Optogenetics used to kick start gene that plays role in neural defects

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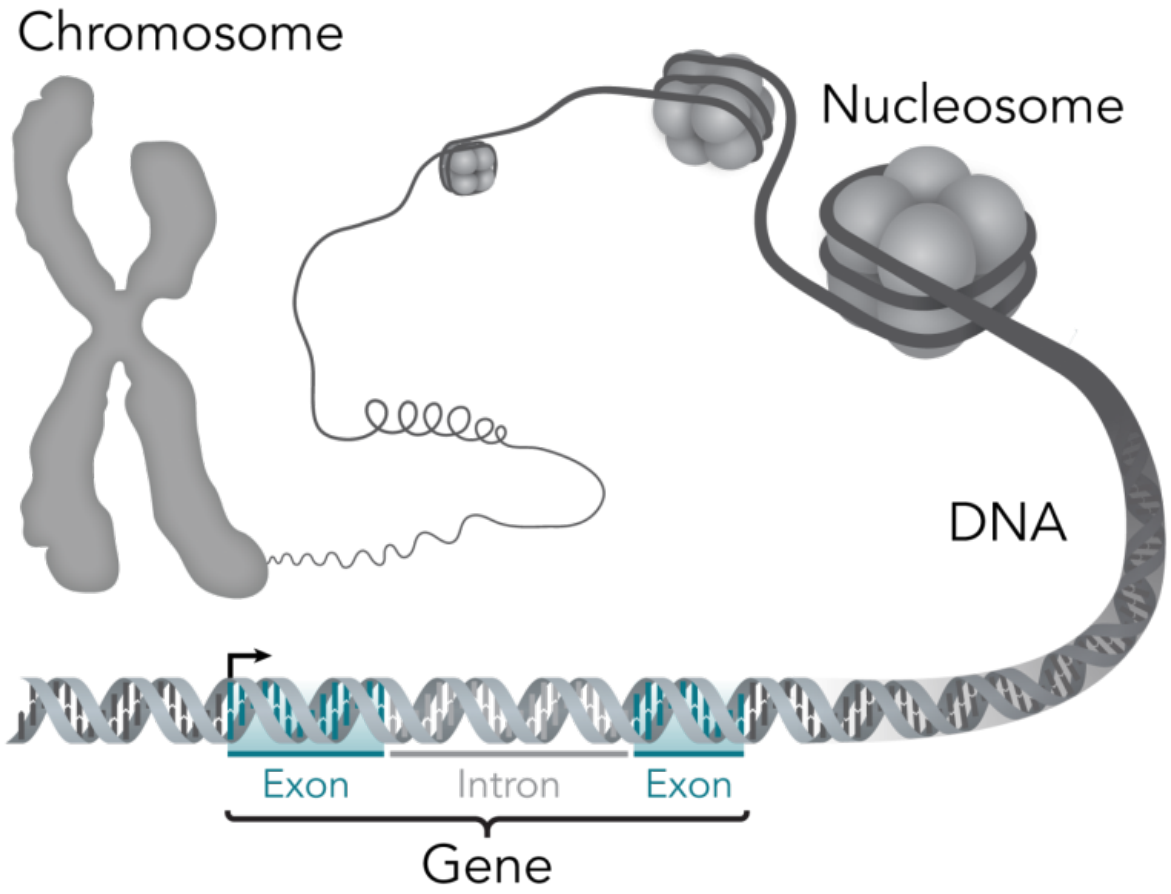

This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas

Purdue University and Indiana University School of Medicine scientists were able to force an epigenetic reaction that turns on and off a gene known to determine the fate of the neural stem cells, a finding that could lead to new therapeutics in the fight against select cancers and neural diseases.

Joseph Irudayaraj, a Purdue professor of agricultural and biological engineering, and Feng Zhou, a professor and neuroscientist at the Indiana University School of Medicine, have developed an optogenetic toolbox that brings together proteins and enzymes that methylate or demethylate a gene called Ascl1. Alteration of the methylation pattern in a specific gene with the optogenetic proteins would allow scientists to turn that gene on or off and produce desirable neurons among other cell types.

"If we can alter the epigenetic state at a specific location of a gene, then we can turn that gene on or off for personalized medicine," Irudayaraj said.

The findings, published in the journal *Nature Scientific Reports*, have implications for a number of diseases and maladies.

"By the ability of determining the fate of stem cells, one day it may be applied to produce neurons in Down syndrome, or reduce malignancy of glioma, a cancer in the brain," Zhou said. "By altering the methylation marks at a specific location of the gene, we have shown that the state of a cell can be altered."

Epigenetics is the study of changes in chemical modifications on top of a

gene based on external or environmental factors rather than changes in a DNA sequence. Optogenetics involves the utilization of light-sensitive proteins to alter the genetic or epigenetic profile in a cell or organism.

The researchers' findings detail the ability to modify the methylation profile of the Ascl1 gene in a site-specific manner, thereby controlling gene expression. DNA methylation involves adding a methyl group to the cytosine base of DNA, utilizing a family of enzymes called DNA methyltransferases (DNMTs). DNA demethylation is the removal of a methyl group from the cytosine bases using enzymes called Ten-Eleven Translocation, or TET.

Irudayaraj and his team attached these cytosine-modifying enzymes DNMT3A/TET to light-sensitive protein pairs to demonstrate site-specific methylation/demethylation. Zhou and his team introduced those light-sensitive proteins into neural stem cells and found that when they shined a blue light, the methylation modifying enzyme DNMT3A/TET and the gene target came together, adjusting the methylation of the gene.

"It's almost like putting a worm on a hook, and putting it in the water to catch a fish when it comes along. Once the light goes on, the hook and the fish come together and you catch the fish," Irudayaraj said.

The ability to activate or deactivate a gene, specifically those that suppress or promote a disease condition, could be a valuable tool for cancer therapeutics as well. The team plans to take the findings, done on neural stem cells, to mouse model systems.

"We want to apply this to therapeutics or toxicology," Irudayaraj said. "Essentially the applications are very broad. It can also include nervous system malfunctions, including addiction."

More information: Chiao-Ling Lo et al. Epigenetic Editing of Ascl1

Gene in Neural Stem Cells by Optogenetics, *Scientific Reports* (2017). DOI: 10.1038/srep42047