



Contents lists available at ScienceDirect

Quaternary International

journal homepage: www.elsevier.com/locate/quaint

Human genetic adaptation to high altitudes: Current status and future prospects

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
AMPK
Evolution
Fetal growth
HIF
Pregnancy

ABSTRACT

The question of whether human populations have adapted genetically to high altitude has been of interest since studies began there in the early 1900s. Initially there was debate as to whether genetic adaptation to high altitude has taken place based, in part, on disciplinary orientation and the sources of evidence being considered. Studies centered on short-term responses, termed acclimatization, and the developmental changes occurring across lifetimes. A paradigm shift occurred with the advent of single nucleotide polymorphism (SNP) technologies and statistical methods for detecting evidence of natural selection, resulting in an exponential rise in the number of publications reporting genetic adaptation. Reviewed here are the various kinds of evidence by which adaptation to high altitude has been assessed and which have led to widespread acceptance of the idea that genetic adaptation to high altitude has occurred. While methodological and other challenges remain for determining the specific gene or genes involved and the physiological mechanisms by which they are exerting their effects, considerable progress has been realized as shown by recent studies in Tibetans, Andeans and Ethiopians. Further advances are anticipated with the advent of new statistical methods, whole-genome sequencing and other molecular techniques for finer-scale genetic mapping, and greater intradisciplinary and interdisciplinary collaboration to identify the functional consequences of the genes or gene regions implicated and the time scales involved.

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1. Has genetic adaptation to high altitude occurred?

There has been a longstanding debate as to whether genetic adaptation to high altitude has occurred. Joseph Barcroft (1872–1947), an early leader in high-altitude physiology (see, for example (Physiol, 2016)), was of the opinion that it had not taken place. He stated “The acclimatised man is not the man who has attained to bodily and mental powers as great in Cerro de Pasco [Peru, elev 4300 m] as he would have in Cambridge (whether that town be situated in Massachusetts or in England). Such a man does not exist. All dwellers of high altitudes are persons of impaired physical and mental powers” (Barcroft, 1925). This view was contested by another pioneer, Carlos Monge M (1884–1970), who stated “Biologically we have shown that the Andean carries in his organism the hereditary and ancestral soma which permits life at the very great altitudes that mark certain large inhabited areas of

South America” (Monge-M, 1948). The debate continues (Kayser, 2013a,b; Léon-Velarde and Villafuerte, 2013a,b), with arguments stemming from differences in disciplinary orientation and the sources of evidence being considered.

Disciplinary orientation influences the way in which the term *adaptation* has been interpreted. Physiologists generally use the term to refer to any physiological response regardless of whether the response is likely to be beneficial or otherwise affect the chance(s) of being able to live or reproduce, *i.e.*, reproductive success, whereas evolutionary biologists or geneticists restrict its usage to those responses likely to influence reproductive success. Barcroft followed the first usage by, for example, referring to the physiological characteristics of both high-altitude newcomers and natives without recognizing that some of the newcomers might have been suffering from the usually non-life threatening, but nonetheless discomfiting, symptoms of acute mountain sickness (West, 2016). Persons using *adaptation* in an evolutionary context employ it in the latter sense; for example, the evolutionary biologist Theodosius Dobzhansky defined it as “any feature of structure, function or behavior that enables the organism to live and reproduce in a given environment” (Dobzhansky, 1968). Usage here is confined to this latter sense.

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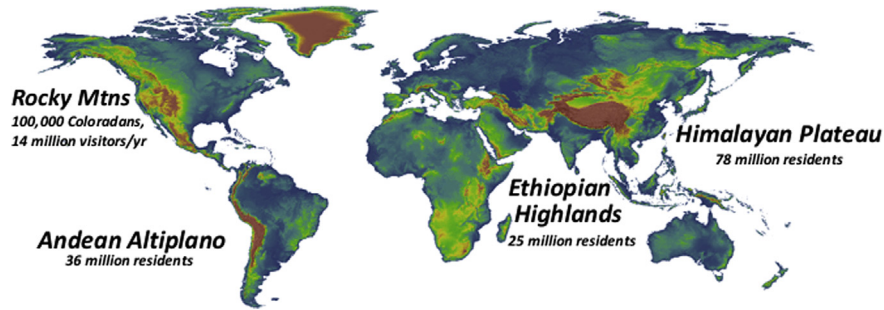


Fig. 1. High-altitude (>2500 m or 8250 ft) regions of the world where human populations permanently reside and approximate numbers of residents (Moore et al., 1998b; Jarvis et al., 2008).

There are at least five sources of evidence by which adaptation to high altitude may be assessed. One is simply the presence of populations that have long resided at high altitude, conventionally defined as > 2500 m (8250 ft) as that is the altitude at which arterial O_2 saturation begins to fall. Of the four major high-altitude regions of the world (Fig. 1), Native Americans resided seasonally at high altitude for millennia but permanent populations, largely of European origin, only for the past 150 years and hence not the longer time horizons required for genetic adaptation.² Of note, there are no permanently inhabited communities at altitudes >2500 m in Europe. Archeological evidence for human occupation on the Andean Altiplano extends back as far as ~14,000 years (Rademaker et al., 2014), ~30,000 years on the Himalayan Plateau (Malassé and Gaillard, 2011; Jeong et al., 2014), and from 500 to ~70,000 years in the Ethiopian Highlands (Huerta-Sanchez et al., 2013), although the permanence of such residence continues to be debated (Capriles and Albarracín-Jordan, 2013; Rademaker et al., 2016) and year-round residence was probably not possible until plant and animal domestication was complete (Aldenderfer, 1999; Prates et al., 2013; Dong et al., 2016). However, while the presence of populations at high altitude is useful (Beall, 2007), the information provided is limited since residence alone cannot distinguish between degrees of adaptation nor can it provide information about the specific genes or physiological mechanisms involved.

