

Genes and the fertility of Tibetan women at high altitude in Nepal

Tibetans have lived at altitudes above 3000m (~10,000') for at least 10,000 years and consequently have distinctive biological traits including unexpectedly low levels of hemoglobin, the molecule that carries oxygen. Genes accounting for such hemoglobin levels were recently identified and occur at uniquely high frequency among Tibetans. The likely mechanism for this high frequency is higher fertility and child survival for those people with the low-hemoglobin forms of those genes. This research will test the hypothesis that Tibetan women at high altitude in Nepal with the low-hemoglobin variants of the genes have more surviving children than those with the other variants. 1350 women of Tibetan ethnicity residing at 3000m or higher who have completed their reproductive careers will provide DNA for typing the genes called *EPAS1*, *EGLN1* and *HIF1α* that were previously found to regulate the response to hypoxia (low oxygen availability) such as that occurring at high altitudes. In addition, measurements of hemoglobin concentration, oxygen saturation of hemoglobin as well as information on these women's fertility history and the survival of their children will be collected. The expected outcome is that women with the forms of the genes that are most frequent among Tibetans will have lower hemoglobin concentration, higher oxygen saturation of hemoglobin, and more surviving children. Those results will connect a severe environmental stress to biological and genetic variation and reproductive success to build a case for natural selection operating in a human population and improve understanding of the processes of adapting to new environments. This U.S. – Nepalese collaborative research has health implications at all altitudes because these genes are necessary for intrauterine development and play central roles in the biology of diseases as diverse as osteo- and rheumatoid arthritis, heart failure, and cancer.