Andean, Tibetan, and Ethiopian patterns of adaptation to high-altitude hypoxia

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Synopsis Research on humans at high-altitudes contributes to understanding the processes of human adaptation to the environment and evolution. The unique stress at high altitude is hypobaric hypoxia caused by the fall in barometric pressure with increasing altitude and the consequently fewer oxygen molecules in a breath of air, as compared with sea level. The natural experiment of human colonization of high-altitude plateaus on three continents has resulted in two—perhaps three—quantitatively different arterial-oxygen-content phenotypes among indigenous Andean, Tibetan and Ethiopian high-altitude populations. This paper illustrates these contrasting phenotypes by presenting evidence for higher hemoglobin concentration and percent of oxygen saturation of hemoglobin among Andean highlanders as compared with Tibetans at the same altitude and evidence that Ethiopian highlanders do not differ from sea-level in these two traits. Evolutionary processes may have acted differently on the colonizing populations to cause the different patterns of adaptation. Hemoglobin concentration has significant heritability in Andean and Tibetan samples. Oxygen saturation has no heritability in the Andean sample, but does among Tibetans where an autosomal dominant major gene for higher oxygen saturation has been detected. Women estimated with high probability to have high oxygen saturation genotypes have more surviving children than women estimated with high probability to have the low oxygen saturation genotype. These findings suggest the hypothesis that ongoing natural selection is increasing the frequency of the high saturation allele at this major gene locus.

Introduction

Research on humans at high-altitudes contributes to understanding the processes of human adaptation to the environment and evolution. The unique stress at high altitude is hypobaric hypoxia caused by the fall in barometric pressure with increasing altitude and the consequently fewer oxygen molecules in a breath of air as compared with sea level (Dry air contains 20.93% oxygen at all altitudes. Air at higher temperature or humidity has slightly less oxygen. For example, air at 92% humidity and 15°C contains ~20.7% oxygen while air at 92% humidity and 25°C contains ~20.3% oxygen.). Hypobaric hypoxia becomes progressively more severe with increasing altitude and stresses biological systems because a steady, uninterrupted supply of oxygen is required for metabolism in the mitochondria. It is generally assumed that the oxygen transport system evolved mainly under "normoxia" at sea level. At the same time, it should be noted that a period of global hypoxia, characterized by oxygen levels of ~16%, occurred around 250–150 million years ago when early terrestrial vertebrates were evolving (Huey and Ward, 2005). Since then, oxygen levels have been similar to present-day levels. Some have hypothesized that the human ancestral phenotype evolved under conditions of mild hypoxia (Hochachka *et al.*, 1998). Subsequent geological, vegetational, and archaeological analyses of one productive locality that has yielded many important hominid fossils over a span of millions of years indicate that the sites were at an altitude of 500–600m, below the altitude thought to induce hypoxic stress (*e.g.*, Bonnefille *et al.*, 2004; Redfield *et al.*, 2003; Quade *et al.*, 2004). Thus, the assumption that hominid evolution occurred under normoxia and the corollary that high-altitude hypoxia is a physiological stress, seems reasonable for this review. At high altitude the oxygen transport system must offset ambient hypoxia in order to maintain tissue oxygen levels to support maintenance, growth and development, and reproduction. Indigenous human populations reside on the Andean, Tibetan, and East African plateaus and have done so for millennia. High-altitude, hypobaric, hypoxia is an unavoidable, lifelong, severe stress imposed upon every resident regardless of age, sex or individual characteristic. Because traditional societies did not and do not adapt behaviorally to create non-hypoxic microclimates, people must adapt biologically. Theoretically,

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a chronic stress eliciting a biological response is a likely natural laboratory in which to detect evolution honing adaptations to improve the response. The purpose of this contribution to the symposium "Adaptations for Life at High Elevations" is to present an overview of the patterns of adaptation of the indigenous high-altitude human populations on the Andean, Tibetan, and East African plateaus and to present evidence of ongoing natural selection on one arterial-oxygen-content trait among Tibetans. At the request of the symposium organizers, the review focuses on the author's work. The topic has been reviewed in greater detail elsewhere (*e.g.*, Beall, 2001; Moore *et al.*, 1998; Ward *et al.*, 2000).

