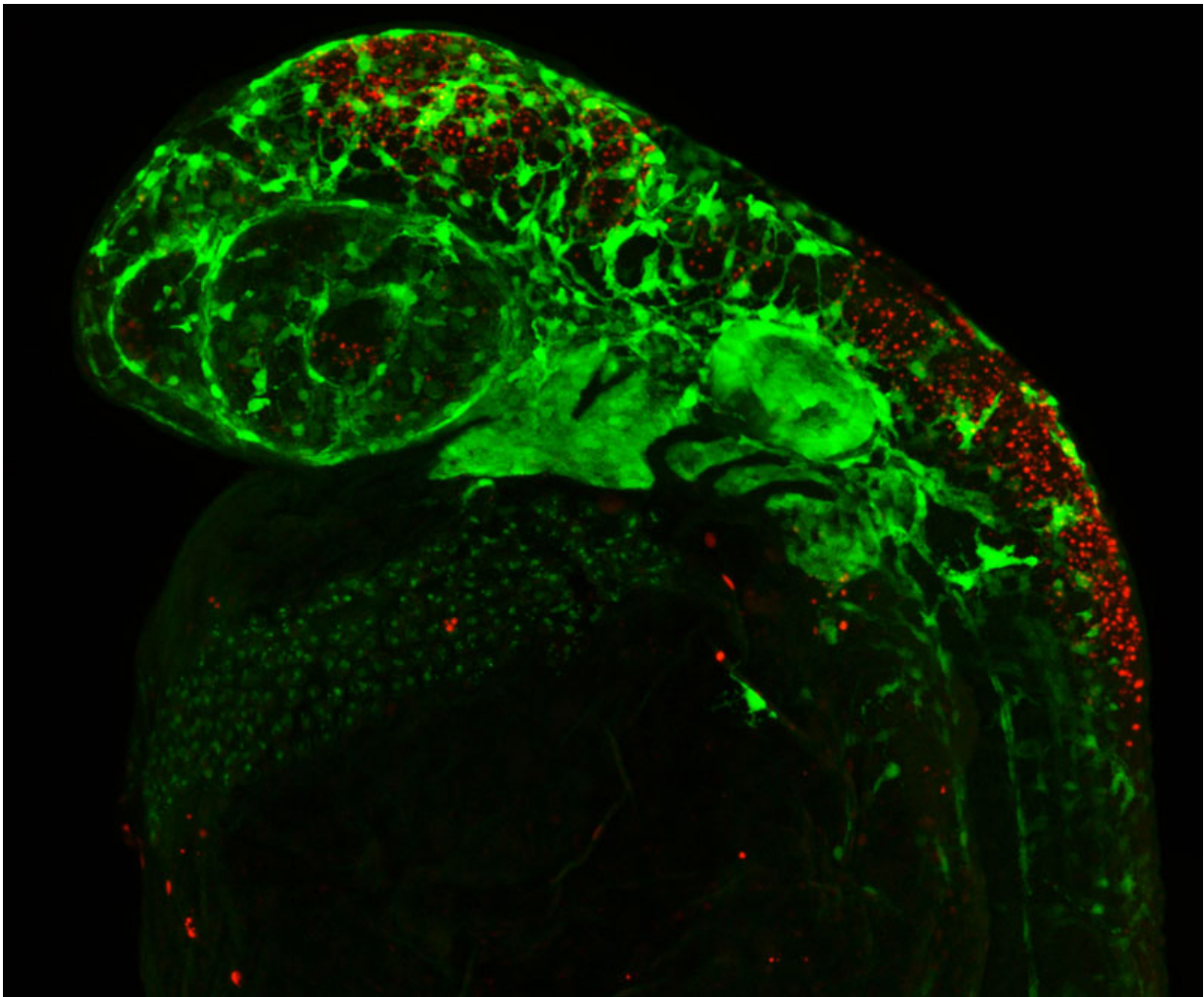


Similarities unite three distinct gene mutations of Treacher Collins syndrome

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Cell death (labeled in red) within the neural crest cell progenitor population results in a reduced population of neural crest cells (labeled in green) in a *polr1d* mutant zebrafish embryo. Credit: Trainor Lab

Scientists at the Stowers Institute for Medical Research have reported a detailed description of how function-impairing mutations in *polr1c* and *polr1d* genes cause Treacher Collins syndrome (TCS), a rare congenital craniofacial development disorder that affects an estimated 1 in 50,000 live births.

Collectively the results of the study, published in the current issue of *PLoS Genetics*, reveal that a unifying cellular and biochemical mechanism underlies the etiology and pathogenesis of TCS and its possible prevention, irrespective of the causative gene mutation.

