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Evolutionary adaptation to high altitude: a view from in utero

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Abstract

A primary focus within biological anthropology has been to elucidate the processes of evolutionary adaptation. A. Roberto Frisancho helped move anthropology towards more mechanistic explanations of human adaptation by drawing attention to the importance of the functional relevance of human variation. Using the natural laboratory of high altitude, he and others asked whether the unique physiology of indigenous high-altitude residents was the result of acclimatization, developmental plasticity and/or genetic adaptation in response to the high-altitude environment. We approach the question of human adaptation to high altitude from a somewhat unique vantage point; namely, by examining physiological characteristics – pregnancy and pregnancy outcome -- that are most closely associated with reproductive fitness. Here we review the potent example of high-altitude native population's resistance to hypoxia-associated reductions in birth weight, which is often associated with higher infant morbidity and mortality at high altitude. With the exception of two recent publications, these comparative birth weight studies have utilized surnames, self-identification and/or linguistic characteristics to assess ancestry, and none have linked 'advantageous' phenotypes to specific genetic variations. Recent advancements in genetic and statistical tools have enabled us to assess individual ancestry with higher resolution, identify the genetic basis of complex phenotypes and to infer the effect of natural selection on specific gene regions. Using these technologies our studies are now directed to determine the genetic variations that underlie the mechanisms by which high-altitude ancestry protects fetal growth and, in turn, to further our understanding of evolutionary processes involved in human adaptation to high altitude.

Keywords

Pregnancy; hypoxia; fetal growth; birth weight; SNP

Studies of human adaptation have long sought to determine whether the unique physiology that characterizes native altitude populations is the result of genetic adaptation to high altitude (defined here as >2500 m). Several unique features of the high-altitude environment make it well suited for studying genetic adaptation. Unlike the majority of environmental stressors such as temperature, malnutrition or disease threats, the hypoxia of high altitude is pervasive in that it affects all residents, all the time. Oxygen, even more than food or water, is essential to human life. But unknown is the extent to which the ability to adapt -- that is, the ability to survive and reproduce successfully -- to high altitude is due to time-dependent changes that can be acquired by all (or nearly all) persons (i.e., acclimatization), changes

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acquired during growth and development (i.e., developmental adaptation) and/or to genetic factors; it is only the latter set of events that can be truly called evolutionary adaptation.

The pendulum has swung back and forth concerning the likelihood that genetic factors are involved. Some studies, many of which used exercise performance as the criteria for adaptation, have concluded that genetic factors were not the primary determinant of human population's ability to adapt to high altitude (see Hurtado 1964). Others using overall body growth or the growth of selected organ systems, such as the lung, have emphasized the importance of developmental processes (Frisancho and Baker 1970). More recent studies include roles for genetic factors, developmental influences as well as environmental characteristics or attributes acquired during adulthood and recognize the conceptual challenges involved in teasing apart these multiple determinants (Brutsaert 2001; Frisancho, et al. 1997; Frisancho, et al. 1995). We approach the question of human adaptation to high altitude with a somewhat different focus; namely, by studying pregnancy to identify the factors promoting reproductive success during the phase of the lifecycle that poses the greatest mortality risk prior to the end of the reproductive period and is thus the most closely connected to reproductive fitness. Pregnancy is a critical period not only from the perspective of the reproductive fitness of the mother, but also from that of the father and, of course, the infant. While the predictors of reproductive success can be approached from the vantage point of mother, father or infant, we have chosen to focus on the effects of high altitude on physiological characteristics of the mother and, in turn, their relationship to fetal growth and neonatal well-being. So doing, we hope, enables a finer scale and more accurate assessment of the contribution of genetic factors to processes of human adaptation.

This review is composed of three sections. First we consider a brief history of studies at high altitude as well as some of the important study design and related factors that influence our ability to detect evolutionary adaptation. Such considerations involve the conceptual underpinnings of what is meant by "adaptation", some of the inherent biases or limitations of earlier work, and the breakthroughs provided by the studies of A. Roberto Frisancho and others for incorporating the important dimension of time into their designs (Baker and Little 1976; Frisancho and Baker 1970). Second, we compare population studies of maternal/fetal adaptation to high altitude that have been conducted in recent years by our and other groups to determine whether multigenerational high-altitude residents are protected from altitude-associated reductions in fetal growth relative to newcomer groups. Here we also consider whether differences in maternal physiological responses to pregnancy can account for such population differences or whether fetal, placental or other factors are more likely responsible. Third, we discuss new genetic approaches for studying adaptation and, in particular, those that can be applied to complex phenotypes. So doing shows how such approaches have enhanced our capacity to identify the genetic basis of complex phenotypes and to infer the effect of natural selection on gene regions. We end with some suggestions for areas in which future research is needed for furthering our understanding of genetic adaptation.