Exposition

Scientific study of human adaptation to high-altitude hypoxia started with the 1890 publication by François Viault with the title "On the large increase in the number of red cells in the blood of the inhabitants of the high plateaus of South America." Viault counted his red cells before going to altitude and at 15 and 23 days of acclimatization in Morococha, Peru (4540m). The number increased from a sea-level count of 5 million to 8 million red cells/cc blood. He also compared himself with resident Europeans and two Andean natives. Thus, the first published study established the conventions of reporting on hematological characteristics and of comparing populations. Until the 1970s nearly all research on human adaptation to high altitude took place in the Andes. Andean highlanders had distinctive morphological and physiological characteristics that seemed adaptive in the sense that they might offset hypoxic stress (Baker and Little, 1976; Monge, 1978). Consistent with Viault's findings, hematocrit (the percent of whole blood that is comprised of red blood cells) and hemoglobin (the protein in red blood cells that carries oxygen) concentration of Andean highlanders was progressively higher in an altitude dose-response fashion (*e.g.*, Cosio, 1972). This response was interpreted as advantageous because blood with more of the hemoglobin carrier molecule could carry more oxygen to offset the sparser pool of oxygen molecules in the ambient air. The same general pattern was found among individuals of low-altitude, European ancestry living at 1600m (5,280′) and 3100m (10,230′) in the Rocky Mountains of the United States (e.g., Okin *et al.*, 1966). The consistent response of the population of European ancestry which had not been exposed to the opportunity for natural selection to improve the adaptive response to chronic, lifelong hypoxia (although lowlanders are exposed to transient hypoxia during everyday life) and the Andean population which had been exposed to the opportunity, suggested that the universal human hematological response to high-altitude hypoxia was to elevate hemoglobin concentration in an altitude-dependent manner starting at least as low as 1600m.

Beginning in the 1970s and early 1980s, researchers asked whether the Andean response characterized all indigenous populations and began to study the inhabitants of the Himalayas and the Tibetan Plateau. The finding that Tibetans (including Sherpas) did not have elevated hemoglobin concentrations was viewed skeptically initially because it was so contrary to expectation and because it is a trait affected by other environmental influences such as iron nutrition (*e.g.*, Morpurgo *et al.*, 1976). Studies taking into consideration possible confounding factors confirmed that Tibetans live at altitudes as high as 4000m (13,200′) without an appreciable elevation of hemoglobin concentration above sea-level reference values (*e.g.*, Beall and Reichsman, 1984; Beall *et al.*, 1998). Above 4000m, Tibetans exhibit an increase in hemoglobin concentration (*e.g.*, Beall *et al.*, 1987); the Tibetan sample residing at the highest altitude (median of 5000m or 16,500′) has the highest reported value. These findings are illustrated in Figure 1 which presents the mean values of large, screened samples of high-altitude native adult males reported by the author. A pair of Andean and Tibetan samples at ∼3900m was collected explicitly for comparative purposes. The Andean sample had 21% (more than one standard deviation) higher hemoglobin concentration than its Tibetan counterpart (Beall *et al.*, 1998). As for the third major high altitude area, the East African highlands of Ethiopia, the situation with respect to hemoglobin concentration resembles the Tibetans. The sole study of hemoglobin concentration in a healthy, screened sample at 3530m in Ethiopia reported a hemoglobin concentration virtually the same as found at sea level (Beall *et al.*, 2002). These and others' findings (*e.g.*, Garruto *et al.*, 2003) established that an elevation in hemoglobin concentration is not a universal response to high-altitude hypoxia at altitudes as high as ∼4000m. The Tibetan population responds to elevations above 4000m with increased hemoglobin concentration whereas the Andean population responds to elevations of 1600m. That is, the Tibetans require a much stronger stimulus and have a smaller response. The classic model of high-altitude erythrocytosis (increase in red cell mass) based on Andean highlanders may be unique to them among indigenous highlanders.

Another trait reported for high-altitude samples is the percent of hemoglobin that is carrying oxygen, called the percent of oxygen saturation of hemoglobin or, simply, oxygen saturation. This measure is also often used to quantify the degree of physiological stress.

