Rare developmental disorder linked to tumor-suppressing protein

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CHARGE, which affects 1 in 10,000 babies, is an acronym whose letters stand for some of the more common symptoms of the condition: coloboma of the eye, heart defects, atresia of the choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness.

Originally, the researchers were examining the tumor-suppressive properties of the protein, called p53, not investigating developmental disorders. But when a mouse model developed a strange set of deficiencies, the researchers followed a trail of clues that led them to link p53 with CHARGE syndrome.

"It was a very big surprise and very intriguing," said Jeanine Van Nostrand, PhD, lead author of a paper describing the research and a former Stanford graduate student, now at The Salk Institute for Biological Studies. "P53 had never before been shown to have a role in CHARGE."

The paper will be published online Aug. 3 in *Nature*. The senior author is Laura Attardi, PhD, professor of radiation oncology and of genetics.

Cellular quality control regulator

The researchers originally created a mouse model that expressed a mutated form of the protein, known as p53, to investigate the behavior

of p53 in suppressing tumors. Mice expressing only the mutated protein survived. But to their surprise, heterozygous mice, or those with one copy of the mutated p53 and one normal copy, developed symptoms of CHARGE and died in utero.

P53 is a cellular quality-control regulator. When it spots an ailing cell, it triggers other proteins to kill the cell or arrest its division. In a developing human or mouse, other proteins switch off p53 so it doesn't inadvertently kill important cells. The mutated form of p53 created by the researchers had a disabled off-switch, but it also couldn't communicate with other proteins to spark the cellular death. Therefore, a mouse containing only the mutated p53 survived to adulthood.

But when mice had one copy of a mutated p53 gene and one normal copy, the resultant proteins formed hybrids. These hybrid p53 proteins couldn't be turned off, but they retained the ability to trigger cellular death. Interestingly, these proteins only affected certain types of cells, causing the symptoms of CHARGE. The results suggest that p53 may play a role in other developmental disorders, Attardi said.

"It really reiterates how carefully p53 must be regulated," Attardi said. "It needs to be turned on at the right time and place. If it's not, it can cause damage."

CHARGE linked to gene mutation

The mechanisms of CHARGE syndrome remain a mystery, although it has been linked to a mutation in a gene called CHD7. Attardi's team examined the connection between p53 and CHD7. They discovered that the CHD7 protein can keep p53 turned off.

By linking p53 with CHARGE, this study elucidates molecular pathways that could be used to develop CHARGE therapies, said co-author Donna

Martin, MD, PhD, associate professor of pediatrics and of human genetics at the University of Michigan Medical School and an expert on CHARGE.

More information: Inappropriate p53 activation during development induces features of CHARGE syndrome, *Nature*, DOI: 10.1038/nature13585

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