THE IMPORTANCE OF STUDY DESIGN FOR DETECTING ADAPTATION

Impressive are the great many persons and nationalities that have contributed to our knowledge of how humans respond to the physiological challenges of residence at high altitude. Such work extends back to the 19th century (Thomas, et al. 2001). During the 20th century, landmark studies were done in Colorado that demonstrated the fundamentals of ventilatory and hematological acclimatization (Torrance and Reeves 2001) as well as the reduction in exercise capacity occurring in response to high altitude (Reeves, et al. 2001) . Important too were studies done in South America, as summarized in Carlos Monge M.'s 1948 book, *Acclimatization in the Andes* (Monge 1948), and the continuing work carried in

Peru by Alberto Hurtado (Hurtado 1964) , Carlos Monge C. (Monge and Monge 1966), Emilio Marticorena (Marticorena, et al. 1969) and in Bolivia by Enrique Vargas, Mercedes Villena, Hilde Spielvogel and others in the 1960s or so. Mountaineering expeditions particularly in the Himalayas also added significantly to our knowledge (Lahiri and Edelman 1969; Lahiri and Milledge 1967; Pugh 1960-1961) and helped to demonstrate the limits of human physiological adaptation to hypoxia.

Missing from many of these early studies was the incorporation of a population perspective. Since evolution ultimately acts on the genetic variation present within a population, rather than an individual, the population is the key component for the study of evolutionary adaptation. The anthropological community was among the first to recognize this with the studies initiated by Paul T. Baker and his students in Nuñoa, Peru (Baker and Little 1976). This project succeeded in training a whole generation of anthropologists including A. Roberto Frisancho who is being honored in this symposium and many others who continued to work at high altitude, including Cynthia Beall, Ralph Garruto, Larry Greksa, Jere Haas, and Charles Weitz. Their studies and those of their students continue to exert important influences in biological anthropology and related disciplines today.

In addition to a population perspective, a second key concept for recognizing evolutionary adaptation to high altitude is the relationship between genotype and phenotype. Central to modern evolutionary theory is that the phenotype (P) is determined by genetic factors (G) operating in both additive and interactive fashions with environmental influences (E) or $P = G + E + (E \times G)$. In humans and other mammals, differentiating between phenotype and genotype is not as simple as it might first appear. This is due to the inherent difficulties in distinguishing between genetic attributes from those that are acquired as a result of prenatal, postnatal, or later-in-life influences (Brutsaert 2001). “Environment” in this context is not just the physical environment (such as high altitude) but also the influences of age, nutrition, disease or other factors that affect the expression of genetic traits. Another challenge is the ubiquity of the interactive effects of genes and the environment in which they are expressed, leading some to question whether there is any such thing as a purely genetic or environmental trait (Lewontin 2001). Also central to modern evolutionary theory is that while multiple factors affect gene frequency (flow, drift, mutation, natural selection), only natural selection exerts systematic and directional effects. Finally even though effects on fertility and mortality are the cornerstones of evolutionary process, the ability to differentiate between them is limited by the fact that human beings are mammals and therefore subject to the limitations imposed by the very nature of mammalian reproduction in which it is difficult to differentiate between effects on fertility vs. mortality during the early intrauterine period.

A third key element was a more formal recognition of the importance of study design. The study designs used in much of the work carried out by 19th and 20th century pioneeers contained some important limitations. One was that truly most studies were done on “man” at high altitude (Baker and Little 1976) with few including female participants. A second consideration was that differences between “adaptation” and “acclimatization” were not always recognized. Acclimatization or the time-dependent physiological changes occurring in response to high altitude within an individual’s lifetime was not always differentiated from “adaptation”, that is Darwinian adaptation, or changes occurring across generations. This was likely due in part to the inherent difficulties in distinguishing between them, as commented upon above. 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 (Frisancho, et al. 1997). Exemplifying this, Tom 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 (Brutsaert, et al. 2003). A third and final consideration was that transportation, linguistic familiarity, access to interpreters, and other logistical considerations meant that early studies and, in fact, most investigations through the ~1980s were conducted in locales that could easily be accessed but were not necessarily representative of the population at large. For example, early studies were done in mining communities that were on rail or other major transportation lines where genetic admixture or environmental or occupational hazards (e.g., dust exposure) were present. Another important consideration pertaining to study design was that, while the early work was essentially descriptive, improvements in sampling, data collection and other means permitted the testing of more mechanistic hypotheses. Such changes included, for example, the incorporation of control groups and use of sophisticated, migrant study designs with controls for age of onset and duration of high-altitude exposure.

