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Current Opinion in Genetics & Development

Human adaptation to extreme environmental conditions

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Modern humans inhabit most of earth's harshest environments and display a wide array of lifestyles. Biological adaptations, in addition to technological innovations, have enabled these geographical and cultural explorations. The study of these adaptations helps not only to fundamentally understand our evolution as a species, but also may have increasing relevance as genomics transforms fields such as personalized medicine. Here we review three cultural and environmental shifts that have brought about adaptations in modern humans; the arctic, high altitudes, and a subsistence dependent on breath-hold diving.

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Introduction

As modern humans emerged a few hundred thousand years ago and spread inside and outside Africa, they encountered a number of new and challenging environments. Some of the most extreme environments in which you find humans today include hypoxic high altitudes, arid deserts, and the cold and barren environments of the arctic. Humans have conquered these environments largely through technological innovations including fire, clothing, dwellings, advances in hunting equipment and practices, and methods for food and water storage. However, there have likely also been accompanying biological adaptations, where humans have undergone genetic and physiological changes to survive the conditions of the environment. Such cases are not only intriguing from an anthropological perspective, but are also of interest as study systems for understanding human physiology and genetics. Compared to model organisms, the study of genetics in humans is challenged by the absence of experimentation on whole living organisms. However, cases where humans live in extreme environments provide an opportunity to understand the human physiological response to these conditions. Similarly, genetic adaptations (i.e. heritable phenotypic changes driven by natural selection) provide an opportunity to understand the genetic variation that underlies physiological differences among humans as well as the genetic components of importance for the response to changes in the environment. The last ten years have seen a number of studies using genetic analyses of populations adapted to extreme environments to identify causal genes or genetic variations affecting human physiology. In this review, we will discuss three examples of adaptation: to life in the arctic, to high altitude, and to a lifestyle based on diving.

Adaptation to life in the arctic

The arctic environment is perhaps one of the most inhospitable environments on earth. However, multiple different cultures have adapted to this environment, including Siberian peoples such as the Chukchi and the Evenks, Europeans such as the Sami, and Native North Americans, most famously the Inuit. Although there have been many hypotheses regarding human adaptation to the arctic environment, until recently there was very little work investigating any genetic basis of proposed phenotypic adaptations in arctic peoples. However, several recent studies have identified a number of variants that have been under selection as part of adaptation to diet or cold in the circumpolar region.

Clemente *et al.* [1] showed that *CPT1A*, a regulator of mitochondrial long-chain fatty-acid oxidation, has been under strong selection in Northeast Siberians. The selected allele is, in modern populations, associated with hypoketotic hypoglycemia and high infant mortality. However, Clemente *et al.* argue that it might have conferred a metabolic advantage for the Northeast Siberian populations in dealing with their traditional high-fat diet. A similar example of adaptation to high fat diet in arctic populations was provided by Fumagalli *et al.* [2]. They identified strong selection affecting Fatty Acid Desaturases (*FADS*) genes in Inuit from Greenland. These genes encode the rate-limiting enzymes in the synthesis of long-chain polyunsaturated fatty acids (PUFAs), including omega-3 fatty acids. The traditional diet of the Inuit is primarily based on fish and marine mammals and is, therefore, rich in long-chain omega-3 PUFAs. Perhaps as an evolutionary response to this, the adaptive mutations in the Inuit decrease the rate of

endogenous synthesis of the long chain PUFAs, resulting instead in a build-up of short chain PUFAs, which are ordinarily obtained from a vegetarian diet. The mutations in the FADS genes selected in the Inuit are presumably an adaptation to a high fat diet based on marine animals with strong downstream phenotypic effects, including major effects on height, weight, insulin, total cholesterol, and LDL cholesterol. The direction of the effects is consistent with a protective effect on cardiometabolic phenotypes, and can be quite substantial, including an observed change in weight of more than 4 kg in the homozygous state.

