MedicalXpress

Researchers uncover genetic basis for some birth defects

November 10 2008

A multidisciplinary research team at Case Western Reserve University led by Gary Landreth, Ph.D., a professor in the School of Medicine's Department of Neurosciences, has uncovered a common genetic pathway for a number of birth defects that affect the development of the heart and head. Abnormal development of the jaw, palate, brain and heart are relatively common congenital defects and frequently arise due to genetic errors that affect a key developmental pathway.

The research, titled "Mouse and human phenotypes indicate a critical conserved role for ERK2 signaling in neural crest development" is published in the November 10 issue of the *Proceedings of the National Academy of Sciences* of the United States of America.

Landreth, also the senior author of the study, developed a mouse model of these disorders by removing a gene central to this developmental pathway, called ERK2. He, together with Dr. William Snider at the University of North Carolina, discovered that the mice missing the gene for ERK2 in neural crest cells had developmental defects resembling those of human patients with a deletion that includes this gene. The patients have features that are similar to DiGeorge syndrome, which is associated with cardiac and palate defects. Interestingly, the ERK2 gene is central to a well-known pathway already associated with a different distinct group of cardiac and craniofacial syndromes that include Noonan, Costello, Cardiofaciocutaneous syndrome, and LEOPARD syndrome.

Landreth enlisted the help of Michiko Watanabe, Ph.D., professor of Pediatrics at Case Western Reserve University School of Medicine to look at the mouse hearts. She and her team found that they had characteristic heart defects resembling those seen in the patients with ERK2 deletions.

"Given Dr. Watanabe's findings, we determined that we had in fact developed animal models that mimicked the human deletion syndrome," said Landreth. "This work sheds light on how these developmental errors occur."

Remarkably, Dr. Sulagna Saitta, a human geneticist at Children's Hospital of Philadelphia had identified children who had comparable heart defects as well as subtle facial differences. These children were all missing a very small region of chromosome 22 that contained the ERK2 gene.

Saitta agreed that the similarity in the anatomic structures affected in the mice and those in the patients who have lost one copy of this gene suggest that ERK2 and its pathway members are essential for normal development and might lead to these birth defects. These findings link together several distinct syndromes that are each characterized by cardiac and craniofacial abnormalities and show that they can result from perturbations of the ERK cascade.

Landreth and his team will take these findings back to the lab and find out exactly why cells need ERK2 during embryogenesis.

To access the full study go to Proceedings of the National Academy of Sciences of the United States of America Web site: www.pnas.org/content/early/200 … c5-a1da-472459fa7f2c

Source: Case Western Reserve University