A fourth and equally important factor for assessing the ability of the early human physiological studies for detecting evolutionary adaptation was the choice of functional outcomes or endpoints. Because maximal exercise performance represents the integrated sum of all the components of the oxygen transport system and perhaps also because of the physical rigors of the high-altitude environment, a strong -- almost universal -- focus of this early work was on exercise performance. Again, the value of exercise performance as an endpoint is not being questioned -- it is of clear relevance for an understanding of oxygen transport, is precisely quantifiable, and allows for testing of competing mechanistic hypotheses. But the relevance of maximal exercise capacity for determining the variables most closely related to evolutionary adaptation -- fertility and mortality -- is open to question. Inability to perform exercise limits reproductive fitness and pregnancy, by virtue of its effect on raising metabolic rate, constitutes a form of low-level exercise. But the modest levels of exertion during pregnancy and characterizing most populations most of the time are not well reflected in studies of maximal exercise performance. This is not a new observation; often recognized is the need for a test that assesses the ability to endure more sustained exercise. However, the design of such a test and its validation remain elusive.

A fifth study-design feature of importance for our ability to detect adaptation is the recognition of a time dimension. A time dimension was important in the early studies of acclimatization with, for example, ventilatory acclimatization being shown as a time-dependent fall in arterial PCO_2 and a consequent rise in arterial O_2 saturation. The growth studies conducted by A. Roberto Frisancho (e.g., Frisancho and Baker, 1970) showed, through comparison of age groups, a delayed adolescent growth spurt in high-altitude adolescents, illustrating another important example of the usage of time. Whether by cross-sectional comparison of different age groups or, better yet, longitudinal assessment, the inclusion of time provides an invaluable dimension for assessing the functional relationship between two (or more) parameters. Longitudinal studies, rather than cross-sectional ones, are especially valuable given the changes in environmental and cultural circumstances confronted by different cohorts in the rapidly developing regions where high-altitude and other such studies are being carried out. Pregnancy studies also use a time dimension and have the advantage of being able to be carried out over a relatively short, and hence more manageable time span. High-altitude studies have also been particularly useful in this regard. For example, the first demonstration that slowed fetal growth rather than shortened gestation, was responsible for population-scale reductions in birth weight was made at high altitude (Moore 2001b). Pregnancy studies were a part of the projects in Peru carried out by one of Paul Baker’s students, Jean McClung (McClung 1969) but have been a particular focus of our group in Colorado and now Wake Forest University. An advantage for our Colorado studies was that we were only 100 miles from high-altitude communities and hence could readily carry out longitudinal studies to address whether and if maternal characteristics of oxygen transport were responsible for the birth-weight reductions observed (Moore 1990; Moore, et al. 1982b).

A sixth and final important consideration pertaining to the advancement of study design was the availability of sophisticated equipment for monitoring physiological function non-invasively. Among such advances were the availability of pulse oximeters for measuring arterial O_2 saturation, transcutaneous bilirubin monitors, Doppler ultrasound instruments for assessing vessel diameter and flow velocity and in turn estimating blood flow, and the recent advent of gene chip methods for quantifying genetic variation on a scale that could not have been imagined as recently as a few years ago.

POPULATION COMPARISONS OF MATERNAL/FETAL ADAPTATION TO HIGH ALTITUDE

High-altitude environments are advantageous for addressing the question of evolutionary adaptation not only because of the pervasive nature of hypoxia but also due to the variation present among world populations in the generational duration of high-altitude habitation. Research efforts focusing on human adaptation to high altitude have been concentrated in the Andes and the Himalayas due primarily to the antiquity and relative isolation of human settlements in these regions, as well as the recent migration of lowland populations to the Andean or Tibetan Plateaus. In southern Peru and northern Bolivia extensive exploitation of major highland obsidian deposits and dental morphology suggest that humans moved from the coastline of Peru into the Andean Plateau approximately 10,000 years ago (Burger, et al. 2000; Piperno and Dillehay 2008). Today, nearly seven million persons reside on the *Altiplano*, where some communities can be found up to 5000m (Aldenderfer 2003),(West 2002). Likewise, archaeological artifacts indicate that hominids lived along the fringes of the Tibetan Plateau at least 2 million years ago (Brown 1999; Dennell, et al. 1988; Etler 1996), visited the Plateau’s higher steppes 25,000 – 50,000 years ago (Sensui 1981; Zhimin 1982) and lived, at least temporarily, on the Plateau 18,000 - 20,000 years ago (Aldenderfer and Zhang 2004; Huang 1994; Zhang and Li 2002). Clearly, the duration of human residence in the Andean and Himalayan highlands is extensive and therefore likely sufficient for natural selection to have occurred in response to the pressures exerted by the high-altitude environment. The largely European-derived inhabitants of the high-altitude regions of Colorado and Utah, the European or other nationalities that settled in the Andean Plateau of South America, and the Han (“Chinese”) populations immigrating recently to the Tibetan Plateau of western China provide a natural group for comparison with high-altitude derived populations.

