Tibetan adaptation to high altitude occurred in less than 3,000 years

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(PhysOrg.com) -- A comparison of the genomes of 50 Tibetans and 40 Han Chinese shows that ethnic Tibetans split off from the Han less than 3,000 years ago and since then rapidly evolved a unique ability to thrive at high altitudes and low oxygen levels.

The genome-wide comparison, performed by evolutionary biologists at the University of California, Berkeley, uncovered more than 30 genes with DNA mutations that have become more prevalent in Tibetans than Han Chinese, nearly half of which are related to how the body uses oxygen. One mutation in particular spread from fewer than 10 percent of the Han Chinese to nearly 90 percent of all Tibetans.

"This is the fastest genetic change ever observed in humans," said Rasmus Nielsen, UC Berkeley professor of integrative biology, who led the statistical analysis. "For such a very strong change, a lot of people would have had to die simply due to the fact that they had the wrong version of a gene."

The widespread mutation in Tibetans is near a gene called EPAS1, a so-called "super athlete gene" identified several years ago and named because some variants of the gene are associated with improved athletic performance, Nielsen said. The gene codes for a protein involved in sensing oxygen levels and perhaps balancing aerobic and anaerobic metabolism.

The new findings could steer scientists to till-now unknown genes that

play a role in how the body deals with decreased oxygen, and perhaps explain some diseases, including schizophrenia and epilepsy, associated with oxygen deprivation in the womb, he said.

Nielsen and his colleagues in China and Europe report their findings in the July 2 issue of the journal *Science*.

Nielsen, a computational evolutionary biologist, mines genomic information to discover genetic changes driven by natural selection as humans and animals have adapted to new environments. Changes in the frequency of DNA mutations are one clue.

"You look for rapid evolution in genes because there must be something important about that gene forcing it to change so fast," he said. "The new finding is really the first time evolutionary information alone has helped us pinpoint an important function of a gene in humans."

Adaptation to low oxygen levels has allowed many peoples, from Andeans to Tibetans, to live at high altitude. When people from lower elevations move above about 13,000 feet, where oxygen levels are about 40 percent lower than at sea level, they typically tire easily, develop headaches, produce babies with lower birth weights and have a higher infant mortality rate. Tibetans have none of these problems, despite lower oxygen saturation in the blood and lower hemoglobin levels. Hemoglobin, which gives blood its red color, binds and transports oxygen to the body's tissues.

Nielsen used genome data produced by the Beijing Genomics Institute (BGI) in Shenzhen, China's flagship genome center, to tease out the genetic changes associated with these physiological changes.

"We're looking for footprints of past selection to find something functional in our genome," Nielsen said.

BGI researchers obtained DNA from 50 Tibetans living in the Tibet Autonomous Region of China and 40 Han Chinese from Beijing. The Tibetans lived in two villages located at elevations of 4,300 meters (14,100 feet) and 4,600 meters (15,100 feet). All reported at least three generations of ancestors had lived at the same site. After obtaining informed consent, the Chinese researchers took blood samples from the participants and measured oxygen saturation, red blood cell concentration and hemoglobin content in their blood.

Back in the lab, the BGI team isolated only the active genes, or exons, from each individual, then used next-generation sequencing technology to sequence these so-called exomes. This involved cutting the DNA into many short pieces, sequencing each about 18 times with state-of-the-art Illumina sequencing machines, and then using overlaps to help reassemble the complete genome of each person. That work was directed by Jun Wang of BGI and the University of Copenhagen in Denmark.

Nielsen and post-doctoral fellows John E. Pool, Emilia-Huerta Sanchez and Nicolas Vinckenbosch conducted the analysis at UC Berkeley, locating all point mutations, called single-nucleotide polymorphisms (SNPs), in the 90 genomes and then comparing Tibetan and Han separately to a control group of 100 Europeans (Danes).

The analysis revealed that the common ancestors of Tibetans and Han Chinese split into two populations about 2,750 years ago, with the larger group moving to the Tibetan plateau. That group eventually shrank, while the low-elevation Han population expanded dramatically. Today, the Han Chinese are the dominant ethnic group in mainland China. The Tibetan branch either merged with the people's already occupying the Tibetan plateau, or replaced them.

"We can't distinguish intermixing and replacement," Nielsen said. "The Han Chinese and Tibetans are as different from one another as if the

Han completely replaced the Tibetans about 3,000 years ago."

The Tibetan and Han Chinese genomes are essentially identical in terms of the frequency of polymorphisms in the roughly 20,000 genes, though some 30 genes stood out because of dramatic differences between the Tibetans and the Han.

"We made a list of the genes that changed the most," Nielsen said, "and what was fascinating was that, bing!, at the top of that list was a gene that had changed very strongly, and it was related to the response to oxygen."

The SNP with the most dramatic change in frequency, from 9 percent in Han Chinese to 87 percent in Tibetans, was associated with lower red blood cell count and lower hemoglobin levels in Tibetans. That variation occurred near a gene called EPAS1, which earlier studies suggest is involved in regulating hemoglobin in the blood as a response to oxygen levels. The mutation may be in a transcription factor that regulates the activity of EPAS1.

Tibetans carrying only one allele with this mutation had about the same hemoglobin concentration as Han Chinese, but those with two mutated alleles had significantly lower hemoglobin concentration. However, they all have about the same oxygen concentration in the blood. For some reason, individuals with two copies of the mutation function well in high altitude with relatively low hemoglobin concentration in their blood. The mutation seems to provide an alternative inborn mechanism for dealing with the low oxygen levels, Nielsen said.

Other strongly selected variants were near the genes for the fetal and adult versions of the globin genes, which produce the structural proteins of hemoglobin.

Two other genes showing a dramatic shift in frequency have been linked to anemia, while several other genes have been linked to diseases, including schizophrenia and epilepsy, possibly caused by low oxygen levels in the womb.

Provided by University of California - Berkeley