

Genomic, physiological and social contributions to the survival of post-reproductive ethnically Tibetan women residing at high altitudes in Nepal

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Heritable traits provide the raw materials for natural selection. Identifying relationships among human traits, genotypes, reproduction, and survival requires considering multiple sources of variation. 1,006 post-reproductive Tibetan women residing above 3000m in Nepal provided this information in 2012. Two loci in the oxygen homeostasis pathway showed the largest estimated allele frequency changes since divergence from an ancestral Han population. *EGLN1* encodes a cellular oxygen sensing protein. *EPAS1* encodes a transcription factor that induces genes required for the response to hypoxia. *EPAS1* associated with unelevated hemoglobin concentration, which associated with greater reproductive success after controlling for sociocultural influences. We report on a seven-year follow-up of 553 of those women residing above 3500m in Upper Mustang, Nepal. Fifty-six had died, 45 had moved away; 428 participated in 2019. Surviving women averaged 53 ± 10 (SD) years at baseline compared with 64 ± 10 (SD) years among non-survivors. Survivors and non-survivors did not differ in hemoglobin concentration measured in 2012 nor in *EGLN1* allele frequencies. Three *EPAS1* SNP sites showed significant ($p=10^{-2}$ - 10^{-3} corrected for multiple testing) allele frequency differences between survivors and non-survivors, although none associated strongly with hemoglobin concentration. Interpretation of these results is not straightforward; perhaps SNP sites affecting survival differ from those affecting hemoglobin concentration. In contrast, married women and those with high Relative Wealth Rank ($p \leq 0.05$ Chi-Squares) had higher reproductive success and higher chance of surviving. Studies of natural selection in people must incorporate sociocultural factors with comparatively large effects.

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