As mentioned above, we consider that pregnancy and the prenatal period should be particularly sensitive periods for examining selective advantage given that the reproductive fitness of three individuals may be diminished as a result of an unsuccessful pregnancy. For this reason, numerous comparative studies of maternal physiology during pregnancy and/or perinatal health outcome between migrant and native high-altitude populations have been used to illustrate human adaptation to high altitudes. Moreover, the potent effect of high-altitude on birth weight and perinatal health outcome provides an easily identifiable phenotype that presumably decreases reproductive success.

Residence at high altitude exerts one of the most powerful effects on fetal growth, reducing birth weight more than 100 g per 1000 m elevation gain as a result of slowed fetal growth rather than shortened gestation (Jensen and Moore 1997; Krampl, et al. 2000; Lichty, et al. 1957; Unger, et al. 1988). As a result, gestation at high altitude increases the number of infants born small-for-gestational age (SGA) three-fold (Julian, et al. 2007). The effect of altitude to reduce birth weight is apparent in all high-altitude populations that have been studied to date, however infants born to women of highland origin are less affected than those born to women of lowland origin (Julian, et al. 2007; Vargas, et al. 2007; Zamudio, et al. 2007). For example, at altitudes ranging between 3600 – 4100 m in Bolivia Andean infants weigh ~ 300g more than Europeans at birth and are born SGA one-third as often, whereas there is no birth weight difference between ancestry groups at 400 m (Julian, et al. 2007). After accounting for the birth-weight influences of maternal hypertensive complications of pregnancy, parity, maternal body weight and the number of prenatal visits, European relative to Andean ancestry increased the risk of being born SGA at high altitude nearly five-fold (Julian, et al. 2007).

Tibetans, a geographically and genetically distinct high-altitude population, are also protected from reduced birth weight with altitude. Tibetans weighed more than Han newborns in Lhasa, Tibet, (Moore 2001a) and experienced only one-third the altitude-associated reduction in birth weight compared with Han (“Chinese”) infants living across the same 2700–4800 m altitude gradient in the Tibetan Autonomous Region of southwestern China (Moore, et al. 2004). Similar results have been reported by Tripathy et al. who found that Tibetan infants born at high altitude (Leh, India; 3521 m) weighed more than populations of low-altitude origin, but nearly 300 g less than at lower altitudes (Bylakuppe; 800m or Chandragiri, India; 970m). As a result, Tibetans were less often of low birth weight (< 2500 g) at both low and high altitude compared with other groups (Tripathy and Gupta 2005). Likewise Yangzom et al. reported that Tibetan infants weighed more and were less often SGA than non-Tibetan (i.e. Han [Chinese] or Hui [Muslim]) infants born in Lhasa (Yangzom, et al. 2008).

It is important to acknowledge that while factors commonly associated with low birth weight (e.g., poor nutrition, low socioeconomic status, primiparity, short maternal stature or limited health care access) likely contribute to birth-weight variation within each population, they do not appear responsible for these ancestry-related differences in fetal growth at high altitude. In fact, differences in such maternal body size or socioeconomic factors likely operate to minimize, not exaggerate, birth-weight differences among these groups. In other words, short maternal stature, poor nutritional status, and limited health care availability are more characteristic of the indigenous compared with the newcomer populations in the higher-altitude regions of Bolivia or Tibet and thus, Andean and Tibetan infants would be expected to weigh *less*, not more, than their European or Han counterparts (Julian, et al. 2007; Vargas, et al. 2007; Wilson, et al. 2007),(Larrea and Freire 2002; Pimental and García 1995),(Moore, et al. 2001b). However the data, as summarized above, suggest the opposite. In fact when ancestry-group differences in maternal body size or socioeconomic factors variables are taken into account using multiple regression analysis, the birth-weight differences between European and Andean groups enlarges (Haas 1981; Julian, et al. 2007). Moreover, the protection of birth weight at high altitude is intermediate in infants born to women of mixed European-Andean ancestry and demonstrates a dose-dependent relationship with ancestry such that women with greater Amerindian ancestry deliver infants of greater birth weight at high altitude. This is true whether ancestry was assessed via surnames or gene markers (Bennett, et al. 2008; Julian, et al. 2008b; Julian, et al. 2007; Wilson, et al. 2007; Zamudio, et al. 2007).

That the Andean and Tibetan populations demonstrate protection from altitude-associated reductions in fetal growth even after other factors influencing birth weight are taken into account as well as the “dose-dependent” nature of this protective effect suggests that genetic factors are likely involved. Additional support for genetic involvement comes from the observation that developmental factors are not able to account for altitude-associated variation in fetal growth at high altitude. Our studies in Colorado and our as well as Jere Haas’ observations in Bolivia demonstrate that birth-weight reductions are similar among infants born to European newcomers as those born to women of European ancestry who were born and raised at high altitude of 1-2 generations' high-altitude residence (Moore, et al. 1982a; Moore, et al. 2001a; Weinstein and Haas 1977; Hageman, personal communication).

