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A Review of Anthropological Adaptations of Humans Living in Extreme Conditions and Health Implications

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A Review of Anthropological Adaptations of Humans Living in Extreme Conditions and Health Implications

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Understanding gene variations in people living under extreme conditions has the potential of curing diseases caused by exposure to heat, cold, fatty diets, hypoxia, and pathogens. One candidate gene associated with heat resistance is *ACE1*, encoding angiotensin-converting enzyme 1. Associations have also been made between cold resistance or fatty diets and polymorphisms of several genes including *ACTN3*, encoding alpha-actinin-3, and *CPTIA*, encoding carnitine palmitoyltransferase 1A. A prominent role in resistance to hypoxia has been given for polymorphisms of *EPAS1*, encoding endothelial PAS domain protein 1, and *EGLN1*, encoding Egl-9 family hypoxia inducible factor 1. Variants conferring human resistance to pathogens include *HBB*, encoding hemoglobin subunit beta, and *ACE2*, encoding angiotensin-converting enzyme 2. Genetic knowledge concerning malaria and hypoxia should continue to promote advances in gene therapy.

Introduction

Biological variation in the human population can help physicians and scientists personalize treatments to serve public health better. Research on the genetic variability of different populations may influence medical treatment of certain diseases via drugs or changes in diet. Although humans share over 99% of their hereditary information, some groups have diverged in phenotype as a consequence of living in extreme environments, such as Tibetans living at high altitudes, Siberians and Inuits living in extreme cold, and sub-Saharan Africans living in malaria-endemic regions (Ilardo and Nielsen 2018). Knowledge about genetic variation within such groups may aid the treatment of diseases caused by exposure to heat, cold, fat diets, and hypoxia (Table 1). In particular, genetic knowledge of specific populations may lead to gene therapy of

vulnerable individuals.

Table 1 Gene variants associated with adaptations to extreme conditions

Adaptation	Gene variants	Proteins	References
UV radiation, heat	*TYR, MITF ,ACE1*, *HSP90AA1*	angiotensin-converting enzyme 1	*Add refs for TYR and MITF Caro-Consuegra et al. 2022; Feng et al. 2021; Heled et al. 2004; Moran et al. 2006; Saternus et al. 2015
cold, fat diets	*ACTN3*, LCT, *FABP1*, *FABP2, FADS1*, *FADS2*, *FADS3, CPTIA*, *LRP5*, *LEPR*, *LEP*, *TRPM8, UCP1, UCP3*	lactase, fatty acid binding protein 1 and 2, fatty acid desaturase 1, 2, and 3, carnitine palmitoyltransferase 1A, low-density lipoprotein receptor-related protein 5, transient receptor potentiation channel subfamily M	Almon et al. 2010; Cardona et al. 2014; Chen et al. 2019; Fisher et al. 2007; Friedlander et al. 2013; Fumagalli et al. 2015; Garcés Da Silva et al. 2018; Greenberg et al. 2009; Heianza et al. 2018; Hancock et al. 2011; Igoshin et al.

		member 8; uncoupling protein 1, uncoupling protein 3, brain derived neurotrophic factor	2019; Key et al. 2018; Li et al. 2018; Manco et al. 2017; Nikanorova et al. 2021; Ojeda-Granados et al. 2016; Parajuli et al. 2021; Robitaille et al. 2004; Stan et al. 2005; Wagh et al. 2012; Wyckelsma et al. 2021
hypoxia	*EPAS1*, *EGLN1*	endothelial PAS domain protein 1	Aggarwal et al. 2010; Bai et al., 2022; Brutsaert et al. 2019; Buroker et al. 2012; Huerta-Sánchez et al. 2010; Jacovas et al. 2022; Julian and Moore 2019; Peng et al. 2017; Petousi and Robbins. 2014; Simonson et al.

