

Understanding genetic synergy in cleft palate

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Like mechanics fixing a faulty engine, Youssef A. Kousa, M.S., D.O., Ph.D., says researchers will not be able to remedy problems related to *IRF6*, a gene implicated in cleft palate, until they better understand how the gene works.

Credit: Children's National Health System

Like all of the individual elements of fetal development, palate growth is a marvel of nature. In part of this process, ledges of tissue on the sides of the face grow downwards on each side of the tongue, then upward, fusing at the midline at the top of the mouth. The vast majority of the time, this process goes correctly. However, some part of it goes awry for the 2,650 babies born in the United States each year with cleft palates and the thousands more born worldwide with the defect.

For nearly two decades, researchers have known that a gene known as *IRF6* is involved in palate formation. Studies have shown that this gene contributes about 12 percent to 18 percent of the risk of [cleft palate](#), more than any other gene identified thus far. *IRF6* is active in epithelial tissues—those that line cavities and surfaces throughout the body—including the periderm, a tissue that lines the mouth cavity and plays an important role during development.

According to Youssef A. Kousa, M.S., D.O., Ph.D., a child neurology fellow at Children's National Health System, the periderm acts like a nonstick layer, preventing the tongue or other structures from adhering to the growing palate and preventing it from sealing at the midline. While researchers have long suspected that *IRF6* plays a strong role in promoting this nonstick quality, exactly how it exerts its influence has not been clear.

"Gaining a better understanding of this gene might help us to eventually address deficits or perturbations in the system that creates the palate," Dr. Kousa says. "Like a mechanic fixing a faulty engine, we will not be able to remedy problems related to this gene until we know how the gene works."

In a study published July 19, 2017 by *Journal of Dental Research*, Dr. Kousa and colleagues seek to decipher one piece of this puzzle by investigating how this key gene might interact with others that are active during fetal development. The researchers were particularly interested in genes that work together in a cascade of activity known as the tyrosine kinase receptor signaling pathway.

Because this pathway includes a large group of genes, Dr. Kousa and colleagues reasoned that they could answer whether *IRF6* interacts with this pathway by looking at whether the gene interacts with the last member of the cascade, a gene called *SPRY4*. To do this, the researchers worked with experimental models that had mutations in *IRF6*, *SPRY4* or both. If these two genes interact, the scientists hypothesized, carrying mutations in both genes at the same time should result in a dramatically different outcome compared with animals that carried mutations in just one gene.

Using selective breeding techniques, the researchers created animals that had mutations in either of these genes or in both. Their results suggest that *IRF6* and *SPRY4* indeed do interact: Significantly more of the oral surface was adhered to the tongue during [fetal development](#) in experimental models that had mutations in both genes compared with those that had just one single gene mutated. Examining the gene activity in the periderm cells of these affected animals, the researchers found that doubly mutated [experimental models](#) also had decreased activity in a third gene known as *GRHL3*, which also has been linked with cleft lip and palate.

Dr. Kousa says the research team plans to continue exploring this interaction to better understand the flow of events that lead from perturbations in these genes to formation of cleft palate. Some of the questions they would like to answer include exactly which gene or genes in the tyrosine kinase receptor signaling pathway specifically interact with *IRF6*—since *SPRY4* represents just the end of that pathway, others genes earlier in the pathway are probably the real culprits responsible for driving problems in palate formation. They also will need to verify if these interactions take place in humans in the same way they occur in preclinical models.

Eventually, Dr. Kousa adds, the findings could aid in personalized prenatal counseling, diagnosis and screening related to cleft palate, as well as preventing this condition during pregnancy. Someday, doctors might be able to advise couples who carry mutations in these genes about whether they are more likely to have a baby with a cleft palate or determine which select group of pregnancies need closer monitoring. Additionally, because research suggests that *GRHL3* might interact with nutrients, including inositol, it might be possible to prevent some cases of cleft palate by taking additional supplements during pregnancy.

"The more we know about how these [genes](#) behave," Dr. Kousa says, "the more we can potentially avoid fetal palate development going down the wrong path."

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