Scientists Correct a Pathogenic Gene Mutation in Human Embryos

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Using the CRISPR-Cas9 gene editing technique, researchers have corrected for the first time a mutation implicated in hypertrophic cardiomyopathy—a heritable heart condition that is the most common cause of sudden death in otherwise healthy young athletes—in human embryos. Successfully correcting the mutation during embryonic development would prevent the defect from being passed on to future generations.

In a *Nature* study, a team led by scientists from Oregon Health & Science University fertilized oocytes from healthy donors with sperm from a heterozygous male carrier of the *MYBPC3* mutation. Inheriting a single copy of the *MYBPC3* gene mutation can lead to hypertrophic cardiomyopathy, which affects ≈1 in 500 people overall and is characterized by left ventricular hypertrophy, myofibrillar disarray, and myocardial stiffness. *MYBPC3* mutations account for ≈40% of all genetic defects causing hypertrophic cardiomyopathy and can also cause other inherited cardiomyopathies, including dilated cardiomyopathy and left ventricular noncompaction.

After fertilization and development of embryos, the investigators used CRISPR–Cas9 to cut the mutant gene sequence and then monitored how the embryos repaired the DNA breaks.

In most cases, the breaks were repaired efficiently using the nonmutated copy of the gene from the unaffected donor as a template. As a result, ≈2/3 of targeted embryos contained 2 mutation-free copies of the *MYBPC3* gene. There was no evidence of off-target mutations, and mosaicism—a circumstance in which edited DNA appears in some but not all cells—was minimal.

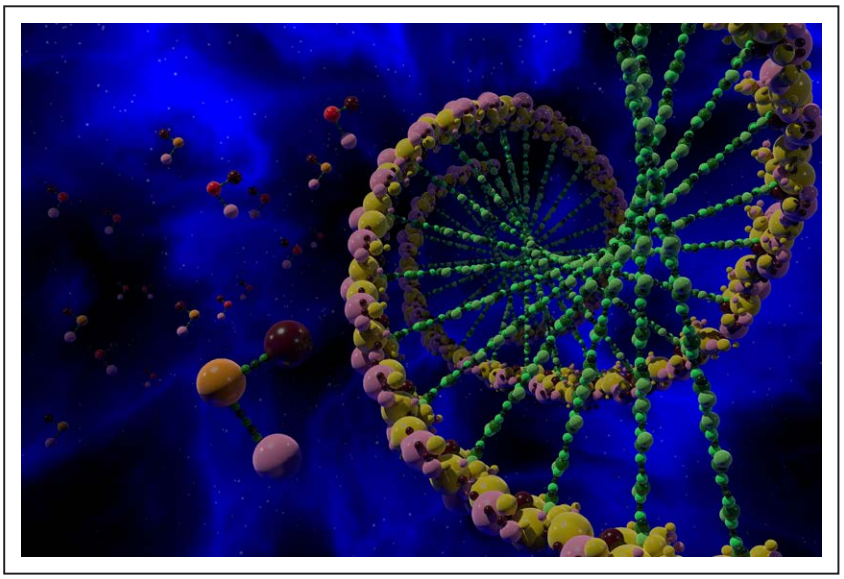

Illustration of CRISPR CAS 9.

The efficiency and accuracy of the approach suggest that it has the potential to be used to correct heritable disorders in human embryos by preimplantation complementation of genetic mutations.

"The mechanism of DNA repair in human embryos appears unique and different than that in somatic cells," noted coauthor Paula Amato, MD, MCR. "If this germline gene-editing technology is ultimately proven safe and efficient, it could prevent the transmission of serious genetic diseases from parents to their children and future generations."

The advance could have wide-ranging applications if it continues to show promise in additional studies. More than 10 000 monogenic inherited disorders have been identified, affecting millions of people worldwide. Because many of these disorders are diagnosed later in life, the underlying mutations escape natural selection and are often passed on to offspring.

Various technical and ethical considerations must be addressed before the method can be used clinically, however. For example, although they were rare in this study, unintended mutations are a serious concern, and reports have demonstrated off-target DNA damage induced by CRISPR–Cas9. Also, con-

troversies exist over the prospect of using gene editing techniques to enhance human traits and capacities, such as physical strength and intelligence, and over which medical conditions or disabilities should be altered or cured.

A recent report by the National Academy of Sciences and the National Academy of Medicine recommends that gene editing for enhancement should not be allowed at this time, and broad public input and discussion should be solicited before allowing clinical trials for editing of nonheritable (somatic) cells for any purpose other than treating or preventing disease or disability. Although heritable germline editing trials must be approached with caution, the report noted that caution does not mean prohibition.

Such editing is currently not permissible in the United States because of an ongoing prohibition on the US Food and Drug Administration's ability to use federal funds to review "research in which a human embryo is intentionally created or modified to include a heritable genetic modification." Various other countries have signed an international convention that prohibits germline modification. Moving forward, the committee that issued the report stressed the need for broad participation and input by the public, along with ongoing reassessment of both health and societal benefits and risks associated with heritable germline editing.

Some experts question whether germline editing would add considerable value to preimplantation genetic diagnosis, which allows prospective parents carrying heritable disease–causing mutations to select embryos with normal versions of the genes in question. The authors of the *Nature* article noted that in cases when only 1 parent carries a heterozygous mutation, 50% of embryos should be mutant, but "targeted gene correction can potentially rescue a substantial portion of mutant human embryos, thus increasing the number of embryos available for transfer." Such gene correction may be most beneficial if it can be used when both parents are homozygous for a disease-related gene variant, but it may be challenging to correct homozygous mutations in embryos when both alleles are mutant and no nonmutated copy of the gene can be used as a template during DNA repair.

Ma H, et al. Correction of a pathogenic gene mutation in human embryos. *Nature*. 2017;548:413–419. doi: 10.1038/nature23305.

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