			2010; Tashi et al. 2017; Yang 2017; Yi et al. 2010; Zhang et al. 2021

Exposure to Ultraviolet Radiation and Heat

People living near the equator receive an exceptionally high amount of ultraviolet radiation (UV index 20 as opposed to 8 in Northern zones (https://www.grida.no/resources/7130). Such radiation can damage the skin, but is absorbed by darker surfaces. Ancestral populations carried genetic variants (polymorphisms) associated with darker skin that helped them adapt to exposure to ultraviolet radiation. Dark skin is caused by higher melanin levels, which are regulated by genes such as the *TYR* gene, which encodes tyrosinase, the enzyme that catalyzes the conversion of tyrosine to melanin (Feng et al. 2021; Saternus et al. 2015), plus several other genes related to skin pigmentation (Quillen et al. 2019), including *MITF*, which encodes the melanocyte inducing transcription factor (Caro-Consuegra et al. 2022).

The genetic basis of heat tolerance in desert-living populations is lacking and has only begun to be investigated in humans in general (Hosokawa et al. 2019). During exercise-related heat tolerance of male Caucasian volunteers, changes in body core temperature and heat storage differed depending on polymorphisms of *ACE1*, encoding angiotensin-converting enzyme 1, the DD genotype being more tolerant than ID+II genotypes grouped together (Heled et al. 2004). The enzyme belongs to the renin-angiotensin system critical in thermoregulation via vascular and renal mechanisms (Finberg et al. 1977; Kosunen et al. 1976). *ACE1* variants are hypothesized to confer an advantage in thermoregulation although predisposing to hypertension (Moskowitz 1996). Likely relevant to the human response are heat shock proteins, since, after recovery from exercise, HSP70 (heat shock protein family A member 1A derived from the *HSPA1A* gene), and HSP90 (protein isoforms derived from five genes including *HSP90AA1*) levels found in lymphocytes were higher in a heat tolerant than a heat intolerant group of men (Moran et al. 2006).

Occupants of sub-Saharan Africa have adapted to an environment with endemic

mosquito-borne malaria via genetic variants in genes such as *HBB*, which encodes beta-globin. Although some *HBB* genetic variants increase resistance to malaria, they also can cause sickle-cell disease, the most common genetic disorder in the world in which the most severe form is sickle cell anemia. Sickle-cell disease is an autosomal recessive disorder caused by a mutation in the *HBB* gene. In individuals homozygous for the mutation, C-shaped, or sickle-shaped, blood cells stick together and clog blood vessels, causing symptoms of acute chest syndrome, stroke, hypersplenism, aplastic crises, nocturnal enuresis, bone pain, avascular necrosis, chronic leg ulcerations, delayed growth, and priapism (Serjeant 2013). The lack of blood flow and the deterioration of renal function can also reduce chances of combating infections such as pneumonia because of a deficiency in cell defense and attack mechanisms. Medications easing the symptoms of sickle-cell disease include hydroxyurea, which makes red blood cells less likely to assume a sickle shape and increases their size (McGann and Ware 2015), l-glutamine, which reduces pain caused by oxidative stress (Cox et al. 2020), and voxelotor (GBT440), which increases blood viscosity (Dufu et al. 2018), each with significant side-effects. To establish a life-long cure, several types of gene therapy are underway, including one based on delivering the fully functional *HBB* gene (Eisenstein 2021), a life-saving option for some patients provided they travel away from a malaria-plagued zone.

The genetic response to heat stress is all the more relevant with rising temperatures on the planet (Beall et al. 2012). Future directions in research include examining the genomic consequences of thermal shifts in evolution via phylogeographic approaches (Cortés et al. 2020).

Exposure to cold weather and high fat diets

Adaptation to cold weather is linked with a genetic characteristic present in 18% of the world's population, an allele of *ACTN3* causing a loss of alpha-actinin-3 (Friedlander et al. 2013), selectively expressed in fast-twitch muscle fibers (Mills et al. 2001). As a result of changes in skeletal muscle thermogenesis, people lacking *ACTN3* maintain a core body temperature better during cold-water immersion than those possessing the gene (Wyckelsma et al. 2021). A lack of *ACTN3* not only seems to favor cold endurance but also running endurance (Ivarsson and Westerblad 2015).

The relation between alpha-actinin-3 and endurance running has been extended to animals, since mice lacking *Actn3* displayed higher cytochrome oxidase expression in skeletal

muscle and longer endurance while running on a treadmill (MacArthur et al. 2007). The null mutant muscle also showed better force recovery from fatigue (MacArthur et al. 2008). However, their fast-twitch muscle fibers were more prone to break when eccentrically stretched (Haug et al. 2022).

