DOI: https://doi.org/10.17816/ecogen630869
Review Article

Populations of the Caucasus as an object for studying the process of adaptation to conditions of high-altitude hypoxia

Murat A. Dzhaubermezov [1, 2], Natalia V. Ekomasova [1, 2], Rustam N. Mustafin [3], Ongar S. Chagarov [4], Yuliya Yu. Fedorova [1], Liliya R. Gabidullina [1], Alfiya Kh. Nurgalieva [1], Darya S. Prokofyeva [1], Elza K. Khusnutdinova [1, 2]

[1] Ufa University of Science and Technology, Ufa, Russia;
[2] Institute of Biochemistry and Genetics, Ufa Federal Research Center of the Russian Academy of Sciences, Ufa, Russia;
[3] Bashkir State Medical University, Ufa, Russia;
[4] Moscow State University named after M.V. Lomonosov, Moscow, Russia

ABSTRACT

The work examines the main mechanisms responsible for the process of acclimatization of the population of high mountain regions to the conditions of hypobaric hypoxia. The purpose of this review is to describe the pathways of genetic, epigenetic and physiological control in the adaptation of indigenous populations of highlands to reduced barometric pressure and oxygen tension in the environment. It has been shown that populations living in different high-mountain regions demonstrate different ways of adaptation in response to a decrease in the partial pressure of oxygen in the inspired air. The changes that occur in the body in response to stressful conditions are extremely diverse. These include changes in the respiratory, cardiovascular, hematological systems and cellular adaptation. In this review, we examine genomic variations leading to evolutionary adaptation to life at high altitudes, gene expression, pathophysiological and metabolic features, and long-term adaptation in various high-altitude populations. We also consider the peoples of the Caucasus as one of the most promising populations for further study of complex adaptation mechanisms.

Keywords: hypoxia; highlands; Caucasus; *EGLN1*; *XOC8*; *SPRTN*; *EPAS1*; *HIF1A*.

To cite this article
Dzhaubermezov MA, Ekomasova NV, Mustafin RN, Chagarov OS, Fedorova YuYu, Gabidullina LR, Nurgalieva AKh, Prokofyeva DS, Khusnutdinova EK. Populations of the Caucasus as an object for studying the process of adaptation to conditions of high-altitude hypoxia. *Ecological genetics*. 2024;22(3):277–292. DOI: https://doi.org/10.17816/ecogen630869

Received: 06.05.2024 **Accepted:** 12.08.2024 **Published online:** 20.08.2024

DOI: https://doi.org/10.17816/ecogen630869
Обзорная статья

Популяции Кавказа как объект изучения процесса адаптации к условиям высотной гипоксии

М.А. Джаубермезов [1, 2], Н.В. Екомасова [1, 2], Р.Н. Мустафин [3], О.С. Чагаров [4], Ю.Ю. Федорова [1], Л.Р. Габидуллина [1], А.Х. Нургалиева [1], Д.С. Прокофьева [1], Э.К. Хуснутдинова [1, 2]

[1] Уфимский университет науки и технологий, Уфа, Россия;
[2] Институт биохимии и генетики Уфимского федерального исследовательского центра РАН, Уфа, Россия;
[3] Башкирский государственный медицинский университет, Уфа, Россия;
[4] Московский государственный университет имени М.В. Ломоносова, Москва, Россия

АННОТАЦИЯ

В работе рассмотрены основные механизмы, отвечающие за процесс акклиматизации населения высокогорных регионов к условиям гипобарической гипоксии. Целью данного обзора является описание путей генетического, эпигенетического и физиологического контроля при адаптации коренного населения высокогорья к снижению барометрического давления и напряжению кислорода в окружающей среде. Показано, что популяции, проживающие в разных высокогорных регионах, демонстрируют различные способы адаптации в ответ на понижение парциального давления кислорода во вдыхаемом воздухе. Изменения, происходящие в организме в ответ на стрессовые условия, крайне многообразны. К ним относятся изменения в дыхательной, сердечно-сосудистой, гематологической системах и клеточной адаптации. В данном обзоре мы рассматриваем геномные вариации, ведущие к эволюционному приспособлению к жизни на высокогорье, экспрессию генов, патофизиологические и метаболические особенности, а также долгосрочную адаптацию в различных высокогорных популяциях. Рассмотрены народы Кавказа как одни из наиболее перспективных популяций для дальнейшего изучения комплексных механизмов адаптации.