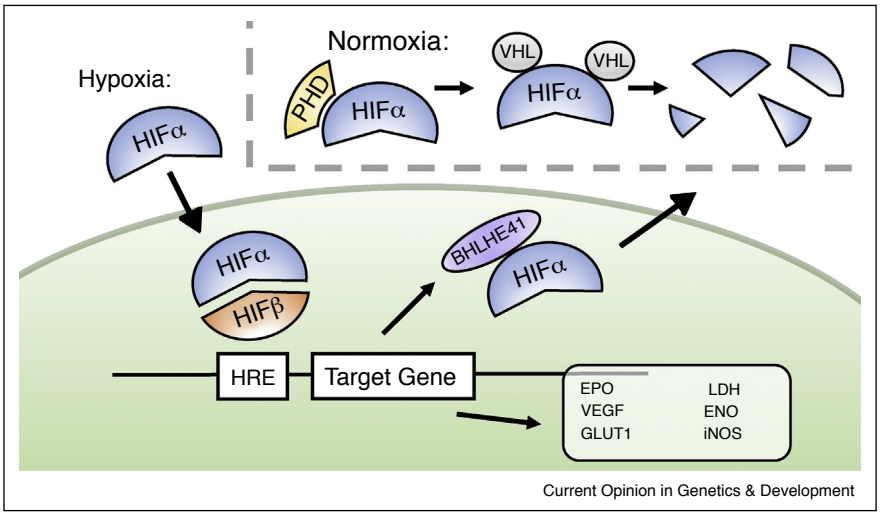
In addition to adaptations to dietary changes, recent research combining modern and ancient DNA suggests strong positive selection may have acted on an endogenous response to cold temperatures [3••]. Allele frequencies of a variant upstream of the gene *TRPM8,* which encodes a receptor involved in sensing and reacting to cold through physiological thermoregulation (reviewed in Ref. [4]), appear to increase along a latitudinal cline. Although the ancestral allele appears to be protective against migraines, the derived allele provides the benefit of diminishing physiological responses to cold temperatures.

High-altitude adaptation

There are at least three populations that have been proposed to have adapted to the hypoxic conditions of high altitude; the Amhara in Ethiopia, the Quechua and Aymara in the Andes, and Tibetans and other people in and around the Himalayas and the Tibetan plateau (reviewed in Ref. [5]).

