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Research discovers chromosome therapy to correct a severe chromosome defect

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Geneticists from Ohio, California and Japan joined forces in a quest to correct a faulty chromosome through cellular reprogramming. Their study, published online today in *Nature*, used stem cells to correct a defective "ring chromosome" with a normal chromosome. Such therapy has the promise to correct chromosome abnormalities that give rise to birth defects, mental disabilities and growth limitations.

"In the future, it may be possible to use this approach to take cells from a patient that has a defective chromosome with multiple missing or duplicated genes and rescue those cells by removing the defective chromosome and replacing it with a normal chromosome," said senior author Anthony Wynshaw-Boris, MD, PhD, James H. Jewell MD '34 Professor of Genetics and chair of Case Western Reserve School of Medicine Department of Genetics and Genome Sciences and University Hospitals Case Medical Center.

Wynshaw-Boris led this research while a professor in pediatrics, the Institute for Human Genetics and the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UC, San Francisco (UCSF) before joining the faculty at Case Western Reserve in June 2013.

Individuals with ring chromosomes may display a variety of birth defects, but nearly all persons with ring chromosomes at least display short stature due to problems with cell division. A normal chromosome is linear, with its ends protected, but with ring chromosomes, the two

ends of the chromosome fuse together, forming a circle. This fusion can be associated with large terminal deletions, a process where portions of the chromosome or DNA sequences are missing. These deletions can result in disabling genetic disorders if the genes in the deletion are necessary for normal cellular functions.

The prospect for effective counter measures has evaded scientists—until now. The international research team discovered the potential for substituting the malfunctioning ring chromosome with an appropriately functioning one during reprogramming of patient cells into induced pluripotent stem cells (iPSCs). iPSC reprogramming is a technique that was developed by Shinya Yamanaka, MD, PhD, a co-corresponding author on the *Nature* paper. Yamanaka is a senior investigator at the UCSF-affiliated Gladstone Institutes, a professor of anatomy at UCSF, and the director of the Center for iPS Cell Research and Application (CiRA) at the Institute for Integrated Cell-Material Sciences (iCeMS) in Kyoto University. He won the Nobel Prize in Medicine in 2012 for developing the reprogramming technique.

Marina Bershteyn, PhD, a postdoctoral fellow in the Wynshaw-Boris lab at UCSF, along with Yohei Hayashi, PhD, a postdoctoral fellow in the Yamanaka lab at the Gladstone Institutes, reprogrammed skin cells from three patients with abnormal brain development due to a rare disorder called Miller Dieker Syndrome, which results from large terminal deletions in one arm of chromosome 17. One patient had a ring chromosome 17 with the deletion and the other two patients had large terminal deletions in one of their chromosome 17, but not a ring. Additionally, each of these patients had one normal chromosome 17.

The researchers observed that, after reprogramming, the ring chromosome 17 that had the deletion vanished entirely and was replaced by a duplicated copy of the normal chromosome 17. However, the terminal deletions in the other two patients remained after

reprogramming. To make sure this phenomenon was not unique to ring chromosome 17, they reprogrammed cells from two different patients that each had ring chromosomes 13. These reprogrammed cells also lost the ring chromosome, and contained a duplicated copy of the normal chromosome 13.

"It appears that ring chromosomes are lost during rapid and continuous cell divisions during reprogramming," said Yamanaka. "The duplication of the normal chromosome then corrects for that lost chromosome."

"Ring loss and duplication of whole chromosomes occur with a certain frequency in stem cells," explained Bershteyn. "When chromosome duplication compensates for the loss of the corresponding ring chromosome with a deletion, this provides a possible avenue to correct large-scale problems in a chromosome that have no chance of being corrected by any other means."

"It is likely that our findings apply to other ring chromosomes, since the loss of the ring chromosome occurred in cells reprogrammed from three different patients," said Hayashi.

"In theory, the way you could potentially correct a chromosome with deletions or duplications is to make a ring out of it and then get rid of the ring chromosome during reprogramming," added Wynshaw-Boris. "Ring chromosomes are quite rare, but chromosome abnormalities are much more common and cause a variety of severe birth defects. So far, it is only possible to do this chromosome therapy for cells in culture, not in human beings. However, it may be useful to use this for tissue repair of birth defects and other abnormalities found in individuals with chromosomal abnormalities as techniques for regenerative medicine are developed in the future."

More information: Cell-autonomous correction of ring chromosomes

in human induced pluripotent stem cells, DOI: 10.1038/nature12923