A second source of evidence is the physiological response(s) being considered. Since O_2 is relatively insoluble, in vertebrates it must be actively transported via the O_2 transport system (Fig. 2). Therefore, physiological responses to the reduced O_2 availability or hypoxia present at high altitude can be directly measured as the change in each O_2 transport component. Studies by pioneering high-altitude physiologists such as Bruce Dill, Jack Reeves, Bob Grover and others focused on exercise performance in young, healthy men (Dill et al., 1931; Reeves and Grover, 2001) for which a convenient measure is the maximum level of oxygen consumption (VO_2 max, i.e., that at which there is no further rise in VO_2 during an at least 30 s increase in workload). While VO_2 max has the advantage of being an overall measure of the operation of the O_2 transport system (Fig. 2), organisms seldom operate at maximal levels of exertion and therefore the relevance of VO_2 max for the ability to live and/or reproduce is unclear. Thus more functional measures are recommended. Among these are the altitude-associated reduction in birth

weight (Haas et al., 1980; Moore, 1990), increased frequency of preeclampsia (Moore et al., 1982; Palmer et al., 1999), increased infant mortality and morbidity (Wiley, 1994; Moore et al., 2001a; Beall et al., 2004), slowed childhood and adolescent growth (Frisancho, 1969; Beall et al., 1977; Greksa and Haas, 1982), elevated pulmonary artery pressure (Ppa) (Cruz-Jibaja et al., 1964; Banchemo et al., 1966; Groves et al., 1993; Hoit et al., 2011), or the prevalence of the maladaptive syndrome known as chronic mountain sickness (CMS) (Moore et al., 1998a; Léon-Velarde et al., 2005) as such conditions vary among highland populations and can interfere with the ability to live and/or reproduce in the high-altitude environment.

A third source of evidence is the time period over which the physiological response(s) to high altitude is (are) being assessed. Those responses that occur in newcomers within minutes to days or months, termed acclimatization (Fig. 3), include an almost immediate increase in ventilation (V_E) and contraction of plasma volume that serve to increase the partial pressure of O_2 in the arterial blood (pO_2) and hemoglobin (Hb) concentration respectively, and therefore help offset the fall in arterial SAO_2 saturation (SAO_2) and O_2 content due to the reduced partial pressure of O_2 in the inspired air. The plateau increase in V_E requires several days and

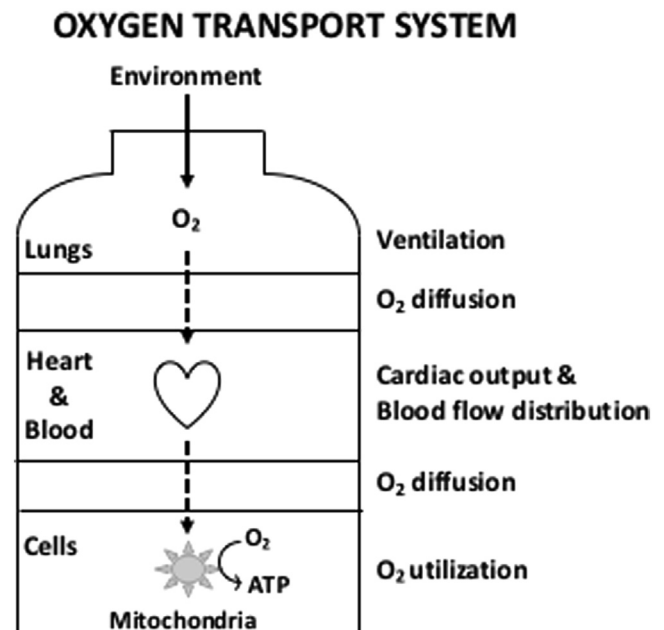


Fig. 2. The O_2 transport system is comprised of two pumps (the lungs and the heart) and two diffusion steps. The lungs bring in O_2 from the atmosphere and the heart pumps it via the blood throughout the organism. O_2 diffuses across the alveolar membrane to enter the blood where it is reversibly bound to hemoglobin, and then diffuses from the blood into cells where it is consumed in the mitochondria to generate chemical energy in the form of adenosine triphosphate (ATP).

² The question as to how much time is required for genetic adaptation depends on the numbers of genes involved and the strength of natural selection operating on the gene or genes in question. While its answer is outside the scope of this review, it is generally assumed that ~8–10,000 years of high-altitude residence is required based on the amount of time during which natural selection likely operated on other human biological traits such as hemoglobin S or lactase deficiency. Flint, J., Harding, R.M., Boyce, A.J., Clegg, J.B., 1998. The population genetics of the haemoglobinopathies. *Baillieres Clin Haematol* 11, 1–51.

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