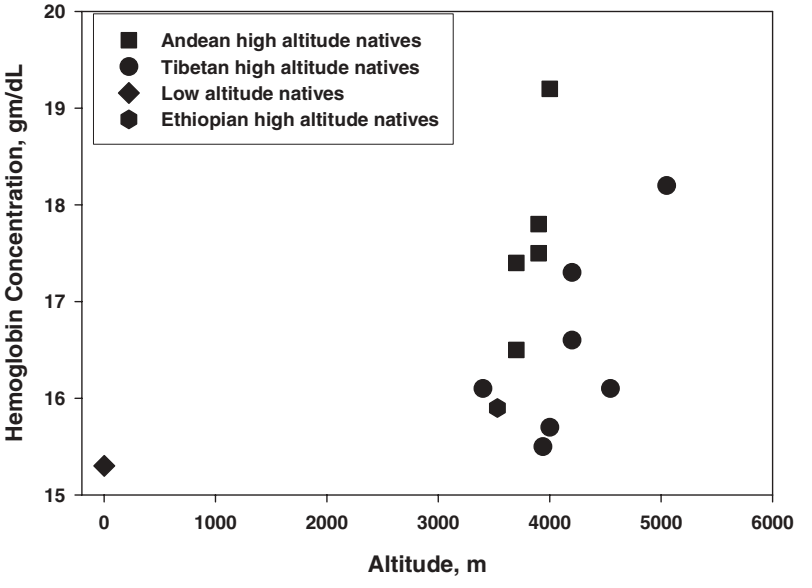

Fig. 1 Samples of Andean high-altitude native males have higher mean hemoglobin concentrations than samples of Tibetans and Ethiopians (sources Beall *et al*., 1990; Beall *et al*., 1998; Beall *et al*., 2001, Beall and Reichsman 1984; Beall and Goldstein, 1990; Beall *et al*., 1987; Beall *et al*., 2002, and unpublished data, C.M.B.).

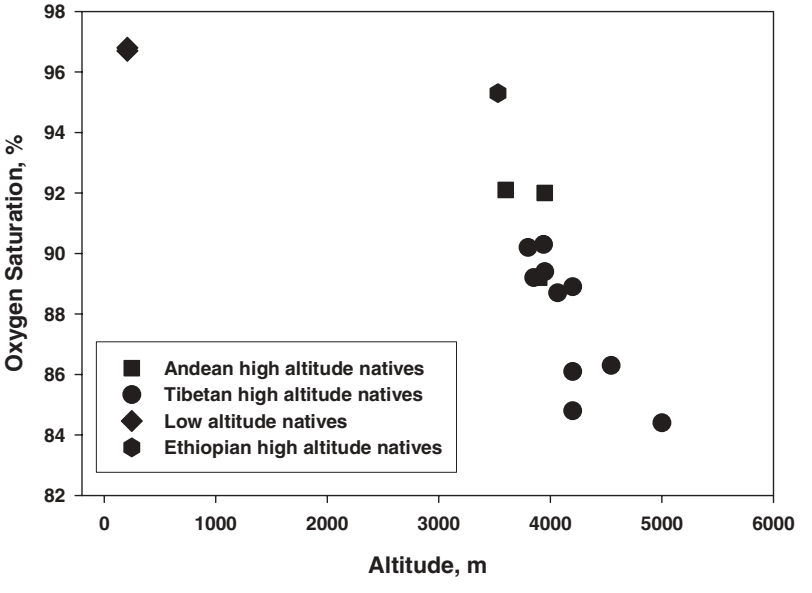

Fig. 2 A sample of Ethiopian high-altitude natives has a mean percent of oxygen saturation within sea-level normal values while samples of Andean high-altitude natives are hypoxic and samples of Tibetans are more profoundly hypoxic (sources Beall *et al*., 1999; Beall *et al*., 1992; Beall *et al*., 2001; Beall *et al*., 1997; Beall and Goldstein 1990; Beall 2000, Beall *et al*., 2002; and unpublished data, C. M. B.).

Oxygen saturation decreases immediately and profoundly upon acute exposure to high altitude (above 3000m), reflecting the lower partial pressure of oxygen in the ambient air (*e.g.*, Reeves *et al*., 1993). Figure 2 illustrates that Andean and Tibetan highlanders both have lower oxygen saturations than the 97–98% found at sea-level. That is consistent with expectations of hypoxemia under ambient hypoxia. Figure 2 presents the mean values of oxygen saturation for adult samples reported by the author. Tibetans exhibit a clear altitude dose-response relationship. A pair of samples at ~3900m collected explicitly for comparative purposes is noteworthy because the Andean sample had 2.6% (one standard deviation) higher oxygen saturation than the Tibetan sample, implying that they were less stressed by hypoxia at the same altitude (Beall *et al*.,

Table 1 Three patterns of adaptation of indigenous high-altitude populations (mean values of samples collected or analyzed by the author, with the exception of arterial O_2 content at sea level*

	O_2 Sat., %	Hemoglobin conc., gm/dL (adult males)	Arterial O_2 Content, mLO_2/100mL blood (calculated)	Arterial Hypoxemia	Erythrocytosis (increased red cell mass)
Sea Level	97	15.3 gm/dL	21.1	Absent	Absent
Ethiopia, 3530m	95	15.6 gm/dL	21.1	Absent	Absent
Tibet, 4000m	89	15.8 gm/dL	19.2	Present	Absent
Bolivia, 4000m	92	19.1 gm/dL	24.4	Present	Present

*Altman and Dittmer, 1972–74; Beall *et al.*, 1999; Beall *et al.*, 1998; Beall *et al.*, 2002; Beall *et al.*, 1997.

