Chapter 10

AN EVOLUTIONARY MODEL FOR IDENTIFYING GENETIC ADAPTATION TO HIGH ALTITUDE

Lorna G. Moore[1], Mark Shriver[2], Lynne Bemis[3], and EnriqueVargas[4]
[1]Colorado Center for Altitude Medicine and Physiology (Division of Emergency Medicine), PhD Program in Health and Behavioral Science, and Department of Anthropology [2]Department of Anthropology, Pennsylvania State University, State College, PA [3]Division of Medical Oncology, Department of Medicine, University of Colorado at Denver and Health Sciences Center, Denver, CO [4]Instituto Boliviano de Biología de Altura, La Paz, Bolivia.

Abstract: Coordinated maternal/fetal responses to pregnancy are required to ensure continuous O_2 delivery to the developing organism. Mammals employ distinctive reproductive strategies that afford their young an improved chance of survival through the completion or the reproductive period. Thus, mortality prior to the end of the reproductive period is concentrated in the earliest phases of the lifecycle. At high altitude, fetal growth restriction reduces birth weight and likely compromises survival during the early postnatal period. Population variation in the frequency of the altitude-associated increase in intrauterine growth restriction (IUGR) demonstrates that multigenerational Tibetan and Andean high-altitude populations are protected compared with shorter duration, European or Han (Chinese) residents. This experiment of nature permits testing the hypothesis that genetic factors (a) influence susceptibility to altitude-associated IUGR, (b) act on maternal vascular adjustments to pregnancy determining uteroplacental blood flow, and (c) involve genes which regulate and/or are regulated by hypoxia-inducible factors (HIFs). Serial, studies during pregnancy as well as postpartum in Andean and European residents of high (3600 m) and low (300 m) altitude will permit evaluation of whether uteroplacental O_2 delivery is lower in the European than Andean women and, if so, the physiological factors responsible. Comparisons of HIF-targeted vasoactive substances and SNPs in or near HIF-regulatory or targeted genes will permit determination of whether these regions are distinctive in the Andean population. Studies coupling genetic and genomic approaches with more traditional physiological measures may be productively employed for determining the genetic mechanisms influencing physiological adaptation to high altitude.

Key Words: adaptation, hypoxia, hypoxia inducible factor (HIF), IUGR, natural selection, preeclampsia, uteroplacental ischemia

Hypoxia and Exercise, edited by R.C. Roach *et al.*
Springer, New York, 2006.

INTRODUCTION

Studies of human physiological adaptation to high altitude (defined here as >2500 m or 8000 ft) have long sought to determine whether or not there are genetic factors involved. Such efforts have been hindered by the inherent difficulties in distinguishing between genetic attributes *vs*. those that are acquired as a result of prenatal, postnatal, or later-in-life influences (9). In the language of geneticists, the phenotype (P) is a function of genetic (G) and environmental (E) influences plus the interactions between them (G x E); rarely, are only genetic factors responsible for visible traits. Interaction is so ubiquitous that some have questioned whether any influence is purely genetic or environmental (47). Such interactions include the influences of age, nutrition, disease or other kinds of environmental characteristics on the expression of genetic traits. For example, at high altitude, the larger lung volumes of lifelong, Andean high-altitude residents reflect both developmental exposure and a hereditary potential for larger lung dimensions (19). In addition. Brutsaert and co-workers have shown that the extent of an individual's physical fitness -- largely a function of acquired traits such as habitual exercise levels and training -- influences the extent to which genetic factors confer protection from an altitude-associated decrement in maximal exercise capacity (8).

The purpose of this article is to describe a model for identifying the genetic and/or genomic contribution to human adaptation to high altitude. Specifically, this model lays the groundwork for applying the analytical techniques described in this volume by Shriver *et al.,* to the adaptive challenge of fetal growth restriction posed by residence at high altitude. For reasons elaborated upon below, because the risk to survival prior to the end of the reproductive period is greatest during the period of pre- and early post-natal life, we elect to focus on fetal growth restriction as our index of high-altitude adaptation. Since genetic changes occur over generations and hence require long periods of time, we also choose to compare populations with and without multigenerational exposure to high altitude, while proposing to make provision for controlling for differences between groups unrelated to high-altitude exposure.

DEFINING ADAPTATION

From a genetic perspective, evolution can be defined as change in gene (allele) frequency over time. Four factors are involved– mutation, genetic drift, gene flow and natural selection – but only one of these, natural selection, is directional. Natural selection is also the force of greatest interest to physiologists since, generally, it is the effects of genes on the organism's ability to adapt to the environment that is of paramount concern. "Adaptation" in an evolutionary context refers to the ability to live and reproduce in a given environment (17). In principle, adaptations can be grouped into those affecting fertility (the production of live offspring) and mortality (in an evolutionary context, the ability of the organism to survive until the end of its reproductive period). "Fitness" is the net result of influences on both fertility and mortality, sometimes simply referred to as reproductive success. Distinguishing between adaptations affecting fertility and mortality can be difficult, especially in mammals that, as a group, shelter their young within their mother's uterus, making early mortality difficult to detect.