Researchers pinpoint genetic pathway of rare facial malformation in children

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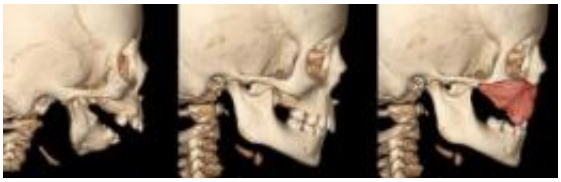

This is a 3-D CT scan of child with ACS.Pictured is a lower jaw is small and malformed (left); same-aged child with normal jaw (middle); lower jaw of child with ACS inverted over upper jaw of normal skull (right). Credit: Seattle Children's Research Institute

Researchers at Seattle Children's Research Institute and their collaborators have discovered a pair of defective genes that cause a rare congenital malformation syndrome that can make it impossible for the child to breathe or eat properly without reparative surgery. In a study led by Michael L. Cunningham, MD, PhD, medical director of the Seattle Children's Hospital's Craniofacial Center, a research team pinpointed two genes known as PLCB4 and GNAI3 in a genetic pathway that affects children with auriculocondylar syndrome (ACS). ACS is a rare disorder in which a child's bottom jaw develops as an upper jaw and, in some cases, incorrectly fuses to the base of the skull.

As part of the study, the DNA of five children with similar facial features characteristic of ACS was sequenced. Cunningham and his colleague Mark J. Rieder, PhD (University of Washington) used exome

sequencing, selectively sequencing those regions of the patients' DNA believed to constitute the majority of disease-causing mutations. The study, to be published in the May edition of *American Journal of Human Genetics*, is one of the first genomic studies to identify causative mutations in two genes for the same disorder in the same pathway in a single analysis, Dr. Cunningham said.

While children with ACS have normal cognitive development, severe cases may require an immediate tracheostomy, feeding tubes, and ultimately extensive facial reconstructive surgery to allow them to eat and breathe properly.

"Although ACS is rare, our findings suggest that these genes may also play a role in more common disorders of the jaw and ears," said Dr. Cunningham, who is also chief of the division of craniofacial medicine and professor of pediatrics in the Department of Pediatrics at the University of Washington School of Medicine. "It's possible that more common jaw problems, like the lower jaw abnormality known as Robin sequence and other skull and facial abnormalities such as craniofacial microsomia, are also caused by genes in this pathway."

ACS, a syndrome first described by scientists in 1978, is believed to affect less than one in 50,000 births, though the precise frequency is not known. It is not uncommon for the condition to be misdiagnosed or for diagnosis to be delayed. According to Dr. Cunningham it was the precision of case choice that allowed this discovery.

Of the five cases studied, two of the parents did not have this condition but were carriers for the mutation. "Now that we know the genetic pathway for ACS, we will be able to better identify and counsel people who have normal facial appearances but carry these genes, about the likelihood of passing on this mutation to their children," Dr. Cunningham said.

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Provided by Seattle Children's Research Institute

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