In order for high altitude to be considered a selective pressure, it must be clearly associated with lower reproductive fitness as evidenced by greater infant mortality rates and/or morbidity, and not only a reduction in birth weight. Historical accounts at the time of Spanish movement into South America during the 16th century illustrate the potent challenge that high altitude posed to reproductive success. Father Cobo, a 16th century missionary, noted that in Jauja, Peru (3400 m) the indigenous high-altitude populations were "…healthiest and where they [reproduce] the most prolifically is in these same cold air-tempers, which is quite the reverse of what happens to the children of the Spaniards, most of whom when born in such regions do not survive" (Cobo 1897). Scientific inquiries conducted within the last 60 years reveal similar, albeit less dramatic findings. In Colorado, neonatal mortality rates were nearly twice as high (≥2740 m) relative to lower altitudes (<2130 m) during the 1960s and 1970s (McCullough, et al. 1977) (Table 1). Suggesting that low birth weight is not advantageous at high altitude, infants of low birth weight born above 2730 m had higher mortality rates relative to infants of normal birth weight (McCullough, et al. 1977). In Peru Mazess demonstrated that the neonatal mortality rate was nearly two-fold greater for infants born at high (Nuñoa, 3030 m) relative to low altitude (338 m) (Mazess 1965) (Table 1). In contrast, Beall found that low birth-weight infants born at 3860 m (Puño, Peru) had lower infant mortality rates than low birth-weight infants born at 600 m (Tacna) (Beall 1981). However, infant mortality was lower at high than low altitude across all birth weights, not just in the low birth-weight group, suggesting that some factor such as access to health care was likely responsible. In Bolivia, intrauterine and infant mortality increases with altitude (Giussani 2002; Keyes, et al. 2003); altitude increased infant mortality in both rural and urban areas, although rates were higher in the former. Likewise, available data indicate that neonatal mortality is higher in highland compared with lowland Himalayan regions. Neonatal mortality rates were reported to be 144 or 42.1/1000 live births in Ladakh, India (3500m) or Lhasa, Tibet (3658m), respectively; these figures are more than double the rate seen in lower-altitude areas of China (Wiley 1994; Yangzom, et al. 2008) (Table 1). As judged by maternal reproductive history, Tibetan infants also had lower pre and postnatal mortality than did Han infants in remote regions of Tibet where health care is equally limited for both ethnic groups (Moore, et al. 1998). Other studies in the more urban setting of Lhasa have found equivalent infant mortality rates between Tibetan and non-Tibetan babies (Yangzom, et al. 2008).

The interpretation of these mortality data is complicated by the fact that, outside of Colorado, all studies examining the effect of high altitude on infant mortality have been conducted in developing countries where access to health care and the quality of health care are often limited. In addition, the lack of comprehensive vital statistics means that births and infant deaths occurring outside of a hospital setting are likely not recorded and the contribution of factors such as prematurity, maternal complications of pregnancy or neonatal complications cannot be assessed. The effect of high altitude on infant mortality in areas such as Colorado may also be obscured by recent improvements in access to health care in the higher-altitude regions. For these reasons, it is difficult to assess the impact of reduced birth weight on reproductive fitness at high altitude. Given the clear elevation in mortality risk accompanying reduced birth weight or intrauterine growth restriction at low altitudes (Bartels, et al. 2005; Gilbert 2003) and the absence of any convincing evidence that this is not the case at high altitude, we consider it likely that reduced birth weight at high altitude diminishes reproductive fitness.

Concerning morbidity, infants born at high altitude have lower arterial oxygen saturations (SaO_2) and higher pulmonary artery pressure (Ppa) relative to their low-altitude counterparts. As was the case with birth weight, the effect of altitude to reduce SaO_2 and increase Ppa is diminished in infants of native high-altitude ancestry. In Lhasa, SaO_2 in the first two days of life was higher in Tibetans (90-94%) than in Han (90-94% vs. 86-92%) and while SaO_2 stabilized in Tibetans shortly after delivery, in Han infants the decline persisted over the 1st four months of life (Niermeyer 2003). Yangzom et al. also reported that non-Tibetan infants were more often cyanotic at birth and required post-delivery oxygen supplementation at high altitudes (Yangzom, et al. 2008). Along similar lines, the two- to three-fold increase in intrauterine growth restriction at high altitudes in Bolivia is accompanied by an increased risk of respiratory disorders in neonatal life (Keyes, et al. 2003). Reduced SaO_2 and higher Ppa (Niermeyer, et al. 1993) increase disease severity and mortality in neonatal and childhood acute respiratory infection, highlighting the likelihood that genetic characteristics associated with a higher incidence of these phenotypic attributes should be subject to intense selective pressure.

