MedicalXpress

Study finds genetic variant plays role in cleft lip

October 6 2008

University of Iowa researchers and collaborators have found, in a previously identified gene, a variation that likely contributes to one in five cases of isolated cleft lip. It is the first time a genetic variant has been associated with cleft lip alone, rather than both cleft lip and palate.

The study provides insight on a previously unknown genetic mechanism and could eventually help with diagnosis, prevention and treatment of cleft lip, which affects more than five million people worldwide. The findings appeared Oct. 5 in the journal *Nature Genetics*.

In 2004, a worldwide team involving the University of Iowa identified the gene IRF6 as a contributor to about 12 percent of cases of the common form of cleft lip and palate. The new finding pinpoints a regulatory part of the IRF6 gene that binds to a protein called AP2. This regulatory part controls how much and when the critical IRF6 protein is made.

The finding involved the lab of University of Iowa Carver College of Medicine faculty member Jeff Murray in collaboration with the University of Iowa lab of Frederick Domann, Ph.D., and adjunct faculty member Brian Schutte, Ph.D. Other investigators in Denmark, Norway, Scotland, Italy, the Philippines, California, and at the National Institutes of Health and the University of Pittsburgh were also critical to the investigation.

"We knew from the earlier study that IRF6 increases the risk of clefting.

There are millions of common variants in the humane genome, but only a fraction have beneficial or harmful functions," said Fedik Rahimov, Ph.D., the lead author of the study and a graduate of the University of Iowa Interdisciplinary Program in Genetics, who worked in Murray's lab.

"We found that a common variant in the IRF6 gene severely disrupts the ability of AP2 to bind to it. This in turn disrupts proper expression of the IRF6 gene," said Rahimov, who is now a postdoctoral research fellow at Harvard Medical School.

The team used computational and biological approaches to conduct the study. First, with assistance from the NIH Intramural Sequencing Center at the National Human Genome Research Institute and based on previous University of Iowa research, the investigators used nonhuman DNA to predict potential regulatory sections around the gene in question.

Regulatory sections are separate from, but affect, the protein coding sections of genes. Regulatory sections are generally highly "conserved," meaning they have not changed much over evolution. However, one of the regulatory sections around IRF6 revealed a single nucleotide variant, so the team focused on the corresponding area in human DNA already identified by a previous UI graduate student.

Next, through a connection with the Lawrence Berkeley National Laboratory at the University of California, the variant was shown to reside in a regulatory element that controls IRF6 expression. The team then studied large DNA collections on cleft lip and palate and found that among nearly 3,000 families those with cleft lip only were far more likely to have the genetic variant.

"It was most striking that this variant was associated with clefts of the lip only," Rahimov said. "We always thought that cleft lip alone and cleft lip with cleft palate were the same disease. Now we see a difference and

will analyze patients with cleft lip separately from those who have both cleft lip and palate."

The investigative work on AP2 involved collaboration between Rahimov and Michael Hitchler, Ph.D., currently a post-doctoral fellow at the University of Southern California and a recent graduate of the University of Iowa Graduate Program in Free Radical and Radiation Biology, who worked in Domann's lab. That lab was studying the role of AP2 in cancer, and so, already had developed research technology to study AP2 binding. Using this technology, the lab was able to rapidly provide evidence that AP2 was bound to the IRF6 regulatory region.

"Mike Hitchler was able to help Fedik show that the IRF6 gene had a bona fide binding site for the AP2 transcription factor, and that this binding site was disrupted by the genetic variant," said Domann, University of Iowa professor of radiation oncology. "This was very solid evidence for understanding this newly discovered mechanism behind cleft lip.

"It's a great example of what can be achieved when investigators from seemingly disparate fields collaborate and cooperate," Domann added.

Source: University of Iowa