Ключевые слова: гипоксия; высокогорье; Кавказ; *EGLN1*; *EXOC8*; *SPRTN*; *EPAS1*; *HIF1A*.

Как цитировать

Джаубермезов М.А., Екомасова Н.В., Мустафин Р.Н., Чагаров О.С., Федорова Ю.Ю., Габидуллина Л.Р., Нургалиева А.Х., Прокофьева Д.С., Хуснутдинова Э.К. Популяции Кавказа как объект изучения процесса адаптации к условиям высотной гипоксии // Экологическая генетика. 2024. Т. 22. № 3. С. 277–292. DOI: https://doi.org/10.17816/ecogen630869

Рукопись получена: 06.05.2024 **Рукопись одобрена:** 12.08.2024 **Опубликована online:** 20.08.2024

ЭКО•ВЕКТОР

BACKGROUND

High-altitude hypoxia is manifested by decreased partial pressure of oxygen in the inhaled air that occurs at high altitudes and causes serious physiological effects on the human body. It is caused by the exponential decrease in barometric pressure with altitude gain, which is characterized by a decrease in pressure by an average of 1 mmHg/10.5 m of altitude gain [1]. Along with a lack of oxygen, aggravating factors in high-altitude conditions include ultraviolet radiation, body dehydration, cooling, physical fatigue, and sudden temperature changes during the day. These factors can cause the development of acute mountain sickness and life-threatening high-altitude cerebral and pulmonary edema [2, 3]. Moreover, hypoxia is a risk factor of various widespread human diseases including coronary heart disease, stroke, anemia, chronic obstructive pulmonary disease, and pulmonary hypertension [4].

There are various classifications of high-mountain regions; however, the most commonly accepted altitude gradations are 1500–3500, 3500–5500, and >5,500 m above sea level [5]. Each of these levels is characterized by certain body responses that lead to physiological adaptation or acclimatization.

Approximately 400 million people worldwide live at altitudes >1500 m above sea level, and over 100 million lowland residents annually visit areas above 2500 m*. Additionally, approximately 82 million people live permanently at altitudes above 2500 m [6]. There are several high-mountain regions where people have lived for millennia, including the Ethiopian Plateau, Tibetan Plateau, and Andes. However, until recently, evidence of settlement of the high-mountain regions of the Old World before the Holocene is unclear. [7]. The latest research data indicate that people of the modern anthropological type began to populate the highland regions in the early Paleolithic period [8]. According to modern research, the earliest traces of *Homo sapiens* penetration (30,000–40,000 years ago) into the highlands are found in Tibet [8]. Furthermore, settlement in the highland regions of South America occurred about 11,500 years ago [9].

To date, the Caucasus is the least studied mountain region. This is surprising as this country has been known since ancient times. Ancient acquaintance with the Caucasus, which is a predominantly mountainous region located between the Black and Caspian Seas on the border of Europe and Asia, occurred long before the Common Era [10]. During the ancient times, it induced legendary and cosmogonic fantasies in the minds of people. In Greek mythology, the Caucasus became the most popular place, associated with the myths of Prometheus, Jason, and Theseus, among others, and Aeschylus (525–456 BC) stated that the Caucasus Mountains, similar to Atlantes, support the sky and serve as a home for the gods [11]. In biblical times, the Caucasus Mountains attracted attention and contributed to myths associated with Noah's Ark, and there are records of the Renaissance that in 1395, Tamerlane climbed Elbrus (the highest peak in the Caucasus and Europe) for jihad [12].

