Study reveals how cleft lip is caused by a combination of genes and environment

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A cleft lip or palate arises from the combined effects of genes and inflammatory risk factors experienced during pregnancy, such as smoking or infections, finds a new study led by UCL researchers.

The study, published in *Nature Communications*, has revealed for the first time how genetic and environmental factors come together to form a cleft lip or palate in a developing fetus.

Cleft lip, with or without cleft palate, is the most common craniofacial malformation seen at birth, affecting one in 700 live births. It can have devastating consequences for babies and their families, as the infants may experience difficulty feeding, speaking, and hearing, and may be at increased risk for ear infections and dental problems.

Senior author Professor Roberto Mayor (UCL Cell & Developmental Biology) said, "It has been known for some time that there is a genetic component to cleft lip, and that some environmental factors such as smoking, stress, infections and malnutrition during pregnancy can also increase the risk of cleft lip. Here, for the first time we have shown how these two factors work together, and why both genetic and environmental risk factors are necessary for a child to be born with cleft lip."

The researchers, based at UCL and the University of São Paulo, were studying families who carry mutations in the e-cadherin gene, which is known to be implicated in cleft lip, but noted that not everyone with the mutation develops a cleft lip. They reproduced this mutation in mice and frogs, which generated malformations similar to the cleft lip in humans, but only when the mice and frogs carrying the mutation were also exposed to inflammation-causing environmental factors. The researchers also found similar effects in human stem cells with both the mutation and inflammation.

The e-cadherin protein plays a role in fetal development, as neural crest cells—the embryonic stem cells that form facial features—move together to form the face. In normal development, the neural crest cells migrate together in two halves, wrapping around the head, before joining

together to form the face. This requires e-cadherin to act as a glue between cells. If the two halves of the neural crest cells do not fully bind together, the infant will be born with a cleft lip or palate.

The mutation identified by the researchers reduces the production of the e-cadherin protein, as DNA methylation reduces transcription, but they found that the mutation alone did not reduce e-cadherin levels enough to cause a cleft lip. It was only when a fetus with the mutation was also exposed to environmental risk factors that drive inflammation throughout the body (which can include smoking, stress, malnutrition or infections), that DNA methylation was increased and e-cadherin levels were too low for the neural crest cells to bind themselves together to fully form the lip and palate.

First author Dr. Lucas Alvizi (UCL Cell & Developmental Biology) said, "Our study is the first to demonstrate in detail how genetic and environmental factors combine to cause a birth defect, while it is also a noteworthy example of epigenetics, as environmental factors influence the expression of a gene."

The researchers hope that their findings will contribute to the development of new treatments or preventative strategies for cleft lip or palate, and clarify the risk factors to help people reduce the chance their baby will develop the condition.

Professor Mayor said, "Testing for this mutation could be a straightforward part of antenatal care, so that if someone carries the mutation, they would be advised to take steps to reduce the risk of inflammation that could combine with the genetic factor to result in a cleft lip. In addition to targeting factors such as smoking, the prescription of anti-inflammatory drugs may also help for at-risk pregnant women."

More information: Neural crest E-cadherin loss drives cleft lip/palate by epigenetic modulation via pro-inflammatory gene-environment interaction, *Nature Communications* (2023). DOI: 10.1038/s41467-023-38526-1

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