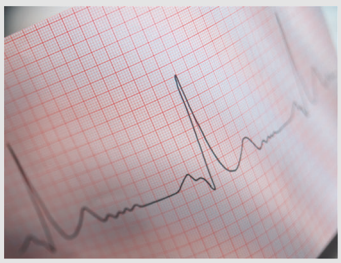
Genetics inMedicine | NEWS

NEWS

Correction of cardiac arrhythmia by in vivo genome editing



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Much ado has been made about CRISPR/Cas9-mediated genome editing and its possible application to human genetic disease. From excitement about therapeutic potential to concerns about risks, unintended consequences, and ethical issues, the conversation has run the gamut. In a recent article in *Circulation Research* (https://doi.org/10.1161/CIRCRESAHA.118.313369), Pan et al. contribute to the discussion by demonstrating successful in vivo use of CRISPR/Cas9-mediated genome editing to correct an inherited cardiac arrhythmia in mice. In their study, the research team used knock-in mice heterozygous for an R176Q pathogenic variant in the *Ryr2* gene as a model for catecholaminergic polymorphic ventricular tachycardia (CPVT). Mice heterozygous for the *Ryr2* R176Q variant (R176Q/+) are susceptible to adrenergic stress-induced VT. The team designed a guide RNA (gRNA) to target the R176Q allele and cloned the gRNA sequence into an adeno-associated virus serotype 9 (AAV9) vector containing *Staphylococcus aureus* Cas9 (SaCas9). The team injected AAV9 carrying either the gRNA construct or a control construct into wild-type (WT) and R176Q/+ mice. Five to six weeks after injection, mice were challenged to mimic adrenergic stress and monitored for VT. None of the R176Q/+ mice treated with the gRNA construct developed VT while 71% of R176Q/+ mice treated with the control construct did. The team found 30% less total *Ryr2* messenger RNA and 25% less total RyR2 protein in R176Q/+ mice treated with the gRNA construct compared with controls. The team observed normalized calcium release in the myocytes of R176Q/+ mice treated with the gRNA construct. No evidence of nonspecific or off-target genome editing was found. Unexpectedly, however, insertions of whole AAV vector genomes were found at the target site in R176Q/+ mice treated with the gRNA construct. The authors suggest that this finding raises safety concerns that should be investigated further. They also question whether the reduced level of total RyR2 protein observed in this study might have unintended effects and suggest that this observation should be investigated further. In humans, more than half of CPVT is caused by pathogenic variants in the *RYR2* gene, many of which are gain-of-function missense variants; mortality is high if left untreated, and current treatments are limited by partial efficacy and risks of adverse effects. The authors conclude that their study shows genome editing approaches may hold promise for the treatment of certain types of inherited cardiac disorders. — *Raye Alford, News Editor*

10 years + $4.7 billion = 1.5 million genomes

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This is the mission of the Earth BioGenome Project (EBP; http://www.earthbiogenome.org). A self-proclaimed "moon-shot for biology," the EBP endeavors to produce an annotated catalog of the genomes of 1.5 million species of eukaryotes, with unbiased representation of all 9000 eukaryotic taxa. The EBP is projected to cost $4.7 billion and is planned for completion within ten years. As described by Lewin et al. in a recent article in *PNAS* (https://doi.org/10.1073/pnas.1720115115), the EBP promises to revolutionize our understanding of life on Earth. Based on the precedent set by the Human Genome Project, the project's leadership also expects substantial economic returns. To achieve its ambitious aim, the EBP Working Group will assemble an international network of collaborators including academic institutions, government agencies, private companies and foundations, nonprofit organizations, and museums, zoos, aquaria, and botanical gardens. The working group is committed to the development of policies and standards that will ensure fair and open access to the project's resources and equitable sharing of project benefits worldwide. The planners expect that the unparalleled scale of the EBP will lead to the development of new analytical tools and algorithms for the scrutiny, annotation, and visualization of genomic data, and for comparative analyses. Anticipated outcomes include discovery of new species, revision of eukaryotic taxonomies, and new insights into the role of biodiversity in the operation and survival of Earth's complex ecosystems. The project's leaders anticipate gaining novel insights into evolutionary processes, relationships, and timelines, and unprecedented capacity to evaluate the consequences of changes in gene regulation and protein sequences. The EBP also foretells delivery of a deeper appreciation of the impacts of climate change, destruction of habitat, and invasive species on biodiversity, and new capabilities to reconstruct ancestral genomes in silico. The planners contend that the species-level knowledge of genomes acquired through this project will support the development of new approaches to conserve and restore biodiversity and ecosystems, improve the quality of the environment, control outbreaks, and create new medicinal and food products, biofuels, and biomaterials. In their *PNAS* article, the project's leaders position the EBP in the context of ongoing projects aimed at sequencing bacteria and archaea and predict that the legacy of the EBP will be "a complete Digital Library of Life that contains the collective biological intelligence of 3.5 billion years of evolutionary history." — *Raye Alford, News Editor*

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