7-2010

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Published in *Science* Vol. 329 no. 5987 (July 2, 2010), pp. 40–41; doi: 10.1126/science.1192481

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Analyses of genomes from Tibetan populations reveal a signaling pathway that may account for high-altitude adaptation.

During the past 100,000 to 200,000 years, anatomically modern humans successfully colonized a diverse range of environments across the planet. Some of the most extreme of these environments are found on the high-altitude plateaus of Central Asia and the Andes. The Tibetan Plateau appears to have been inhabited for ~25,000 years, and permanent settlements have been established at elevations of 3500 to 4500 m (1, 2). Residents of these lofty altitudes descend from a long line of highland ancestors who lived long enough to reproduce in spite of the physiological challenges associated with chronic oxygen deprivation. Thus, studies of indigenous high-altitude residents provide the opportunity to identify genes that may have played a role in hypoxia adaptation. On pages 72 and 75 of this issue [*Science* Vol. 329 no. 5987 (July 2, 2010)], Simonson *et al.* (3) and Yi *et al.* (4), respectively, combine genomic and candidate-gene analyses to identify the genetic basis of high-altitude adaptation in Tibetans. Together with another recent analysis (5), the studies reveal that genes in the hypoxia-inducible factor (HIF) oxygen signaling pathway have been subject to strong and recent positive selection in Tibetan highlanders.

Hypoxic stress impinges on well-characterized physiological pathways related to oxidative energy metabolism, which has facilitated the identification of high-altitude adaptation mechanisms in nonhuman animals (6, 7). An alternative to this candidate-gene approach is to screen DNA sequence variations (polymorphisms) across the entire genome to identify chromosomal regions that have contributed to high-altitude adaptation. This population genomics approach holds the promise of identifying genes whose function and adaptive importance were previously unanticipated.

The high life. Tibetans, who have lived at high altitudes for nearly 25,000 years, survive the low-oxygen environment through a low blood hemoglobin concentration. (Photo: ISTOCKPHOTO.COM)

The HIF family of transcription factors regulates oxygen homeostasis by coordinating the transcriptional response to hypoxia. The human gene *endothelial PAS domain protein 1* (*EPAS1*, also called *HIF2a*) encodes the oxygen-sensitive subunit of the HIF-2 transcription factor and plays an important role in regulating erythropoiesis. After conducting genome scans to identify candidate genes for high-altitude adaptation, association studies demonstrated that noncoding variants in and around the genes *EPAS1, EGLN1* (a regulator of HIF), and *PPARA* (a transcriptional target of HIF) are strongly associated with a reduced blood concentration of hemoglobin in Tibetan highlanders (3–5). Previous studies demonstrated that Tibetan highlanders are characterized by a low hemoglobin concentration relative to lowland natives who have acclimatized to high altitude (1, 8). When lowland natives ascend to high altitude, the acclimatization response to hypoxia involves an increase in red blood cell production, and hence, an elevated hemoglobin concentration. Andean residents at high altitude are also characterized by an elevated hemoglobin concentration. By contrast, Tibetans living at elevations of up to 4000 m present a hematological profile similar to what would be expected at sea level (1).

It may seem counterintuitive that a reduced hemoglobin concentration would be advantageous under conditions of chronic hypoxia at high altitude because having more hemoglobin per unit blood volume increases arterial oxygen content. However, beyond a certain threshold, an increased hemoglobin concentration results in an elevated blood viscosity (because red blood cells make up a greater fraction of the total blood volume), thereby increasing vascular resistance and compromising tissue oxygenation. At high altitude, evidence suggests that the optimal hemoglobin concentration may

actually be quite close to the typical sea-level value (9). The potential fitness consequences of excessive erythropoiesis come into especially sharp focus when considering the effects on pregnancy outcomes at high altitude (10–12), because elevated hemoglobin concentration in the maternal circulation is associated with restricted fetal growth and increased fetal mortality in utero.

Given these adverse effects, why is an increased hemoglobin concentration such an integral part of the acclimatization response to hypoxia in humans? One possible explanation is that the HIF-mediated increase in hemoglobin concentration is a misdirected response to hypobaric hypoxia that originally evolved as a response to anemia. Hypobaric hypoxia and anemia both result in reduced tissue oxygenation, but their root causes differ. In anemia, reduced tissue oxygenation is caused by a curtailed oxygen transport capacity of the blood, and can therefore be rectified by increasing hemoglobin concentration. By contrast, in hypobaric hypoxia, the reduced tissue oxygenation has an external cause: The reduced oxygen tension of inspired air leads to a reduced oxygen saturation of arterial blood. Under these circumstances, a dramatically increased hemoglobin concentration may further impede oxygen delivery to metabolizing tissues. If our hominid ancestors were never forced to contend with the physiological challenges of low-oxygen environments, it might be unreasonable to expect that we would have evolved an appropriate physiological response to chronic hypoxia.

If certain features of the acclimatization response to hypoxia are maladaptive, then many adaptive changes in high-altitude populations may result from selection on genetically based trait variation that counteracts the effects of environmentally induced changes. In the case of hemoglobin concentration in Tibetans, for example, selection has not favored a trait value outside the ancestral range of variation. Instead, selection appears to have favored a blunted erythropoietic response such that hemoglobin concentration at high altitude is maintained at the sea-level status quo. Although the mechanism has yet to be elucidated, it appears that regulatory changes in *EPAS1* and other HIF-related genes have recalibrated the set point for hypoxia-induced erythropoiesis in Tibetans. Andean highlanders have not evolved a similar mechanism for attenuating the erythropoietic response to hypoxia, possibly because of their shorter history of residence at high altitude (1, 10).

It remains to be seen whether hemoglobin concentration represents the direct phenotypic target of selection in Tibetans, or whether changes in hemoglobin concentration represent an ancillary effect of selection on some other physiological trait that is altered by regulatory changes in the HIF cascade. These studies of Tibetan highlanders provide compelling proof of principle that the integration of population genomics and association studies can successfully identify targets of recent positive selection. These results should motivate detailed functional studies that will hopefully reveal the mechanistic basis of fitness variation among alternative genotypes at *EPAS1* and other HIF-related candidate genes for high-altitude adaptation.

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13. Funded by the NIH and the NSF. I thank C. M. Beall and L. G. Moore for helpful discussion.