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Study of zebra fish mouth formation may speak to Fraser syndrome hearing loss

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Using mutant zebra fish, researchers studying the earliest formation of cartilage of the mouth believe they may have gotten a look at a mechanism involved in a genetic defect linked to Fraser syndrome deafness in humans.

Reporting in the Aug. 1 issue of the journal *Development*, they identify a potential developmental pathway worthy of more scrutiny in future research into Fraser syndrome, a many-faceted and rare recessive genetic disease. In humans, a mutation in the gene FRAS1, which plays a role in skin epithelial formation during early development, has been linked to Fraser syndrome. A comparable version of the gene, fras1, in zebra fish is required for stable skeletal formation.

In the study -- done at the University of Oregon's Institute of Neuroscience -- researchers modeled craniofacial symptoms related to hearing loss in Fraser syndrome using mutant zebra fish, focusing on an endodermal pouch (known as p1), which in humans forms the Eustachian tube.

Using tissue labeling and time-lapse microscopy, the research team found "a previously unrecorded, late-forming portion of the first pharyngeal pouch in the zebra fish," said lead author Jared Coffin Talbot, now a postdoctoral researcher at Ohio State University. He earned his doctorate from the UO in 2011.

The newly seen component, researchers wrote, is a fras1-dependent

"endodermal outpocket" -- referred to in the paper as a late-p1. "If this homology can be taken as a guide, then endodermal pouching defects might underlie some ear defects in Fraser patients," they concluded.

"In fras1-mutant fish, some skeletal elements near late-p1 do not form properly during this time period," Talbot said. "However, after this time period, two other skeletal elements that would have normally been separated by late-p1 fuse together in fras1 mutants that lack late-p1. We propose that in normal development late-p1 holds apart skeletal elements found fused in fras1 mutants."

To test that idea, the researchers -- in the lab of Charles B. Kimmel, professor emeritus of biology -- added healthy epithelia tissue from wild-type zebra fish, into fras1-mutant embryos. Doing so allowed for normal facial development in the mutants.

"To my knowledge, the connection between skeletal development and Fraser syndrome deafness has not yet been made in mammals," Talbot said. "The literature has been largely mute as to why skeletal defects are found in fras1 mutants; this is what made it an interesting topic to study, but it does make a direct zebrafish-human connection more difficult to make. We believe that the middle ear and Eustachian tube are the homologous structures to what we're studying in zebra fish."

Fraser syndrome is a poorly understood disorder that can affect multiple parts of the body, but the majority of cases involve the eyes. Canadian geneticist C.R. Fraser described the disease in 1962. The FRAS1 gene previously had been identified as an adhesive and signaling molecule in epithelial tissues. The new paper shows the gene also acts in epithelia to sculpt skeletal shape.

"Specifically, we learned that zebrafish fras1 acts in tissues homologous to the human ear canal to sculpt tissues homologous to the human middle

ear," Talbot said. "To our knowledge, the shape of middle ear bones has not been studied in Fraser syndrome patients, nor has the Eustachian tube. We suggest that these tissues in human Fraser patients may prove highly fruitful."

Co-author John Postlethwait, a UO biologist, says his students often are intrigued when he shows them the similarities in the development of fish gills and their own Eustachian tube. "They know about what happens to their ears when they go up in an airplane, but are surprised at the evolutionary development of that ear-popping sensation," he said.

Another part of the new study also may provide insights into the many other faces of Fraser syndrome: partial webbing of fingers or toes; kidney abnormalities; genital malformations; and complete fusion of the eyelids.

"We carefully controlled for genetic and environmental factors by comparing the left and right sides of inbred zebrafish fras1 mutants raised in petri dishes," Talbot said. "When we did this, we found a remarkable degree of variation in skeletal defects. Our results appear to support the hypothesis that the degree of Fraser symptoms is to some extent determined by chance."

"These findings open a new window on the underlying mechanisms of this rare disorder," said Kimberly Andrews Espy, vice president for research and innovation. "Basic research in genetics at the UO using zebra fish as a tool reveals the fundamental dynamic processes that undergird development and helps to explain how it goes awry in medical conditions."

Provided by University of Oregon