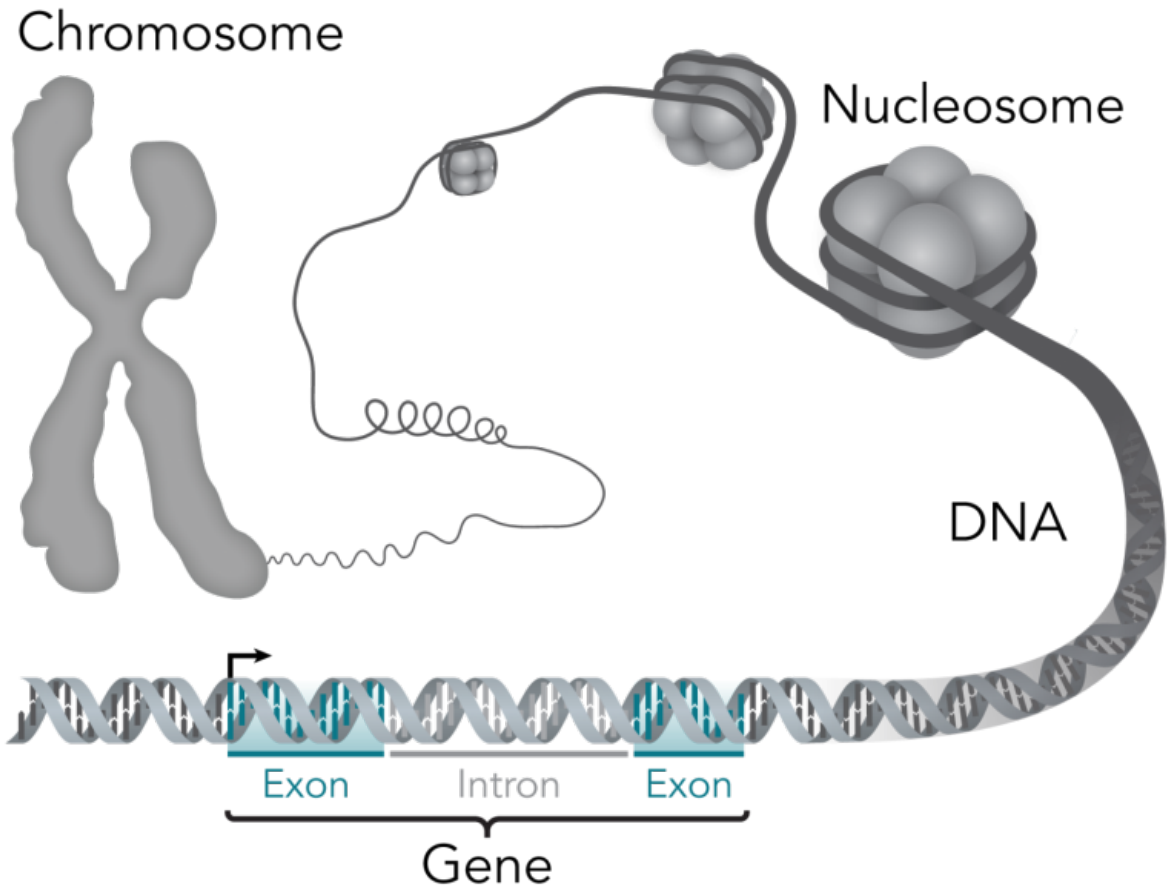
Researchers close to identifying crucial gene for human cleft lip and palate

March 21 2017



This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas

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A group of researchers has found that three siblings born with cleft lip and palate share a common gene mutation associated with the birth defect.

The gene intraflagellar transport 88 (IFT88) ensures transportation antennae (cilia) on embryonic cells travel to the right place, enabling the development of cartilage, bone and smooth muscle in the face and skull.

"Finding this birth defect in every single child in a family is like catching lightning in a bottle because it allowed us to pinpoint the gene mutation that is probably responsible," said Yang Chai, senior author of the study and director of the Center for Craniofacial Molecular Biology at the Herman Ostrow School of Dentistry of USC. "Our finding that the gene IFT88 is involved in cleft lip and palate is unlikely to be mere coincidence."

However, because this study involved only three children, Chai said more investigation is needed to find a causal relationship.

The study—a collaborative effort between the Ostrow School of Dentistry, the Keck School of Medicine of USC, Children's Hospital Los Angeles and the nonprofit Operation Smile—was published in the journal *Human Molecular Genetics* in January.

Operation Smile, an international nonprofit that provides free facial surgeries in developing countries, found and provided support to three siblings—two boys and a girl—in Mexico who were born with cleft lip and palate. Their mother did not have the congenital disorder, but their father did. Surgeons at CHLA repaired the orofacial abnormality.

In America, cleft lip and palate is the most common birth defect, according to data from the Centers for Disease Control and Prevention. An estimated 7,000 children are born with cleft lip and palate every year.

"Although most people are not familiar with cleft lip and palate, it is a common congenital anomaly that impacts survival, feeding, speech and has long-term implications if not repaired early and correctly," said Pedro Sanchez, a co-author of the study, a medical geneticist at CHLA and an assistant professor of clinical pathology and pediatrics at the Keck School of Medicine. "It occurs in approximately 1 in 1000 live births.

"Understanding the underlying causes of craniofacial disorders can one day lead to an intervention that can reduce the severity of this birth defect, thereby lessening the social, emotional and financial burden that these families face."

Genome sequencing locates a key gene mutation

Researchers went through 32,061 unique gene variations to identify IFT88.

"If someone carries this mutation, they may have a higher chance of giving birth to children with cleft lip and palate," said Chai, associate dean of the Ostrow School. "Doctors can provide consultations to these patients before they give birth, so parents can have surgery lined up and seek out proper care for their newborns."

The study of IFT88 may eventually have far-reaching implications. Other congenital diseases tied to a genetic disorder of cilia on embryonic cells include retinal degeneration, hearing defects, polydactyly (extra fingers or toes at birth) and brain malformations.

Animal model supports genome sequencing data

Genome-wide association studies usually use the data of hundreds or thousands of patients to identify a gene mutation, yet it is still an association study.

"In our study, however, the animal model and the human mutation match," Chai said. "In the animal model, there is no doubt. We have shown that 100 percent of the mice who have a single mutation in IFT88 have cleft lip and palate."

Provided by University of Southern California

Citation: Researchers close to identifying crucial gene for human cleft lip and palate (2017, March 21) retrieved 27 April 2024 from https://medicalxpress.com/news/2017-03-crucial-gene-human-cleft-lip.html

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