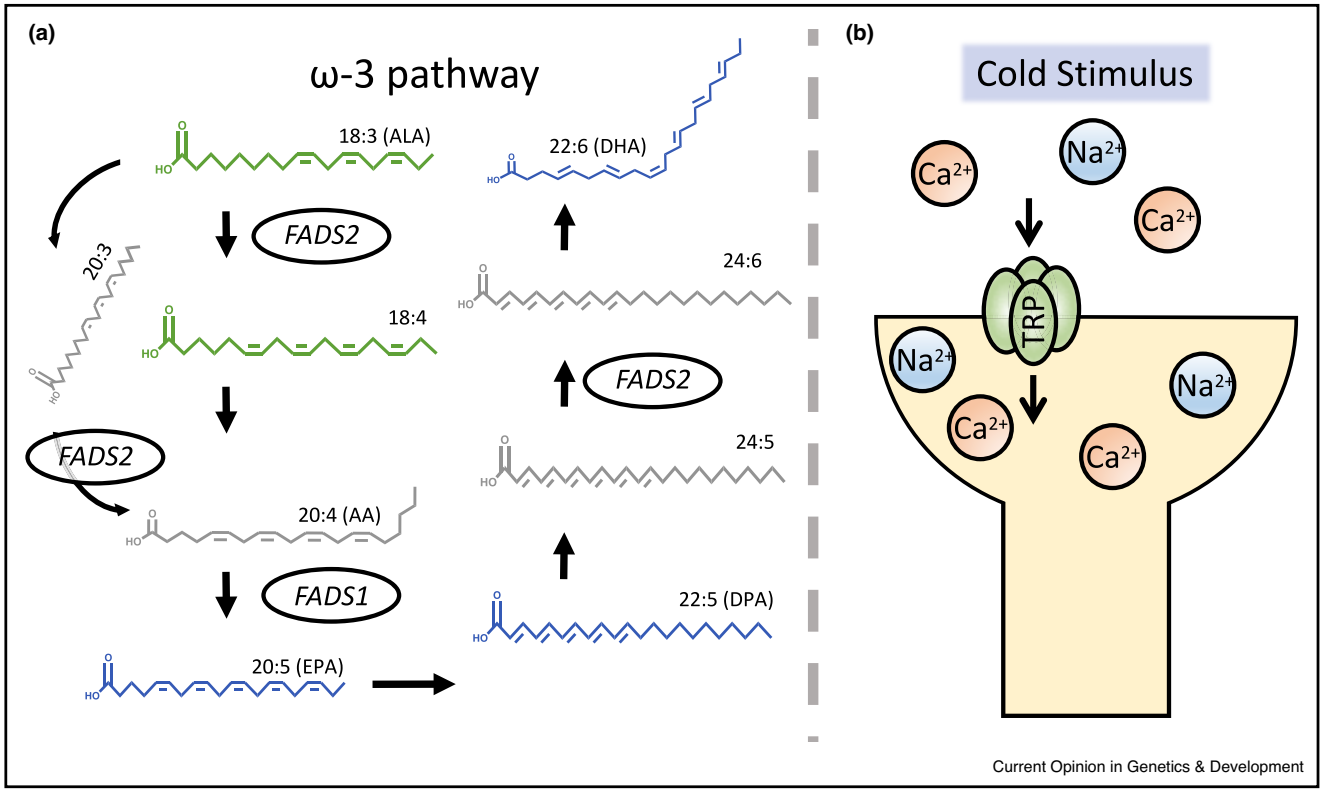
The human body undergoes a well-characterised response to the hypoxic conditions of high altitudes. Low levels of ambient oxygen, resulting from decreased barometric pressure, trigger a response organized by Hypoxia-inducible factors (HIFs). These HIFs induce increased production of erythropoietin (EPO), which promotes the production of red blood cells. The resulting phenotype, polycythemia, is measurable as a characteristically high hemoglobin concentration. The excess red cell mass provides the advantage of enhanced oxygen delivery to tissues, but also increases blood viscosity, thereby putting strain on the circulatory system and potentially complicating pregnancies. Nevertheless, elevated hemoglobin levels in response to high-altitude hypoxia initially appeared consistent across populations, including those with chronic exposure such as Andean highlanders [6]. Thus, it was surprising when it was first observed that Tibetans permanently residing above 3500 m had hemoglobin concentrations far lower than predicted [7], indicating an underlying adaptation that provided an alternative method for responding to hypoxia. Subsequent genomic investigations have revealed numerous signals of natural selection acting on different components of the HIF pathway in Tibetans, most notably *EPAS1* and *EGLN1* [8–11], both of which act early in the HIF signaling pathway. The combination of both genes appears to contribute to the blunted HIF signaling observed in Tibetans. Although a causative mutation may have been identified for *EGLN1* [12••], the causative

Figure 1



The hypoxia inducible factor (HIF) pathway. Under normoxic conditions, the HIFα subunits (including HIF-2α, encoded by *EPAS1*) are hydroxylated by prolyl hydroxylases (PHDs) including PHD2, encoded by *EGLN1*. They subsequently bind to von Hippel–Lindau (VHL) proteins and undergo poly ubiquitination and proteosomal degradation. Under hypxoic conditions, the HIFα subunit is stabilized and is translocated into the nucelus where it dimerizes with the HIFβ subunit along with other cofactors. The heterodimer then binds to hypoxia responsive elements (HREs), activating transcription of HIF target genes. One such gene is *BHLHE41* which, in addition to repressing cell proliferation, also presents the HIFα subunit to a proteasome complex for degradation, thus creating a negative feedback loop.

Figure 2



(a) The Omega 3 pathway. Arrows represent synthesis steps. Molecule colors indicate the dietary source of a given fatty acid: Green is plant based, blue is from marine sources, and grey are intermediates. When indicated, members of the fatty acid desaturase (FADS) family play a role in synthesis steps. **(b)** In response to cold temperatures, transient receptor protein (TRP) cation channels, including *TRPM8*, are activated in dorsal root ganglia (DRG) sensory neurons that innervate the skin.

mutations in *EPAS1* have not yet been identified. Identification of these mutations has been complicated by the fact that there are multiple mutations in perfect linkage disequilibrium because the causative haplotype was introgressed from Denisovans, an archaic human species, into the ancestors of Tibetans [13] (Figure 1).

