

Researchers use mouse model to study craniofacial disorders

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A picture of a palate development in mice: normal (top) and cleft (bottom). Credit: Trainor Lab

Researchers from the laboratory of Paul Trainor, Ph.D., at the Stowers Institute of Medical Research have developed an effective and reliable technique for studying high-arched palate using a mouse model. The methodology could expand research into the genetic aspects of this craniofacial abnormality.

Craniofacial anomalies like high-arched and <u>cleft palate</u> account for one third of all human congenital birth disorders. While there are a number of animal models for studying cleft palate that have provided insight on the biology of that condition, there are very few models for studying high-arched palate.

High-arched palate, also known as "pseudo-cleft" or "vaulted palate," refers to a pronounced curvature of the roof of the mouth. It can lead to enlarged gums, crowded molars and other dental problems, impair speech, and negatively affect a person's quality of life. But its genetic roots remain unclear, in part because researchers have lacked animal models in which to study the condition.

"High-arched palate is under-researched at the basic science level, given its presence in a relatively large number of syndromes," says Zachary Conley, the paper's first author. "A greater understanding of high-arched palate can lead to insights into palatogenesis, or the generation of the palate, as a complex developmental process. Our quantitative methodology sets the stage for further study of this condition."



Mice have long been used in genetic disorder research to mimic human diseases. For this study, Trainor Lab researchers and their collaborators used a mouse model of Treacher Collins syndrome (TCS), a human congenital condition that affects about 1 in 50,000 live births and impairs the bone and tissue development of the head and face, including the palate.

The researchers generated 3-D images of the palates of the mice at several stages of development using nuclear fluorescence imaging, which uses luminous dyes to observe objects that light-based microscopy cannot. Key characteristics—palate shelf length, shelf width, arch height, and arch angle—were statistically analyzed to establish significant, consistent criteria that define high-arched palates. In keeping with standard practices of clinical metrics, the researchers classified as abnormal features measuring more than two standard deviations from those found in the control group mice.

The TCS mice showed signs of palate formation problems during development, and about 46 percent exhibited a soft or fully cleft palate. TCS mice also showed significantly higher arched palate compared to their control counterparts, as defined by shelf height and angle differences—a clear validation of the research team's criteria.

Published online ahead of print in the journal *Developmental Biology*, the study was enabled by a 10-year research effort by the Trainor Lab and collaborators to understand the causes and effects of TCS. "Our work over the last decade has been aimed at understanding how Treacher Collins syndrome occurs, what cells and tissues are affected, and what we might be able to do to prevent it," says Trainor.

One promising finding of the study showed that TCS mice born to mothers with reduced p53 gene function showed no signs of cleft palate.



In prior work, the Trainor Lab linked the p53 gene to an uptick in neuroepithelial cell death and a resulting decline in migrating <u>neural</u> <u>crest cells</u>, which produce most of the cartilage, bone and connective tissue in an embryo's face and head. Without a sufficient supply of these cells, key areas of the developing mouth and nasal cavity fail to grow together and fully form.

In the current study, by generating TCS mice with impaired p53 gene function, the researchers were able to improve, or rescue, the higharched palate phenotype, suggesting a link between tissue formed by cranial neural crest cells and the underdevelopment of the palatal shelf in the pathogenesis of high-arched palate.

In related research, the Trainor Lab and collaborators have recently shown that the neuroepithelial cells that give rise to neural crest cells show a marked sensitivity to oxidative stress, and that maternal antioxidant supplementation can lessen or prevent craniofacial abnormalities in the TCS mouse model. These findings suggest that maternal antioxidant supplementation, which suppresses oxidative stressinduced p53-dependent neuroepithelial cell death, may be a possible avenue for clinical prevention of TCS. The study was published in the Jan. 21, 2016 issue of *Nature Communications*.

"We've used a pharmacological approach of prenatal antioxidant supplementation to reduce craniofacial anomalies in TCS mice," says Daisuke Sakai, PhD, first author of the paper and former postdoc in the Trainor Lab currently at Doshisha University, Japan. "Our findings provide new insights into potential therapeutic avenues for prevention of Treacher Collins syndrome."

"Our recent papers highlight the fundamental importance of basic biology in understanding clinical problems, by defining the origins of birth defects and their possible prevention" Trainor says.



Provided by Stowers Institute for Medical Research

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