

HEMOGLOBIN CONCENTRATION, PULSE, AND LIFETIME REPRODUCTIVE SUCCESS AMONG ETHNIC TIBETANS AT HIGH ALTITUDES IN NEPAL

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Since the 1970s, Tibetan and Sherpas, mainly from Nepal, transformed the study of high-altitude adaptation. In particular, the distinctively unelevated hemoglobin of Tibetans and Sherpa, compared with that of Andean highlanders and acclimatized lowlanders, has drawn attention and led to the hypothesis that it represents an adaptation resulting from natural selection. This presentation reports a test of the hypothesis that genetic variants in the oxygen homeostasis pathway associate with hemoglobin concentration and reproductive success. A sample of 1006 post-reproductive Tibetan women residing at altitudes from 3000 to 4100 m in Nepal provided reproductive histories by interviews in native dialects, physiological measurements, and DNA from saliva samples. Regression analyses selected influential covariates of the number of pregnancies, livebirths, and children surviving to 15 years. Genomic analyses tested for associations with physiological and reproductive success variables. Beneficial alleles with signals of selection at EPAS1 SNP sites (but not EGLN1) associated with unelevated hemoglobin concentration. Unelevated hemoglobin concentration associated with greater lifetime reproductive success measured as the probability a pregnancy progressed to a livebirth. Yet the EPAS1 variants did not associate with pregnancy outcome, likely due to insufficient statistical power. EPAS1 did not associate with pulse although lower pulse associated with more pregnancies and live births. A genome-wide polygenic model of adaptation identified genes unrelated to hypoxia, favoring lower pulse, more livebirths, and fewer child deaths. The findings illustrate the complexity of identifying adaptations. They support the hypothesis that selection is acting against elevated hemoglobin concentration, pulse, or another correlated trait among Tibetans at high altitude.