

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.

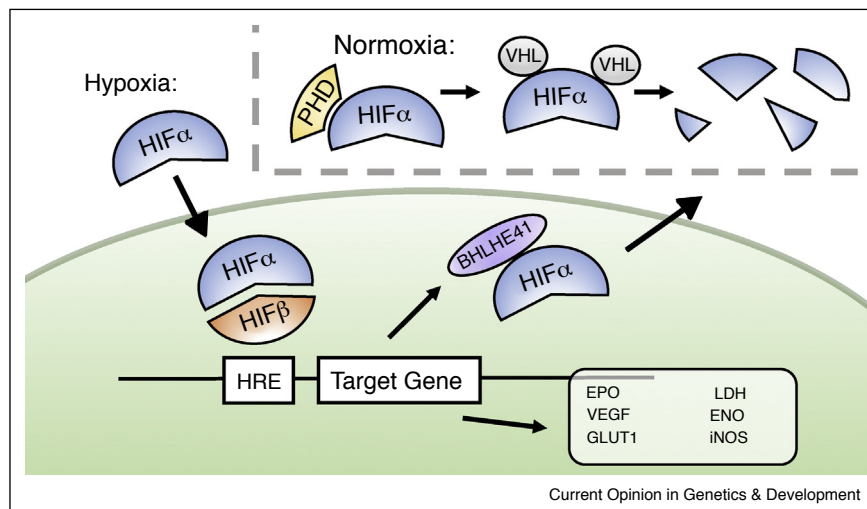
High-altitude adaptation

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

Figure 1



The hypoxia inducible factor (HIF) pathway. Under normoxic conditions, the HIF α subunits (including HIF-2 α , 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 hypoxic conditions, the HIF α subunit is stabilized and is translocated into the nucleus where it dimerizes with the HIF β 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 HIF α subunit to a proteasome complex for degradation, thus creating a negative feedback loop.

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