1999; Beall *et al.*, 1997). The findings from the sole Ethiopian sample, at 3530m, are unique because the average oxygen saturation is within normal sea level ranges. They imply that enough oxygen is transferred to arterial blood to avoid hypoxemia despite ambient hypoxia.

Hemoglobin concentration and oxygen saturation together determine arterial oxygen content. Table 1 compares three high-altitude samples with sea-level reference values to summarize three different patterns of adaptation. The classic Andean pattern is characterized by high hemoglobin concentration, low oxygen saturation, and an arterial oxygen content that is actually about 16% higher than sea-level reference values. The Tibetan pattern is characterized by essentially sea-level hemoglobin concentration until very high altitudes are attained, profoundly low oxygen saturation, and an arterial oxygen content that is about 10% lower than sea-level references values. Represented by a single study, the Ethiopian pattern is distinguished by levels of hemoglobin concentration, oxygen saturation, and arterial oxygen content comparable to those of healthy sea-level populations. Considering these measures from a single study, it is as if the Ethiopian sample were not living at high altitude.

The two traits described are among many that distinguish Andean and Tibetan high-altitude natives. For example, Andean highlanders have relatively lower resting ventilation, hypoxic ventilatory response, exhaled nitric oxide, and stronger hypoxic pulmonary vasoconstriction (Beall *et al.*, 1997; Beall *et al.*, 2001; Groves *et al.*, 1993). Thus, the natural experiment of human colonization of three high plateaus has resulted in two—perhaps three—biological outcomes. This raises the question of the underlying processes and the hypothesis that evolutionary processes produced this biodiversity, perhaps by acting differently on variation in the ancestral or founding populations. Addressing the hypothesis requires addressing the question of the genetic bases of these traits because evolution by natural selection requires genetic variation in heritable traits.

Population genetic differences among the three high-altitude populations have been suggested as the explanation for the different patterns, however consistent differences in mean values (even though many traits are involved) is not necessarily evidence of genetic differences and, furthermore, they do not provide information on genetic variation within populations necessary for evolution by natural selection. Because the genetic loci for these quantitative traits are unknown and because these traits are also influenced by age, sex, and other individual characteristics, a different approach was taken in order to analyze the genetic bases of these traits. Quantitative genetics techniques analyze intra-population phenotypic variation among relatives in order to test hypotheses about genetic contributions to the variation. These techniques estimate heritability (h^2), the proportion of total phenotypic variance attributable to genetic relationships among individuals. It takes on values from zero, when none of the variation within the population is due to genetic factors, to one, when all of the variation is due to genetic factors. Heritability is also a measure of the potential for natural selection (which requires genetic variation). Heritability values are specific to a trait in the population from which the sample is drawn; they do not provide information about mean values or about other populations. Quantitative genetic analyses were conducted on the pair of Andean and Tibetan samples at ~3900m (noted above in Figs. 1 and 2). Both had significant, high heritability for hemoglobin concentration of $h^2 = 0.89$ for the Andean sample and 0.64 for the Tibetan sample, indicating that there is genetic variation in both samples and potential for natural selection to act in both samples (Beall *et al.*, 1998). So far, there are no tests of that hypothesis.

With respect to percent of oxygen saturation of hemoglobin, there was no significant heritability for the Andean sample while there was a significant

Table 2 Differential Darwinian fitness of estimated oxygen saturation of hemoglobin genotypes among Tibetan women residing at 4,000m*

	Genotypic mean			
Genotype	**Number of pregnancies**	**Number of live births**	**Number of living children**	**Number of infant deaths**
Low oxygen saturation homozygote	4.6	4.5	1.6**	1.7**
Dominant heterozygote	4.9	4.8	3.6	0.6
High oxygen saturation homozygote	4.8	4.6	3.8	0.3