Maternal physiological studies conducted over the past 25 years have revealed that likely candidates for the protection of fetal growth afforded by high-altitude ancestry include factors that influence the availability of oxygen and/or other nutrients to the fetus including maternal arterial oxygenation (e.g., ventilation, SaO_2, hemoglobin concentration), uteroplacental blood flow, nutrient availability, placental transport and/or feto-placental nutrient uptake. Our studies indicate that maternal arterial oxygenation probably is not the factor responsible for Andeans' or Tibetans' relative protection from hypoxia-associated reductions in birth weight. Specifically, ventilatory sensitivity to hypoxia, resting ventilation, SaO_2, total blood volume and plasma volume increased with pregnancy to a similar extent in Andean and European women residing at high altitude in Bolivia (Vargas, et al. 2007). The pregnancy-related increase in ventilation raised SaO_2 and effectively offset the hemodilutional effect of plasma volume expansion such that arterial O_2 content (CaO_2) remained close to non-pregnant levels in both groups. Similarly, in Lhasa (3658 m) hypoxic ventilatory response and resting ventilations were equivalent between Tibetans and Han during pregnancy and in the non-pregnant state, and CaO_2 was lower, not higher, during pregnancy in the Tibetan compared to the Han women likely as the result of greater plasma volume expansion (Moore, et al. 2001b).

Because uteroplacental blood flow is the primary factor responsible for increasing oxygen delivery to the uteroplacental circulation, we have extensively investigated the relationship between ancestry, variations in uteroplacental blood flow and reduced fetal growth at high altitudes (Julian, et al. 2008a; Julian, et al. 2008b; Moore, et al. 1982b; Wilson, et al. 2007; Zamudio, et al. 1995). In general, these investigations overwhelmingly support the hypothesis that greater uterine artery blood flow contributes to the protective effect of high-altitude ancestry on fetal growth. In particular, our recent studies of uterine artery blood flow during pregnancy at high (3600-4100 m) altitude in Bolivia have revealed that Andeans have profoundly different uterine vascular adjustments to pregnancy relative to Europeans (Wilson, et al. 2007). Uterine artery (UA) blood flow and O_2 delivery were 1.6-fold greater in Andean than European women as the result of greater lower body blood flow in general and a larger pregnancy-associated increase in UA diameter and UA blood flow in particular (Wilson, et al. 2007). Further, these higher levels of UA blood flow were entirely responsible for raising UA oxygen delivery and were related to the heavier birth weights seen in the Andeans vs. Europeans. A recent cross-sectional study also demonstrated that Andeans had greater UA diameters late in pregnancy relative to Europeans residing at high (3600m; La Paz, Bolivia) but also at low altitude (400m; Santa Cruz, Bolivia) (Zamudio, et al. 2007). These observations agreed with our previous observations in Tibet, showing that Tibetans had greater UA blood flow velocity and a larger redistribution of lower extremity flow to favor the UA than Han (“Chinese”) women in the third trimester of pregnancy at high altitude (Moore, et al. 2001b). While these studies support the important role played by Andean and Tibetan populations’ ability to maintain higher levels of UA blood flow during pregnancy at high altitude, it is not clear whether the higher levels of UA blood flow and oxygen delivery in multigenerational vs. shorter-term residents of high altitude *per se* are responsible for conferring protection from altitude-associated reductions in fetal growth, whether such protection is due to greater delivery of other nutrients such as glucose, or whether increased delivery of oxygen, glucose as well as other nutrients are responsible.

Several factors support an evolutionary explanation for the protection of fetal growth in Andeans and Tibetans at high altitude. First, as reviewed above, both populations have resided at high altitudes for a sufficient duration of time for natural selection to have occurred. Secondly, the protection of fetal growth at high altitude is not due to other factors known to influence fetal growth (e.g., socioeconomic or nutritional status, maternal stature or income) and thus, is likely due to inherent biological variation(s) between ancestry groups. Moreover, neither being born and raised at high altitude nor relatively short generational duration of high-altitude residence (e.g., 1-2 generations) are sufficient for such protection of fetal growth, giving credence to the likelihood that genetic rather than developmental mechanisms are involved. Finally, reductions in fetal growth increase infant morbidity and mortality, and thus genotypes protecting fetal growth in the face of hypoxia presumably would be strongly selected for over generations of high-altitude residence. Given that the relative “advantage” of Andean ancestry for fetal growth is apparent exclusively at high altitude, we suggest that the Andean-specific phenotype is reliant on some combination of genetic and environmental factors or, in other words, that maternal genotype modifies the effect of an environmental attribute (chronic hypoxia) on a particular phenotype, namely birth weight. Other examples of such gene by environment interaction include reports that maternal genotype influences the reduction in birth weight due to passive smoke exposure during pregnancy (Wu, et al. 2007). Possible targets for investigation into the genetic factors involved include variations in genes involved in implantation, angiogenic, inflammatory or vasoactive processes, the expression of antioxidant enzymes or other factors influencing the pregnancy-associated rise in UA blood flow, placental transporters or other factors influencing fetal nutrient uptake. Differences in birth weight between ancestry groups may also arise from epigenetic modification, consisting of mitotically and transgenerationally heritable changes in gene expression that are not the result of altered DNA sequence (Anway, et al. 2005; Rakyan, et al. 2002; Rakyan, et al. 2003). Thus changes that result from exposure to endogenous or exogenous factors such as hypoxia during such as gestation and neonatal life may be manifested in future generations. Our recent data -- demonstrating that parent-of-origin influences the effect of high altitude on birth weight (Bennett, et al. 2008) -- suggests that epigenetic factors or other extracellular signals modifying gene expression may indeed be involved. Similar to constitutional genetic variation, epigenetic modifications can convey the effects of environmental exposure across generations.