In addition to *ACTN3*, allele frequencies of *TRPM8*, encoding transient receptor potentiation channel subfamily M member 8, were related with winter temperatures in east Asian populations (Igoshin et al. 2019) as well as ambient temperatures and latitude in northern populations (Key et al. 2018), revealing the importance of a thermal sensor protein in the 15° to 30°C range (Fernández et al. 2011). Downregulated *TRPM8* may lead to cold tolerance based on data in *Trpm8* null mutant mice spending more time under frigid ambient temperatures and displaying longer latencies before paw withdrawal to a cold plate after an injection of icillin (Dhaka et al. 2007).

In a genome-wide analysis study of Siberian populations, polymorphisms related to cold adaptation included *CPTIA*, encoding carnitine palmitoyltransferase 1A, a liver isoform of an enzyme involved in long-chain fatty acid metabolism, as well as *LRP5*, encoding low-density lipoprotein receptor-related protein 5, involved in cholesterol metabolism and bone growth (Cardona et al. 2014). Amid consecutive newborns of Canadian Inuits from Kivalliq (mean daily low of -27 to -32degC from December to February https://en.wikipedia.org/wiki/Kivalliq_Region), a population that migrated from Siberia, 70% were homozygous for the P479L allele of *CPTIA*, 24% were heterozygous, and only 6% were wild-type, lowering enzymatic activity in cultured fibroblasts but causing few medical symptoms of enzyme deficiency (Greenberg et al. 2009) despite the fact that the homozygous null mutation is lethal in the mouse (Nyman et al. 2005).

Greenland Inuits carry polymorphisms of *FADS1*, *FADS2*, and *FADS3*, encoding fatty acid desaturase 1, 2, and 3, respectively (Fumagalli et al. 2015), enzymes involved in converting linoleic acid and alpha-linoleic acid into longer and more unsaturated forms (Zhang et al. 2016). *FADS2* and *FADS3* polymorphisms were likewise associated with red blood cell omega-3 fatty acid levels in Canadian Inuits (Parajuli et al. 2021). Moreover, the frequency distributions of *CPTIA, FADS2*, and *FADS3* variants differed in North relative to South China populations (Li et al. 2018). These polymorphisms may be caused by traditional or modern diets with a high fat content consumed by such populations, a common consequence of adapting to cold weather.

Indeed, *FADS2* variants interacted with polyunsaturated fat acid intake on serum triglyceride levels in a Swedish population (Chen et al. 2019). A loss-of-function *FADS2* allele may be favorable for human health, perhaps in affluent countries, since a null mutation of *Fads2* led to resistance to obesity and atherosclerosis in mice consuming a high fat diet (Stoffel et al. 2014, 2021).

Other links with diet are indicated by polymorphisms associated with serum leptin levels reported in Siberian populations for *LEPR*, encoding the leptin receptor, as well as two genes related to leptin, *UCP1*, encoding uncoupling protein 1, and *BNDF*, encoding brain derived neurotrophic factor (Nikanorova et al. 2021). Allele frequencies of *UCP1* and *UCP3*, encoding uncoupling protein 3, were correlated with winter temperatures in a population genetic analysis (Hancock et al. 2011). Moreover, polymorphisms were reported for both *LEPR* and *LEP*, encoding leptin itself, in brown adipose tissue, crucial for non-shivering thermogenesis, among four continental groups (Sazzini et al. 2014). Leptin is a hormone released from adipocytes from brown and white adipose tissue and involved in fat storage, sending a satiety signal to its receptor situated in the ventromedial and lateral hypothalamus (Klok et al. 2007; Meister 2000).