The length of the Main Caucasian Ridge is >1100 km, and its area is approximately 400,000 km^2. According to various estimates, there are approximately 50 indigenous people in this region, with a total population of approximately 30 million individuals. The highest mountain part of the Caucasus is its central part, located between the stratified volcanoes Elbrus and Kazbek, and all the 5000-meter peaks of Russia and Europe are located in this part of the Caucasus [13]. The Balkars and Karachays, which are Turkic-speaking populations belonging to the Caucasian anthropological type, represent the indigenous population of this region [14]. Based on craniological, somatological, odontological, and dermatoglyphic study results, a conclusion was generated on the aboriginal (Caucasian) origin of the Balkars and Karachays and their relationship with representatives of neighboring people and the insignificant role of the Central Asian component in their ethnogenesis [14–16]. The 2022 census showed that the population of the Balkars in Russia was 125,000 people, and that of the Karachays was 226,3000 people [17]. Forming a single linguistic and cultural population, the Karachays and Balkars are the constituent people of the Kabardino-Balkarian and Karachay-Cherkess Republics. Before the policy of unifying peasant farms began in the 1930s, Balkars and Karachays inhabited >80 mountain villages at altitudes from 1000 m to over 2000 m above sea level [18] (Table 1).

Thus, the populations of the Caucasus are an interesting focus for studying the methods of adaptation to high-altitude conditions. This becomes even more attractive considering the fact that from the Balkars and Karachays (the highest-altitude populations of the Caucasus) alone, during the period from the end of the 19th to the beginning of the 20th century, about 70 guides and climbers emerged, participating in ascents with groups of famous climbers such as Douglas Freshfield, Hermann Woolley, and Moritz Dechy [19]. Currently, various high-altitude search and rescue teams of the Russian Emergencies Ministry are mainly staffed by Balkars and Karachays.

GENETIC AND EPIGENETIC FACTORS

People have adapted to conditions of constant oxygen deficiency at high altitudes in several places, and recent genome-wide studies have shown the genetic basis for

* Cohen JE, Small C. Hypsographic demography: the distribution of human population by altitude. Proc Natl Acad Sci U S A. 1998 Nov 24;95(24):14009-14014. doi: 10.1073/pnas.95.24.14009.

Table. Some villages and their altitudes above sea level

Таблица. Некоторые аулы и высоты их расположения над уровнем моря [18]

Name of settlement	Altitude above sea level, m	Name of settlement	Altitude above sea level, m
Terskol	2150	Yozen	1800
Itkol	2030	Zhapyr-Tala	1780
Baidaevo	1940	Elbrus	1780
Duut	1870	Gubasanty	1770
Achi	1845	Dumala	1735
Tegenekli	1840	Kholam	1700
Shiki	1830	Kala	1700

this adaptation [4, 20, 21]. The most significant genes in this context are *EGLN1, EXOC8,* and *SPRTN*. The *EGLN1* gene encodes the oxygen-sensitive enzyme prolyl hydroxylase 2 (PHD2) and is located in a region with one of the strongest selection signals in Tibetans, which proves convergent evolution in Tibetans and Andean people [22, 23]. A cluster of 13 SNPs (Single Nucleotide Polymorphism) located in the conservative intron of the *EGLN1* gene is of particular interest, which demonstrates high differentiation in the Dagestani Kubachin population and, possibly exhibits genetic pathways of adaptation of the Caucasian people to high altitude [24].

The functional role of polymorphic variants (e.g., rs186996510 and rs12097901) localized in the first exon of the *EGLN1* gene was demonstrated previously, and their adaptive significance for Tibetans was proven. Moreover, the minor allele C of rs186996510 of the *EGLN1* gene, which is detected with high frequency in the inhabitants of the Tibetan Plateau, was not revealed among Andean mountain population representatives [21]. The hypothesis of adaptation in the highland Quechua population, which indicates the presence of genetic variants that provide an advantage in hypoxic conditions, was confirmed in a study of the polymorphic loci rs2491403, rs479200, and rs1769793 of the *EGLN1* gene [20].