In summary, we consider that the challenge of demonstrating whether or not humans have adapted genetically to high altitude has been met. Differences in maternal physiological characteristics clearly exist between migrant and native high-altitude populations, such physiological characteristics are influenced by genetic origin, and these physiological as well as genetic attributes in turn influence reproductive fitness. The new challenge is to determine how such differences in physiological response to pregnancy arise, what specific genes are involved, and how such physiological and genetic factors interact to influence evolutionary process.

NEW GENETIC APPROACHES FOR STUDYING ADAPTATION

Until recently, methods to study the effect of genotype on phenotype and to identify signatures of natural selection in humans were limited. Easily measurable phenotypes were limited, and genotyping methods laborious and expensive. Our ability to assess phenotypes has improved, as described above. Now, with the advent of high-throughput array technology, genomic markers can be measured in high density across the entire human genome. This technology, coupled with rapidly developing statistical methods, increases our ability to 1) find the genetic basis of complex phenotypes and 2) infer the effect of natural selection on gene regions.

Study designs to investigate genetic adaptation to high altitude prior to the advent of high throughput genotyping required assumptions and subsequent estimation of genetic ancestry. Assumptions of genetic ancestry were largely made using geographically isolated high-altitude residents in early studies of ecological design. Studies using a migrant design relied on ancestry estimation through surname analysis (Chakraborty, et al. 1989) or assessment of skin reflectance (Frisancho, et al. 1995), both of which are problematic as proxy measures for genetic ancestry (Brutsaert, et al. 2004). In the cases where ancestry assumption was appropriate, genetic contributions to phenotype were analyzed for simple Mendelian traits through pedigree analysis or heritability estimations. Admixture studies are similar to migrant studies in the estimation of ancestry through individual surnames or skin pigmentation. With the development of high-throughput dense genotyping tools both the problems of the non-Mendelian complexity of many phenotypes and ancestry estimation have been addressed, as well as opened up the possibility of finding evidence of natural selection within the genome.

Methods for gene identification and localization (mapping) of factors contributing to complex phenotypes typically utilize the link between phenotypic variation among individuals with genetic markers. Linkage disequilibrium (LD or the greater than expected occurrence of a genotypic marker with a phenotypic trait) resulting from three possible sources is generally used in genetic analyses. The first source, background LD, refers to the tendency of two loci to be inherited together because of their close physical proximity in the genome (i.e., hitchhiking) (Montana 2004). Such LD is sought in association studies to find markers linked to a phenotype either due to the marker's direct genetic effect on the phenotype or through marker's linkage to the phenotype-affecting gene (Guo and Lange 2000). A second source of LD, mixture LD, refers to the fact that the genome of an individual will reflect a small part of the population gene pool from which it came (Falush 2003). Mixture LD is often utilized in the assessment of individual ancestry (Pritchard, et al. 2000) as it can help to estimate an individual's genetic ancestry or control for population structure, but is not generally informative for gene mapping because it describes markers across the entire genome. Ancestry informative markers (AIMs) or loci that show population-specific allele frequencies can then be used to confirm or question individual-assessed genetic ancestry (Shriver, et al. 2003). A final source of LD, admixture LD, occurs when there are segments of DNA with marker alleles recognizable as having been inherited from a certain ancestral population (Falush 2003). In population mapping, one looks for an association between ancestry-specific markers and the phenotypic trait of interest. It is expected that the trait should most often be found together with markers specific to the ancestral population in which the trait has the highest incidence (Hoggart, et al. 2004). Population mapping can take advantage of admixture LD to map phenotypic traits through utilizing either transmission disequilibrium tests (TDT) (Lee and Yen 2003; McKeigue 1997; Zheng and Elston 1999) or gametic disequilibrium (McKeigue 1998). While TDT approaches require studies of parents and offspring, gametic disequilibrium studies can be done on phenotype-affected individuals as long as they are well-admixed (preferably between 30 to 60%) (McKeigue 1998). Admixture mapping requires the suitable selection of populations to approximate ancestral source populations, optimally from more than one continent or distinctly different and isolated geographical areas.