A variant of *FABP1A*, encoding fatty acid binding protein 1, was associated with plasma levels of triglycerides and low-density lipoprotein-cholesterol in a random sample of German women (Fisher et al. 2007) and interacted with fat intake in regard to plasma apolipoprotein B levels in French Canadian men recruited from a lipid clinic (Robitaille et al. 2004). The latter authors speculated that the *FABP1A* allele in carriers consuming a modern diet with a high fat content inhibits the incorporation of fatty acids to produce and secrete apolipoprotein B from the liver. Gene variants of *FABP2*, encoding fatty acid binding protein 2, were associated with plasma levels of low-density lipoprotein-cholesterol, apolipoprotein B, and total cholesterol in 9- to 16-year old French Canadians (Stan et al. 2005) and plasma triglyceride levels in healthy Venezuelans classified as fat-tolerant or not depending on a lipid challenge test (Garcés Da Silva et al. 2018).

Although not subject to frigid weather, the Maasai tribe of Kenya and Tanzania possess a gene cluster from the cytochrome P450, family 3, subfamily A (*CYP3A*) chromosomal locus, allowing them to oxidize fatty acids and generate useful steroids derived from cholesterol, with the highest association found for *FABP1A* (Wagh et al. 2012). Because most of their nutrients traditionally come from raw meat, milk, and blood, the Maasai tribe ingests large amounts of

cholesterol, yet their blood levels of cholesterol are equal or even lower than most people (Arhem 1989). Genetic analyses of the Maasai have uncovered gain-of-function polymorphisms of *LCT*, encoding lactase, the enzyme that breaks down lactose and thereby permits digestion of milk products, attributed to their tradition of herding cows and goats (Wagh et al. 2012). Lactase persistent young Portugese adults with a polymorphism of *LCT* had higher body adipose mass and weight than lactase non-persistent ones (Manco et al. 2017). On the contrary, lactase persistent Swedish children and adolescents with the same polymorphism of *LCT* consumed fatter dairy products than lactase non-persistent ones without differing in body adipose mass (Almon et al 2010). Likewise, body weight and fat were equivalent in Mexican adults of different ethnic origin with lactase persistent *LCT* polymorphisms as opposed to lactase non-persistent ones (Ojeda-Granados et al. 2016). The opposite results are probably due to the use of different diets. Although a different polymorphism of *LCT* had no effect on body weight and fat in overweight Americans, adipose-related values changed depending on whether they consumed high or low protein diets (Heianza et al. 2018).

Exposure to hypoxia

Genetic variations foster adaptation to one's environment, including places at high altitudes (Shi and Su 2011). In Tibet, the average altitude is 4.3 km (https://en.wikipedia.org/wiki/Tibet). Over the course of millennia, ancestors of people in Tibet progressively lived at higher altitudes and, via natural selection, adapted to these extreme conditions by mitigating the normal increase of hemoglobin concentrations prevailing when oxygen levels plummet (Witt and Huerta-Sánchez 2019). Tibetan people adapted via polymorphisms of the *EPAS1* gene, encoding endothelial PAS domain protein 1, part of the hypoxia-inducible factor (HIF) family of proteins producing red blood cells under hypoxic conditions (Bai et al., 2022; Buroker et a. 2012; Huerta-Sánchez et al. 2010; Peng et al., 2017; Simonson et al. 2010; Yang 2017; Yi et al. 2010; Zhang et al. 2021). *EPAS1* polymorphisms in Tibetan highlanders produce fewer red blood cells than non-mutated *EPAS1*, a characteristic originating with Denisovan hominins. Although Tibetan highlanders share a recent common ancestor with Han Chinese lowlanders, the two differ in regard to *EPAS1* alleles. With fewer red blood cells, high-altitude conditions such as hypercoagulation and hypoxic pulmonary hypertension are mitigated. To compensate for their lack of hemoglobin, highlanders exhale more nitric oxide (Wu and Kayser 2006), a molecule that dilates blood vessels

(Joannides et al. 1995). *EPAS1* polymorphisms occurred in conjunction with a gain-in-function of the *EGLN1* gene, encoding Egl-9 family hypoxia inducible factor 1, so that, at high altitudes, the *EGLN1* haplotype has lowered hemoglobin levels in the presence of the *EPAS1* allele (Tashi et al. 2017). It is assumed that physiological factors such as dilated blood vessels compensate for this lack of hemoglobin. *EPAS1* and *EGLN1* single nucleotide polymorphisms were detected in patients with acute or chronic mountain sickness (Buroker et al. 2012). Together, *EPAS1* and *EGLN1* compose "a central role in oxygen sensing and coordinating an organism's response to hypoxia" (Petousi and Robbins 2014).