The most convincing association was detected in the polymorphic locus rs1769793, which remained significant even after Bonferroni correction for multiple testing ($p = 0.00625$; $\alpha = 0.05$) [20]. Additionally, the polymorphic loci rs2437150 of the *SPRTN* gene and rs2064766 of the *EXOC8* gene are significant ($p < 0.05$) [20]. The *SPRTN* gene is a nuclear metalloprotease involved in DNA repair, and mutations in this gene in humans are associated with genomic instability [25]. Therefore, this gene is crucial for general DNA replication and in the regulation of the replication-associated G2/M checkpoint [25]. Further, *EXOC8* is a component of the exocyst complex involved in targeting secretory vesicles [26].

Notably, variants of vascular system genes such as *ACE*, *CYP11B2*, and *NOS3* are critical in altering the activity of circulating angiotensin II, which significantly affects the physiological parameters of the body in oxygen-depleted conditions. A study of the indigenous population of the Himalayas revealed that the rs1799998 and rs4539 variants of the *CYP11B2* gene are in complete linkage disequilibrium, and a combination of homozygous wild-type genotypes between the 344T/C, Iw/Ic, and A5160C variants, containing all six wild-type alleles, were over-represented in the indigenous people of the Himalayas [27, 28].

Furthermore, the rs1799983 and rs7830 variants of the *NOS3* gene were actively studied in the context of the genetic adaptation of populations to high-altitude hypoxia. It was revealed that the combination of wild types is significantly higher in the Sherpa population [29, 30].

An increase in hematocrit (the volume percentage of red blood cells in the blood) and/or hemoglobin concentration in the peripheral blood causes polycythemia. A study reported that variants of the *EPHA2* and *AGT* genes correlate with susceptibility to high-altitude polycythemia in ethnic Chinese and Tibetan populations [31]. Moreover, if variants rs2291804, rs2291805, rs3768294, rs3754334, rs6603856, rs6669624, rs11260742, rs13375644, and 10907223 of the *EPHA2* gene and rs699, rs4762, and rs5051 of the *AGT* gene showed an association with reduced susceptibility to polycythemia in ethnic Chinese, then rs2478523 of the *AGT* gene showed an increased risk of polycythemia in the Tibetan population [31]. Furthermore, the occurrence and development of chronic obstructive pulmonary disease is regulated by environmental and genetic factors, and under hypoxia occurring in mountain conditions, erythropoietin can satisfy the body's need for oxygen, promoting red blood cell production [32–34]. This was demonstrated using the example of rs1617640 of the *EPO* gene and rs1042713 of the *ADRB2* gene [35, 36].

Endothelial PAS domain-containing protein 1 (EPAS1), also called hypoxia-inducible factor 2 alpha, is a protein encoded by the *EPAS1* gene. It is located on human chromosome 2 and is expressed by endothelial cells [37]. The most specific condition associated with EPAS1 is

adaptation to high-altitude environments [38]. In this regard, natural selection for *EPAS1* has been demonstrated to be associated with lower hemoglobin concentrations in Tibetan highlanders, but not in Andean residents [39–41]. This difference indicates different evolutionary pathways of adaptation to altitude in residents of high-altitude regions.

The potential determinants of the relationship between the genome and hematological status of highland residents are rs11549465 of the *HIF1A* gene and rs1572312 of the *NFIA*-AS2 gene, which is confirmed by a series of studies of the hematological status and aerobic capacity of elite athletes [42–44]. Rs11549465 of the *HIF1A* gene is of greatest interest, owing to the fact that for the Lak population from the Northeast Caucasus, in contrast to the lowland population of the Adyghe (Northwest Caucasus), a significant increase in the ancestral allele C was revealed, which may indicate the existence of certain patterns in adaptation to hypobaric hypoxia [24].