High throughput genotyping technologies have also enabled the search for genes that show evidence of natural selection. As described above, natural selection acts upon individuals based on their adaptive phenotypes. Although natural selection does not act directly upon genes, it affects the frequencies of alleles in a population. Cavalli-Sforza (1966) originally suggested that natural selection may be demonstrated by investigating patterns of population variance and allele frequency (Cavalli-Sforza 1966). Lewontin and Krakauer (1973) refined this idea, by emphasizing that natural selection via the preservation of specific advantageous alleles, differs from other causes of allelic frequency change in populations (mutation, gene flow, and drift) because only natural selection is directional (Lewontin and Krakauer 1973).

Currently, several tests for evidence of natural selection at the genomic level have been developed. The neutral theory of molecular evolution posits that most mutations are selectively neutral (e.g., synonymous mutations, mutations in noncoding regions) and thus can be used to predict the null hypothesis (Nielsen 2001). Such tests for neutrality take into consideration the allelic distribution and levels of population variability as suggested by Cavalli-Sforza (1966) and include the Wright statistic or F_{st} (Wright 1950), LSBL (Shriver, et al. 2003), lnRH (Schlotterer, et al. 2004), Tajima's D (Tajima 1989), Fu and Li's D and F (Fu and Li 1993), and Fay and Wu's H (Fay and Wu 2000).

A combination of these tests can best estimate gene regions that show evidence of natural selection. Once potential, naturally selected gene regions have been identified, the association of genotypes within these regions with adaptive phenotypes can be examined. Thus, genotypic and environmental effects on phenotype can be separately examined, and identification and subsequent testing of gene regions that show evidence of natural selection can help tease out the adaptive value of birth weight at high altitude.

SUMMARY AND CONCLUSIONS

Research efforts over the past 50 years have clearly demonstrated that differences in birth weight and pregnancy outcome exist between populations at high altitude, and that multigenerational high-altitude ancestry exerts a strong, protective influence. Moreover, a vast number of physiological studies demonstrate that increased uterine artery blood flow is a plausible mechanism by which high-altitude ancestry protects fetal growth. Although several factors confound our ability to determine whether it truly reduces reproductive fitness and hence is a maladaptive response at high altitude, it is clear that reduced birth weight impairs reproductive success at low altitude and, in general, both neonatal mortality and morbidity are worse for lower than normal birth-weight babies at high altitude and worse in comparison with low altitude. Since natural selection ultimately acts via systematic variations in reproductive fitness, we consider that the differences in birth weight, neonatal morbidity and mortality observed between migrant and native high altitude populations strongly support the concept that protected fetal growth at high altitude is the result of genetic adaptation. Additional studies and new approaches to the question as to whether reduced fetal size is being selected against or for at high altitude are needed as well as the application of new genomic technologies for identifying the gene regions involved are greatly needed.

Comparative physiological studies have enabled us to identify not only phenotypic differences between populations but also to elucidate the mechanisms by which the phenotypic variation arises and to highlight possible gene candidates for future investigation. Only in recent years has it become possible to examine genetic variation and individual ancestry with high resolution, to identify specific gene regions that are likely to have been acted upon by natural selection, or to begin to address the genetic components of complex phenotypes. As such, our current and future studies are designed to combine the strengths of comparative physiological studies during pregnancy and during the perinatal period with emerging genetic technologies in order to determine the genes involved in protecting long-resident groups from altitude-associated reductions in fetal growth and, in turn, the processes underlying human genetic adaptation to high altitude.

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Table 1

Effect of high altitude on neonatal or infant mortality

	Lower altitudes		**Higher altitudes**	
	Altitude	**Mortality rate**	**Altitude**	**Mortality rate**
North America, Rocky Mountains				
Lichty, et al. (1957)	1600	23.4 [2]	3100	41.6 [1,2]
McCullough, et al. (1977)	<2130	11.9 [2]	>2740	18.5 [1,2]
Unger, et al. (1988)	<2130	6.0 [2]	>2740	6.5 [2]
South America, Andes				
Mazess (1965)	338	28.6 [2]	3030	52.8 [1,2]
Haas, et al. (1980)	400	10.6 [3]	3600	9.3 [3]
Asia, Himalayas				
Wiley (1994)	---	---	3600	144 [3]
Yangzom, et al. (2008)				
Non-Tibetan	---	---	3658	46 [3]
Tibetan	---	---	3658	30 [3]
Moore, et al (2001a)				
Han	<3000	415*	3000-4000	207*
Tibetan	<3000	43*	3000-4000	123*

Adapted from Moore, et al (2001a)

[1] difference in mortality between altitudes <0.05

[2] neonatal mortality rate; death within 28 days after birth per 1,000 live births

[3] infant mortality rate; death within the first year after birth per 1,000 live births

* post-natal mortality rate; duration of time after delivery unavailable