In addition, missense mutations in the *Epas1* gene were revealed in Tibetan horses characterized by facilitated blood circulation and oxygen transport under hypoxic conditions (Liu et al. 2019). Tibetan horses displayed lower hemoglobin concentrations than lowland horses and signs of a convergent *Epas1* signature appeared in cattle and sheep as well as goats, pigs, and dogs (Wu et al. 2020b).

As with Tibetans, polymorphisms of the *EGLN1* gene were discovered in the Quechua population living at an average altitude of 3.6 km (McGrath 2021) on the Andean mountain range of Peru (Aggarwal et al. 2010; Brutsaert et al. 2019), an example of convergent evolution (Greenway et al. 2020; Rocha et al. 2021; Witt and Huerta-Sanchez 2019). *EGLN1* polymorphisms in Quechua people were associated with higher aerobic capacity than lowland people under hypoxic conditions (Brutsaert et al. 2019) and lowered partial pressure of carbon dioxide while maximizing oxygen usage (Julian and Moore 2019), but with an increased risk of developing high-altitude pulmonary edema (Aggarwal et al. 2010). Moreover, different frequencies of haplotype of *HLA-G*, encoding human leukocyte antigen G (histocompatibility complex class 1, G alpha chain), were identified in highlanders relative to lowlanders in the Andes region of South America (Jacovas et al. 2022).

Resistance to hypoxia has been proposed to be mediated by defense and rescue phases of energy demands via adenosine triphosphate (ATP) (Hochachka and Lutz 2001; Hochachka et al. 1996). In the defense phase, a decrease in ATP consumption is modulated by ATP production to balance supply and demand. During the rescue phase, there is overexpression of *EEF1A1*, encoding eukaryotic translation elongation factor 1 alpha 1 as well as transcription factor *HIF1*, encoding hypoxia inducible factor 1 subunit alpha. The accumulation of the EEF1A protein mediates the translation of specific rescue mRNAs, while the HIF1 protein suppresses the

expression of genes involved in ATP-intensive metabolism, such as enzymes involved in the Krebs cycle and gluconeogenesis, but increases the expression of genes involved in cell survival under low ATP turnover, such as glycolytic enzymes (Boothby et al. 2019).

Genetic information of this type may help inform the health care of patients exposed to hypoxia, a central feature of ischemic heart disease, stroke, anemia, and chronic obstructive pulmonary disease (Bigham and Lee 2014) as well as promote gene therapy (Rhim et al. 2013). More favorable preventive measures may also be available to mountain-climbers and tourists entering a plane at a low altitude and exiting the plane at a higher one.

Implications for Disease

Knowledge of genes involved in extreme environments may provide aid in confronting a pandemic, since genetic analyses are underway regarding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a ribonucleic acid (RNA) virus leading to coronavirus disease 2019 (COVID-19) (Mogensen 2022; Ren et al. 2024). Among candidate genes involved in heat tolerance and mentioned above, the *ACE1* I/D polymorphism was associated with COVID-19 disease severity (Almeida et al. 2024). Moreover, subjects with a rare variant in an area on the X chromosome upstream of *ACE2*, encoding angiotensin-converting enzyme 2, the main cell receptor for SARS-CoV-2 entry, had a reduced risk of COVID-19 (Horowitz et al. 2021) and its severity was associated with *ACE2* polymorphisms (Elnagdy et al. 2024), hypoxia being able to modify SARS-Cov-2 cell entry via *ACE2* (Mughis et al. 2023). Among candidate genes involved in hypoxia, *EGLN1* variants were related to COVID-19 severity (Harit et al. 2024). Another gene involved with hypoxia was *HLA-G*. A common allele of *HLA-B*, encoding human leukocyte antigen B (histocompatibility complex class 1, B alpha chain), was associated with the asymptomatic form of COVID-19 infection (Augusto et al. 2023).

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Disclosure statement

The authors declare no conflict of interest.

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