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Genetic profile reveals susceptibility to cleft palate

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For the first time, researchers from the University of Pittsburgh School of Dental Medicine have identified a series of genetic mutations that appear to be linked to significant risk for cleft palate and other dental abnormalities. These are devastating conditions that cause tremendous social isolation, and also are associated with decreased lifespan, a higher risk of cancer and increased susceptibility to psychiatric disorders, even after surgical repair.

As reported in the September issue of *Genetics in Medicine*, Alexandre Vieira, DDS, Ph.D., assistant professor in the Department of Oral Biology, University of Pittsburgh School of Dental Medicine, and colleagues collected and evaluated genetic material from the saliva and blood of more than 500 individuals in family groups with two or more siblings affected with cleft lip or palate, and an additional 100 people from unrelated families whose samples were used for general-population comparison data. The researchers analyzed 1,489 variations in DNA sequences, known as single-nucleotide polymorphisms, in 150 genes.

"We found a group of more than a dozen gene mutations that appear to be significantly associated with cleft lip and palate, as well as other dental abnormalities – predominantly at the locations for ERBB2, CDH2 and IRF6," said Dr. Vieira, who is a pediatric dental specialist. "Here we report, for the first time, an extensive candidate gene analysis for cleft susceptibility, a crucial step that may allow for better estimates of recurrence risk in individual families."

Collecting the genetic data from members of extended family groups living among the 7,000 islands in the Philippines presented its own challenges in the form of typhoons and severe tropical storms, at least one major landslide and frequently thorny local political conditions that restricted areas to which researchers could safely travel. Field researchers were stranded for more than a week and pitched in to help emergency rescue personnel following a massive mudslide on Southern Leyte that caused widespread damage and loss of life in February 2006.

"In some cases, it would be two entire days of travel by boat, car and foot to reach just one family in a remote village," said Dr. Vieira. "It took us about three years to finish the project."

The gene ERBB2 has been associated with aggressive breast cancer, while IRF6 is linked to formation of the connective tissue, such as the palate. CDH2 is a gene associated with left-right asymmetry. Other genes of interest that were identified include MSX1, PVR, PVRL and TGFA.

Associated tooth abnormalities studied included families where people had extra teeth, or teeth that were tiny or missing. Missing teeth was the most frequently observed abnormality, the researchers noted.

Cleft lip and palate is a common birth defect, on average affecting about one in 700 live births worldwide. In general, Asian populations have a higher prevalence of cleft lip and palate at about one in 500 births. Among Caucasians, the rate is one in 1,100, and African populations have the lowest rate at one in 2,500 births.

"In the Philippines, affected people can be completely isolated socially, miserable, alcoholic and heavy smokers with a hard time speaking. Access to care is very difficult," said Dr. Vieira. "The hope is to be able to narrow down the genes that cause clefts and to screen for that risk –

and, eventually, to possibly lead to gene therapy targets, although that may not happen in my lifetime."

Source: University of Pittsburgh