*Adapted from Beall *et al.*, 2004.
**Permutation $p < 0.05$ in a test of the null hypothesis that the low saturation genotypic mean differs from the combined high saturation genotypic means.

heritability of 0.40 for the Tibetan sample and there was evidence of a major gene for oxygen saturation. A major gene is an inferred allele with a large quantitative effect at a segregating autosomal locus (Weiss, 1993). Three major surveys conducted by the author and analyzed using different statistic models have detected a major gene with an autosomal dominant mode of inheritance occurring in four different geographic areas of the Tibet Autonomous Region. Thus, it is not likely to be a chance local phenomenon. Quantitative genetic and segregation analyses of samples from 3800–4065m and from 4450–5450m detected the autosomal dominant allele for higher oxygen saturation which conferred 5–6% higher oxygen saturation. Similar analyses of samples from 14 villages from 3800–4200m detected the autosomal dominant allele for higher oxygen saturation which conferred 10% higher oxygen saturation. (The difference in the size of the genotypic mean differences is probably due to differences in the statistical models.) The frequency of the high saturation allele ranges from 0.55 to 0.78 (Beall *et al.*, 1997; Beall *et al.*, 1994; Beall *et al.*, 2004). The implication is that individuals with one or two copies of this inferred allele experience less physiological hypoxic stress than those who are homozygous recessive at this locus even though all live under the same ambient hypoxia.

These findings about genetic variance have two implications. First, the absence of significant genetic variance in the Andean and its presence in the Tibetan high-altitude population is indirect evidence of population genetic differences because the inference is that the former is genetically homogeneous for that trait while the latter is not. Second, finding the major gene suggests the hypothesis that the higher oxygen saturation allele might be favored by natural selection.

To test the hypothesis that high oxygen saturation genotypes have higher Darwinian fitness, genealogical, oxygen saturation, and female fertility data were collected from 905 households in 14 villages at 3800–4200m in rural areas of the Tibet Autonomous Region. The analyses focused on 691 women 20–59 years of age still married to their first husbands, those with the highest risk of exposure to pregnancy. The effect of the inferred major genotype on fertility was calculated by calculating genotypic probability estimators (Hasstedt and Moll, 1989). Genotypic probability estimators ". . .partially assign an individual to a given genotype. Thus, an individual with genotypic probabilities of .85, .14, and .01 for genotypes dd, Dd and DD would contribute 85% of an observation to genotype dd, 14% to genotype Dd, and 1% to genotype DD." (Hasstedt and Moll 1989, p. 321). The mean number of pregnancies and live births did not differ across estimated oxygen saturation genotypes. It had a small range of variation from 4.6 to 4.9 pregnancies and 4.5 to 4.7 live births (Table 2). In contrast, the average number of surviving children was 3.8 and 3.6 for the estimated high oxygen saturation homozygotes and heterozygotes, respectively, while it was just 1.6 for the estimated low oxygen saturation homozygotes. The higher number of surviving children was explained mainly by lower infant mortality. An average of just 0.5 and 0.8 of the live births born to the estimated high oxygen saturation homozygotes and heterozygotes, respectively, died during infancy. In contrast, an average of 2.5 of the live births born to the estimated low oxygen saturation genotypes died during infancy. This suggests the hypothesis that high-altitude hypoxia acts as an agent of natural selection on the heritable quantitative trait of oxygen saturation via the mechanism of higher infant survival of Tibetan women with high oxygen saturation genotypes (Beall *et al.*, 2004). If this pattern persists, then the frequency of the high saturation allele will increase. The chromosomal location of the major gene remains unknown. Once it is found, then it will be possible to unambiguously genotype individuals in all three high altitude populations and study the biology linking a quantitative adaptive phenotype with a genetic locus under selection.

Summary

The natural experiment of human colonization of high-altitude plateaus on three continents has resulted in two—perhaps three—quantitatively different arterial-oxygen-content phenotypes among Andean, Tibetan and Ethiopian high-altitude populations. Ancestral human biology, adapted to transient, intermittent hypoxia at sea level, did not constrain colonizers to a single adaptive pattern. Measured in terms of mean values of traits contributing to arterial oxygen content, there is abundant evidence of the Andean-Tibetan contrast while investigation of the Ethiopian population is just beginning. There is progress toward understanding the processes that led to the different suites of quantitative traits. Evidence for a genetic basis for a distinctive phenotype is presently strongest for the Tibetan population where there is evidence of ongoing natural selection favoring greater reproductive success among women estimated with high probability to have genotypes for high percent of oxygen saturation of hemoglobin.

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