

Mountain High: Genetic Adaptation for High Altitudes Identified

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First-time whole genome sequencing uncovers the genetic basis of chronic mountain sickness in Andean highlanders

Research led by scientists from the University of California, San Diego has decoded the genetic basis of chronic mountain sickness (CMS) or Monge's disease. Their study provides important information that validates the genetic basis of adaptation to high altitudes, and provides potential targets for CMS treatment. It will be published online August 15 in advance of print in the September 5 issue of *American Journal of Human Genetics*.



Machu Picchu, Peru. (photo credit: Pedro Szekely via flickr.com)

More than 140 million people have permanently settled on high-altitude regions, on continents ranging from Africa and Asia to South America. The low-oxygen conditions at such high altitudes present a challenge for survival, and these geographically distinct populations have adapted to cope with hypoxia, or low levels of oxygen in the blood.

Interestingly, many humans living at high elevations, particularly in the Andes mountain region of South America, are maladapted and suffer CMS. The disease is characterized by an array of neurologic symptoms, including headache, fatigue, sleepiness and depression. Often, people with CMS suffer from strokes or heart attacks in early adulthood because of increased blood viscosity (resistance to blood flow that can result in decreased oxygen delivery to organs and tissues). Past studies of various populations show that CMS is common in Andeans, occasionally found in Tibetans and absent from Ethiopians living on the East African high-altitude plateau.

Therefore, the researchers dissected the genetic mechanisms underlying high-altitude adaptation by comparing genetic variation between Peruvian individuals from the Andes region with CMS and

adapted subjects without CMS, using whole genome sequencing.

They identified two genes, *ANP32D* and *SENP1*, with significantly increased expression in the CMS individuals when compared to the non-CMS individuals, and hypothesized that down-regulating these genes could be beneficial in coping with hypoxia.

“While a number of published articles have described an association between certain genes and the ability for humans to withstand low oxygen at high levels, it was very hard to be sure if the association was causal,” said principal investigator Gabriel G. Haddad, MD, Distinguished Professor and chair of the Department of Pediatrics at UC San Diego School of Medicine, and Physician-in-Chief and Chief Scientific Officer at Rady Children's Hospital-San Diego, a research affiliate of UC San Diego.

The researchers therefore looked at genetic orthologs – corresponding gene sequences from another species, in this case the fruit fly – to assess the impact of observed genetic changes on function under conditions of hypoxia.

“We found that flies with these genes down-regulated had a remarkably enhanced survival rate under hypoxia,” said Haddad.

According to the scientists, their findings have important implications – not only for those who live at high altitudes, but also in treating certain cardiovascular and brain diseases related to low oxygen levels in individuals living at any altitude.

Next steps include whole genome sequencing for the almost 100 remaining patient samples to test if biomarkers exist to predict CMS. The researchers also retrieved skin samples from these individuals, which can be reprogrammed into induced pluripotent stem cells. These IPS cells, with the capacity to become glia or red blood cells, could be used to test resilience to low oxygen levels.

Additional contributors to the study include first author Dan Zhou, UC San Diego Department of Pediatrics; Nitin Udpa and Roy Ronen of the UCSD Bioinformatics and Systems Biology Graduate Program; Tsering Stobdan, Huiwen W. Zhao and Jin Xue, UCSD Department of Pediatrics; Junbin Liang, Yuanping Du, Yi Yin, Lixia Guo, Rui Cao, Yu Wang, Xin Jin, Chen Huang, Wenlong Jia, Dandan Cao, Guangwu Guo, Siqi Liu and Yingrui Li, BGI-Americas, Cambridge, Massachusetts; Otto Appenzeller, New Mexico Health Enhancement and Marathon Clinics Research Foundation, Albuquerque, New Mexico; Jorge L. Gamboa, Vanderbilt University Medical Center; Francisco Villafuerte and David Callacondo, Universidad Peruana Cayetano Heredia, Lima, Peru; Kelly A. Frazer, UCSD Department of Pediatrics, Division of Genome Information Science; and Vineet Bafna, UCSD Department of Computer Science and Engineering.

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