Additionally, predisposition to idiopathic pulmonary arterial hypertension may be a limiting factor for life in highland conditions. In this context, the potential targets for the study are the rs10478694 and rs5369 variants of the *EDN1* gene [45, 46]. Polymorphic variants of the *EDN1* gene have been associated with cardiovascular diseases such as hypertension, coronary heart disease, angina, and acute coronary syndrome [47], which was a reason to study their possible impact on adaptation to high-altitude conditions. The rs2070699 variant of the *EDN1* gene was found to be a potential risk factor for the development of acute mountain sickness [48].

As a result, of the Illumina 1M SNP analysis of the Ethiopian Highlands populations, several candidate genes (e.g., *CBARA1, VAV3, ARNT2*, and *THRB*) were identified for participation in high-altitude adaptation [49]. This was of particular interest as most of these genes had not been previously identified in Tibetan and Andean populations, and the *THRB* and *ARNT2* genes were found to play a role in the HIF-1 (Hypoxia-Inducible Factor-1) pathway. Moreover, it was noted that the variants associated with hemoglobin variation in Tibetans did not affect this trait in Ethiopian populations [50]. This indicates the existence of other pathways for the adaptation of Ethiopian populations to high altitude [51].

However, genetics alone does not elucidate the degree of phenotype variability. Epigenome analysis is one of the methods to determine the environmental impact. Epigenetic modifications include DNA methylation, post-translational modifications of the histone tail, and non-coding RNAs. Various genes encode proteins with HIF proline hydroxylase activity, and among them, *EGLNs* are the most studied; moreover, it has been shown that *EGLNs* act as oxygen sensors that regulate HIFα stability [52]. Additionally, *EGLN1* mRNA has been shown to be induced by hypoxia in various cell types [53–55], and increased mRNA levels are associated with increased EGLN activity [56]. Further, the protein encoded by the *SPRTN* gene may play a role in DNA repair during replication of damaged DNA, and its deficiency in mice causes chromosomal instability and a progeroid phenotype [57].

In La Paz, Bolivia (3640 m), genome-wide differences in DNA methylation have already been reported in peripheral blood mononuclear cells from offsprings of mothers with and without hypertensive pregnancy [58]. Men with severe erythrocytosis, a preclinical form of chronic mountain sickness (CMS), exhibit epigenetic differences compared to healthy controls [59]. The association between adaptive responses and high altitude in a high-altitude Andean Quechua population and its relationship to epigenetic mechanisms has been studied [60]. DNA methylation of the *EPAS1* promoter region and the LINE-1 repeat element in 572 high-altitude (4388 m) and lowland Quechua individuals was analyzed. The high-altitude sample was characterized by low *EPAS1* DNA methylation and higher LINE-1 DNA methylation [60]. Further studies of the association between genome-wide analysis data and DNA methylation levels in the Quechua population showed that local genetic variations are significantly associated with DNA methylation levels for *EPAS1* and *SOD3* [61]. Moreover, it was found that the Tibetan variant of *EPAS1* suppresses expression in the human umbilical cord and placental endothelial cells, and heterozygous *EPAS1* knockout mice exhibited blunted physiological responses to chronic hypoxia [62].

Gonzales and Chaupis [63] demonstrated that men with CMS from the Peruvian Central Andes had increased transcriptional activity of the *SENP1* (SUMO-specific protease 1) and *ANP32D* genes in response to hypoxia compared to men without CMS. The *SENP1* gene product increases the transcriptional activity of androgen receptors and regulates erythropoiesis, which is crucial for the stability and activity of hypoxia-inducible factor 1 (HIF-1α) [63].

The *HIF* gene family encodes transcription factors that respond to the prevailing oxygen level. In hypoxia, oxygen deficiency leads to ubiquitination failure of HIF-1α, which, as a result, moves into the nucleus, binds to HIF-1β, and recruits coactivator proteins to the HIF binding site. Thus, a large number of genes involved in adaptation to hypoxia are activated, including the *VEGF* gene and erythropoietin [64]. CMS is characterized by the expression of key enzymes of glucose metabolism, namely, increased mRNA levels of the *HK2, GLU1,* and *GLU2* genes, which positively correlates with hemoglobin [65]. In 2021, a study of Chinese people living on the plateau revealed differential changes in 145 gene expression, including an increase in the activity of 89 genes and a decrease in 56 genes. The expression products of these genes are involved in the metabolism of hydrogen peroxide and reactive oxygen species and in inflammatory reactions [66].