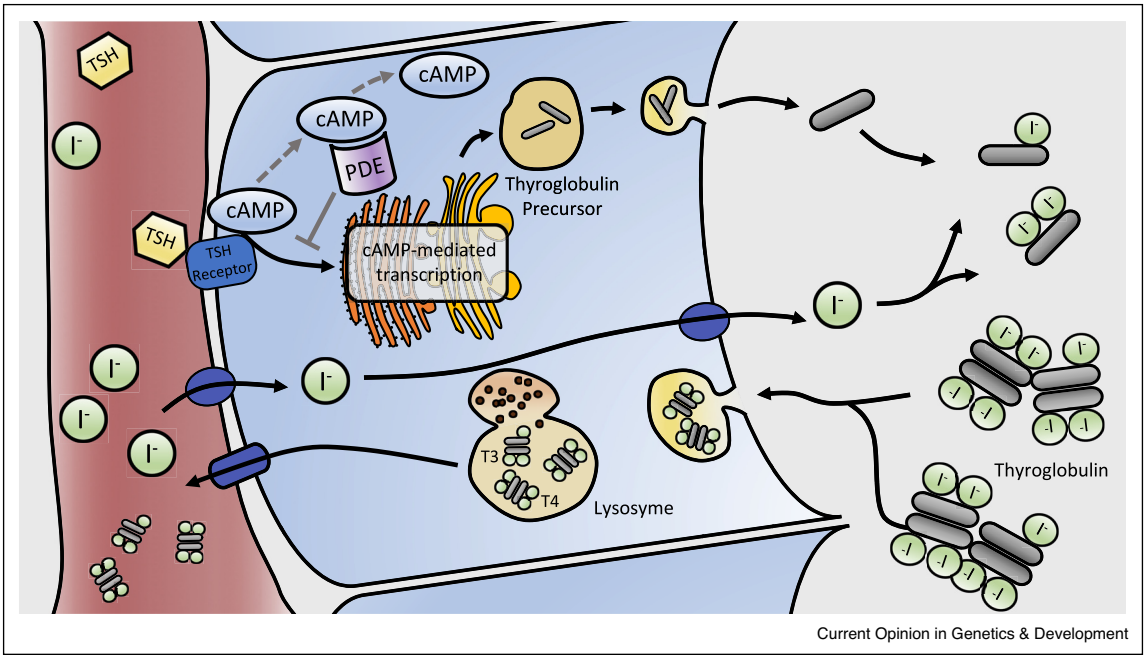
Our understanding of genetic variants in the two other high-altitude adapted populations is somewhat more limited. Ethiopian Amhara appear to have a blunted HIF response similar to the Tibetans [14–16], which may be caused by selection in the gene *BHLHE41*, an upstream regulator of HIF signaling that was the strongest candidate for selection in another study [17]. However, other studies have found other candidates for selection in Ethiopians [14,18], and the genetics of adaptation to high altitude in Ethiopians is generally much less well-understood than that of Tibetans.

High altitude adapted populations in the Andes do not display the same type of blunted HIF signaling as observed in Tibetans and Ethiopians [19,20]. Although several studies have analysed possible candidate genes related to HIF signaling [10,21], and suggested that *EGLN1* might be under selection also in people from the Andes [22], none of the top genes showing the most evidence of selection in the Andes are HIF signaling genes related to red blood cell production [10,21]. Instead, selection appears to have targeted genes such as *FAM213A* which is associated with oxidative stress [31], and *NOS2* [21], which is regulated by HIF-1, plays an important role on the downstream response to hypoxia, and is involved with phenotypes such as blood pressure reduction [23]. Furthermore, a number of genes related to cardiac phenotypes, including susceptibility or protection against atrial fibrillation appear as the most differentiated genes in Andeans [24••]. Although the genetics of altitude adaptation in Andeans still is not fully understood, it appears that Andeans, instead of modulating their production of red blood cells, perhaps have evolved towards mitigating the deleterious effects of a chronically enhanced HIF response (Figure 2).

Adaptation to diving

In addition to populating a vast and varied landscape of severe environments, humans have adopted extreme lifestyles, thus self-imposing conditions of physiological stress.

