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Novel genes associated with risk for oral cleft malformation identified

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An international consortium of scientists, led by researchers at Johns Hopkins University has identified two genes that when altered are closely associated with cleft lip and/or cleft palate. Cleft lip and cleft palate are among the world's most common congenital malformations and occur in one in every 700 births. The finding is the result of the largest family-based, genome-wide study of cleft lip and/or cleft palate conducted to date. The results were published online by the journal *Nature Genetics*.

The study identified four different regions of the human genome likely to contain genes controlling risk for cleft lip and/or cleft palate. Two of these regions, the IRF6 gene on chromosome 1 and a region on chromosome 8, were previously identified in other studies. The current study identified genes MAFB on chromosome 20 and ABCA4 on another part of chromosome 1 as being associated with cleft lip and/or cleft palate.

"We confirmed that the previously identified gene IRF6 and a suspected segment of chromosome eight seem to be frequently altered in people born with clefts," said Terri H. Beaty, PhD, lead author on the study and professor of Epidemiology at Johns Hopkins Bloomberg School of Public Health. "This finding pulls together past work, while identifying new potentially causal genes that help to move the science forward."

The genome-wide association study involved 1,900 families with a baby affected with cleft lip and/or cleft palate from the United States,

Norway, Denmark, the Philippines, Taiwan, China, Singapore and South Korea. Over 500,000 genetic markers (called single nucleotide polymorphisms or SNPs) were used to cover the entire human genome. Researchers compared these SNPs in babies affected with cleft lip and/or palate to those carried by his or her parents to test each marker. The families studied were roughly evenly divided between families of European and Asian ancestry, which allowed the two groups to be compared directly.

The total sample identified four genes strongly associated with risk for cleft lip and/or cleft palate. Families of European ancestry, including European Americans, had the strongest statistical support for the region on chromosome 8. Asian families (from China, Korea, Singapore, Taiwan and the Philippines) had strongest support for IRF6, MAFB and ABCA4 genes. In addition to findings in humans, the investigators showed the MAFB gene was active in the developing head and mouth of embryonic mice, which further argues this gene plays some role in normal development.

"While these findings cannot yet be used to identify infants or families at immediate risk, they do open up important new areas of biological research into the causes of cleft lip and palate," said Beaty. "Fully understanding how several different genes can control risk to common human birth defects will create opportunities for more effective preventive measures in the future."

Provided by Johns Hopkins University Bloomberg School of Public Health