# Researchers discover a mechanism leading to cleft palate

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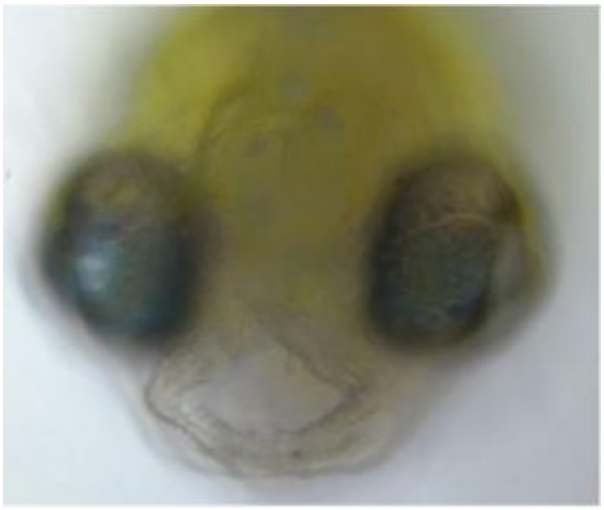

Zebrafish face with cleft palate. Credit: Courtesy of John Postlethwait

By creating a genetic mutation in zebrafish, University of Oregon scientists say they've discovered a previously unknown mechanism for cleft palate, a common birth defect in humans that has challenged medical professionals for centuries.

Many molecular pathways in zebrafish are present in humans and other vertebrates. By studying the induced mutation in zebrafish, the 10-member research team isolated a disruption in early developmental signaling involving Pdgf, a platelet-derived growth-factor protein, and a microRNA known as Mirn140, the researchers write in a paper posted

online in advance of regular publication the monthly journal Nature Genetics.

Mutant zebrafish lacking Pdgf had cleft palate similar to many human babies, showing that this growth factor helps to organize cells that make the palate. It came as a surprise that zebrafish into which the investigators had injected too much Mirn140 also had cleft palate.

MicroRNAs are small gene products, found to be involved in gene expression, that were first described in 1993 by researchers at Harvard University. The term microRNA was introduced in when these single-strand RNA molecules about nucleotides in length were more fully detailed in Science in October 2001 by Gary Ruvkun of Massachusetts General Hospital in Boston.

Mirn140, when operating normally, allows for normal cell signaling by the Pdgfra protein that properly triggers cell migrations necessary for correct oral-cranial building. The researchers showed that Mirn140 blocks the cell's expression of Pdgfra. Thus, cleft palate can result from too little Pdgfra that occurs because of either a mutation in the Pdgfra gene or too much Mirn140.

"We showed that this microRNA regulates the expression of the gene by controlling the migration of precursor cells to the palate-forming area," said principal investigator John H. Postlethwait, a professor of biology and member of the UO's Institute of Molecular Biology and Institute of Neuroscience. "This is a novel mechanism never before described."

A cleft palate is an opening in the roof of the mouth in which the two sides of the palate did not fuse, or join together, during a baby's early development. Cleft palate can negatively affect speech production, feeding, maxillofacial growth and dentition.

The first known attempt to correct the defect occurred in 500 A.D. The defect occurs with or without cleft lip (a separation of the two sides of the lip), on average, in 1 in 600 newborns, according to the Cleft Palate Foundation, but can vary by race. The highest incidence (3.6 per 1,000 births) occurs in American Indians. Palate formation begins after five weeks of gestation in humans and defects can become visible at 17 weeks, according to WebMD's eMedicine.

The findings provide a new window into the mechanisms involved in cleft palate and craniofacial defects, but researchers caution that the findings don't point toward new clinical applications.

"Further exploration of how microRNAs and other factors modulate signaling pathways such as the Pdgf pathway during palatogenesis will assuredly continue to provide insights into the cause of, and possible treatments for, human craniofacial disease," the authors conclude.

Source: University of Oregon