Figure 3



The thyroid hormone synthesis pathway. The binding of the Thyroid Stimulating Hormone (TSH) triggers synthesis of thyroglobulin, a thyroid hormone precursor, through a cAMP-dependent pathway. This pathway can be inactivated by phosphodiesterases (PDEs) such as PDE10A. The thyroglobulin precursor is discharged into the follicle lumen. Enzymes attach idoine to tyrosines (a part of the thyroglobulin molecule), and the iodinated tyrosines are joined together to form T3 and T4. These molecules are endocytosed into the follicle where lysosomal enzymes cleave the thyroid hormones T4 and T3 from thyrogolobulin, and the hormones are released into the blood stream. Decreased expression of PDEs increases the synthesis of thyroglobulin, thus increasing thyroid hormone production.

One such population, the Sea Nomads of Southeast Asia, has built a culture around breath-hold diving. Their marine hunter-gatherer lifestyle frequently necessitates diving to depths of over 100 ft for periods of several minutes. This activity puts a number of strains on the body's terrestrial physiology: the eye loses roughly two-thirds of its refractive power [25]; water exerts one atm of pressure for every 10 m of depth, compressing the air-filled chest cavity; and extended periods of apnea create conditions of acute hypoxia. Until recently, none of these physiological stresses were known to have induced genetic adaptations in diving populations, and it was believed the extraordinary abilities of Sea Nomads were merely achieved through a plastic response to diving. Even the observed superior underwater vision of the Moken [26], a group of Sea Nomads in Thailand, was argued to result from repeated underwater training activity [27].

However, genetic analyses of the Bajau of Indonesia found them to have adapted to acute hypoxia via enlarged spleens [28••], an organ that contracts in response to the dive stimulus to provide an oxygen boost through the expulsion of red blood cells. A genetic variant associated with this trait falls within the gene *PDE10A*, which encodes a phosphodiesterase that affects signaling pathways, including those that regulate thyroid hormone levels (Figure 3). Levels of the thyroid hormone T4 have been shown to dramatically affect spleen size in mice [29], suggesting that the observed large spleens of the Bajau result from modulation of thyroid hormone regulation. Additional candidate genes under Bajau-specific selection with apparent relevance to diving include *BDKRB2*, a gene thought to influence dive-induced peripheral vasoconstriction.

Discussion

In most of the cases of human adaptation discussed in this review, a new extreme environment imposes a perturbation on a physiological process, and the subsequent adaptation returns the process to homeostasis. For example, the low oxygen levels at high altitudes induce a maladaptive physiological response that increases oxygen delivery but at the cost of increased blood viscosity. The resulting adaptations blunt that response to return the system to equilibrium. Similarly, the adaptation in FADS genes in Inuit compensate for a dietary change in fatty acid intake, to restore the fatty acid composition to previous levels. The large spleens observed in the Bajau divers, however, instead present a unique example of selection acting to produce a novel adaptation that enhances functionality. In this sense, the diving example might be the most

relevant for understanding the evolution of novel features.

Lessons learned from human evolutionary biology are critical for the interpretation of human medical studies. The first studies on the possible beneficial effects of omega-3 fatty acids were based on epidemiological studies of the Inuit. However, the Inuit appear to be adapted genetically to a diet rich on omega-3 fatty acids, suggesting that the lessons from the Inuit cannot easily be extrapolated to other populations. Interestingly, recent meta-studies of the effects of omega-3 supplementation based primarily on people of European descent suggest that there are no protective effects of omega-3 supplementation [30].

In the age of personalized genomics, it is becoming increasingly clear that genetic differences between populations must be taken into account by health-care providers. The adaptations discussed here often derive from rare alleles that rise in frequency in a given population rather than *de novo* mutations, therefore they can be expected to be present at certain frequencies in other geographic locations. The influence of these variants on physiology could affect a variety of medical procedures. For example, the variants that allow the Bajau to undergo repeated bouts of acute hypoxia with minimal physiological stress might affect an individual's ability to withstand acute hypoxia during a medical crisis such as traumatic brain injury. In this way, lessons derived from studies of isolated, extreme populations may be important for broader medical purposes.

Conflict of Interest

The authors declare no conflict of interest.

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