Loss-of-function mutations in three human genes, *TCOF1*, *POLR1C* and *POLR1D*, have been implicated in TCS and are thought to be responsible for about 90 percent of the diagnoses of this congenital craniofacial condition.

The clinical manifestations of TCS include facial anomalies such as small jaws and cleft palate, hearing loss, and respiratory problems. Patients with TCS typically undergo multiple surgeries, but rarely are they fully corrective. By uncovering a mechanism of action common to all three genes, Stowers scientists have advanced scientific understanding of TCS etiology and pathogenesis and identified possible new avenues for preventing or treating the birth defect. This latest study from the laboratory of Stowers Investigator Paul Trainor, Ph.D., focused on *Polr1c* and *Polr1d*, whose roles as a genetic cause of TCS were revealed in a 2011 study of a small group of patients who had been diagnosed with TCS but who did not have the *TCOF1* mutation. Unlike *POLR1C* and *POLR1D*, *TCOF1* has been long recognized as a causative gene in TCS and as a result has been more extensively investigated.

"Before we began the study, nothing was known about the role of *Polr1c* and *Polr1d* in craniofacial development," said Kristin Watt, Ph.D., lead author of the *PLoS Genetics* paper and postdoctoral scientist in the

Trainor lab. "Using zebrafish as our animal model, we set out to explore the functional roles of *polr1c* and *polr1d* during embryogenesis and more specifically in craniofacial development."

Trainor, Watt and their collaborators compared the results of their findings on *polr1c* and *polr1d* with their and other labs' previous research results on *Tcof1*. In all three loss-of-function models, the researchers found that the chain of cellular events that led to the TCS phenotype of abnormal craniofacial development originated in ribosomes, the cellular components that translate messenger RNA into proteins. Like the *Tcof1* gene, *polr1c* and *polr1d* mutations were found to perturb ribosome biogenesis, or production of ribosomes, which affects the generation and survival of progenitor [neural crest cells](#), the precursors of craniofacial bone, cartilage and connective tissue.

In animal models of all three [causative genes](#), the scientists determined that deficient ribosome biogenesis triggered a p53-dependent cell death mechanism in progenitor [neural crest](#) cells. As a result of the activation of the p53 gene, developing embryos no longer made the quantity of neural [crest cells](#) needed to properly form the craniofacial skeleton.

However, in the *polr1c* and *polr1d* models as in the *Tcof1* models, Stowers scientists found that by experimentally blocking p53 activation, they could restore the neural crest cell population and thereby rescue the animal models' cranioskeletal cartilage.

Despite the rescue effect, Trainor said that he does not view the "guardian of the genome," as the p53 gene is often called due to its ability to suppress cancer, as the basis of a potential therapy to prevent or reduce TCS during embryonic development. The [p53 gene](#)'s association with cancer makes inhibiting its function too risky, he said.

A less risky and perhaps more effective target for the prevention or

treatment of TCS could be enhancing ribosomes, Trainor said, because the loss-of-function mutations in all three causative genes involve ribosome RNA (rRNA) transcription. *Polr1c* and *Polr1d*, for example, are subunits of RNA polymerases I and III that are essential for ribosome biogenesis.

"Rather than blocking p53, a better approach may be to try to prevent TCS by treating the problem in ribosome biogenesis that triggers the activation of p53 and the loss of neural crest cells," said Trainor.

In their research with zebrafish embryos, Trainor and collaborators also determined that *polr1c* and *polr1d* are spatiotemporally and dynamically expressed, particularly during craniofacial development. Furthermore, zebrafish embryos with the *polr1c* and *polr1d* loss-of-function mutations develop abnormalities in craniofacial cartilage development that mimic the clinical manifestations of TCS in patients. Trainor said that he and his fellow researchers were surprised that mutations in *polr1c* and *polr1d* as well as *Tcof1* specifically affected [craniofacial development](#), because ribosome biogenesis occurs in every cell of the body. The mutation of a gene that is part of the ribosome complex would be expected to be detrimental to each of these cells, he said. However, in the zebrafish models, the mutation appears to primarily affect progenitor neural crest cells. Trainor said that he and his team theorize that progenitor neural crest cells may be particularly sensitive to deficiencies in ribosome biogenesis during embryogenesis.

Thus, the study revealed new animal models for TCS: zebrafish with *polr1c* and *polr1d* loss-of-function mutations. Moreover, the existence of a common mechanism of action may simplify the research, particularly the search for a therapy to prevent or treat TCS. Because of the similarities among the three causative genes, "we may be able to develop creative ways of preventing TCS that will prove effective in at risk individuals who have one of the gene mutations," said Trainor, who has

investigated the molecular origins and development of TCS and related craniofacial developmental disorders for 10 years.

Provided by Stowers Institute for Medical Research

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