then suppression-replacement (hybrid) gene therapy may be a promising strategy for long QT syndrome in general and in theory almost any sudden death-predisposing autosomal dominant genetic heart disease," says Dr. Ackerman. "Of course, we still have a long way to go from nearly curing a patient's heart cells in the dish to effectively treating the whole person. Nevertheless, we are excited by this first critical milestone and look forward to the next step."

In addition to heart disease, researchers at Mayo Clinic's Center for Individualized Medicine are investigating an approach to replace and fix mutated genes in a wide range of genetic disorders.

Provided by Mayo Clinic