Tibetans developed genes to help them adapt to life at high elevations

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Researchers have long wondered why the people of the Tibetan Highlands can live at elevations that cause some humans to become life-threateningly ill - and a new study answers that mystery, in part, by showing that through thousands of years of natural selection, those hardy inhabitants of south-central Asia evolved 10 unique oxygen-processing genes that help them live in higher climes.

In a study published May 13 in Science Express, researchers from the University of Utah School of Medicine and Qinghai University Medical School in the People's Republic of China report that thousands of years ago, Tibetan highlanders began to genetically adapt to prevent polycythemia (a process in which the body produces too many red blood cells in response to oxygen deprivation), as well as other health

abnormalities such as swelling of the lungs and brain (edema) and hypertension of the lung vessels leading to eventual respiratory failure. Even at elevations of 14,000 feet above sea level or higher, where the atmosphere contains much less oxygen than at sea level, most Tibetans do not overproduce red blood cells and do not develop lung or brain complications. The Utah and Chinese researchers found evidence that this might be related to at least 10 genes, two of which are specific genes strongly associated with hemoglobin, a molecule that transports oxygen in the blood.

High-altitude lung and brain complications threaten and even kill mountaineers who scale the world's tallest peaks. Others who find themselves at elevations significantly higher than where they normally live and work also can be stricken with the condition. Adaptations to living at higher altitudes have occurred in humans more than once, such as with people indigenous to the Andes Mountains in South America and people native to high altitude regions in the Ethiopian mountains in Africa. But the Tibetans have evolved genes that others living at similar elevations have not developed, according to Lynn B. Jorde, Ph.D., professor and chair of human genetics at the U of U School of Medicine and a senior author on the study. "For the first time, we have genes that help explain that adaptation," Jorde said.

The study was undertaken after Josef T. Prchal, M.D., a hematologist and professor of internal medicine, approached Jorde about doing genetic analysis related to his research on polycythemia. "What's unique about Tibetans is they don't develop high red blood cells counts," said Prchal, also a senior author on the study who has done research in Tibet. "If we can understand this, we can develop therapies for human disease."

Prchal's request prompted Tatum S. Simonson, a doctoral student in Jorde's lab and first author on the study, to travel to Tibet to collect DNA from people who lived in the region. Working with Ge Re-li,

M.D., Ph.D., director of the Research Center for High Altitude Medicine at Qinhai University Medical School in Xining, China, Simonson took blood samples from 75 people who live in a village 14,720 feet above sea level. After eliminating some samples because of kinship and other factors, she narrowed the blood sample selection to 31 - large enough for statistical validity. These samples were analyzed for 1 million genetic mutations or single nucleotide polymorphisms (SNPs).

The U of U research group then made a list of 247 candidate genes related to processing oxygen or other physiological features potentially associated with Tibetans' ability to thrive in higher elevations.

Two post-doctoral fellows in Jorde's lab, Chad D. Huff, Ph.D., and David J. Witherspoon. Ph.D., and Simonson performed computer analyses to compare the DNA variants in the villagers' blood samples with those from people living at neighboring lower elevations regions. This helped identify genes in the Tibetans that were not found in nearby populations. From this analysis the researchers narrowed the number of candidate genes down to 10, including the two strongly related to hemoglobin.

Although much work remains, and there could be other physiological reasons for the Tibetans' ability to thrive at higher elevations, the researchers believe those 10 genes might have allowed the Tibetans to evolve more efficient metabolisms and not overproduce red blood cells in response to thinner air. The Tibetans also show higher levels of nitric oxide, a molecule that may help get more oxygen to tissues and prevent polycythemia.

"This might help make up for having fewer red blood cells," Jorde said.

A detailed understanding of these changes may eventually lead to targeted therapies for common human maladies, including pulmonary

hypertension and lung and brain edema, which affect people everywhere.

Obtaining permission to conduct research in Tibet is difficult, and the U of U researchers say without the help of Re-Li, senior author on the study, the project may not have been possible.

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