PATHOPHYSIOLOGICAL AND METABOLIC CHARACTERISTICS OF HIGH-ALTITUDE RESIDENTS

Despite the transmission of genetic characteristics that facilitate survival at high altitudes, 5%–33% of highland residents show signs of CMS due to maladaptation to constant hypoxia [67]. CMS is characterized by tinnitus and headache, paresthesia, varicose veins, cyanosis, sleep disturbances, palpitations, and dyspnea [68]. Additionally, long-term hypoxia contributes to an increase in hematocrit and changes in hematological parameters [69], such as excessive erythrocytosis [68]. As a result, blood viscosity increases, promoting flow-mediated vascular dilation, which is noted in individuals living at high altitudes [70].

CMS is often associated with pulmonary hypertension and heart failure. Furthermore, cardiovascular adaptation to hypoxia represents a remarkable model of the regulation of oxygen availability at the cellular and systemic levels [71]. High-altitude pulmonary hypertension with pulmonary arteriolar remodeling and right ventricular enlargement is detected in more severe stages of CMS. The degree of ventricular hypertrophy depends on the severity of hypoxemia [72]. In healthy individuals living in regions located at an altitude of 5100 m above sea level, dilation of the right compartments of the heart and left ventricular concentric remodeling with diastolic dysfunction are observed. These changes are more pronounced in patients with moderate to severe CMS and may represent the limits of cardiac adaptability before progression to heart failure [73]. CMS patients exhibit increased morbidity and mortality and risk of stroke and migraine [74], and CMS contributes to cognitive impairment [75]. This is associated with excessive oxidative–inflammatory–nitrosative stress with increased formation of free radicals and decreased bioavailability of nitric oxide [74]. However, people living at high altitudes have a lower mortality rate from malignant neoplasms owing to the influence of physiological adaptive processes in response to hypoxia [76]. The development of CMS in highlanders is attributed to excess weight, which is associated with metabolic changes and critical ventilation impairment in obesity, which aggravate hypobaric hypoxemia at high altitudes, leading to hypoxemia [77].

Although levels of cholesterol and lipoprotein levels were higher were revealed in Andean residents than in their peers from the Amazon basin, no significant differences were noted in the risk of cardiovascular diseases [78]. Moreover, it was determined that low oxygen levels in the environment prevent the development of atherosclerosis. This is because of an increase in anti-inflammatory cytokine interleukin 10 expression [79]. Further, differences in physiological changes in highland residents of different ethnic groups and countries have been described. For example, Andean residents have a higher hemoglobin concentration than Tibetans. This is reflected in the functional characteristics of people, such that lung ventilation at rest is lower in Andean residents than in Tibetans [80].

Highlanders show increased intracellular pH in the brain due to adaptation to hypoxemia and promotion of glycolysis, DNA synthesis, and cell-cycle progression. Lower intracellular pH was detected in brain astrocytes in highlanders with CMS compared with astrocytes of highlanders without CMS [81]. Severe erythrocytosis is caused by increased transcription of the *EPAS1* gene, which regulates erythroblast proliferation [82]. Testosterone, an erythropoietic hormone, is involved in the development of severe erythrocytosis in individuals with CMS. Men living at normal altitudes have higher androstenedione levels and low androstenedione/testosterone ratio compared with highlanders, indicating reduced activity of 17-beta-hydroxytestosteroid dehydrogenase in the mechanisms of adaptation to living at high altitude.

MORPHOFUNCTIONAL CHARACTERISTICS OF HIGH-ALTITUDE POPULATIONS

When considering the challenges associated with the origin of second-order races, anthropological studies periodically discussed issues on the relationship between the natural–climatic and landscape features of the habitat with a complex of morphophysiological signs characteristic of certain populations, forming their uniqueness and allowing them to be identified as separate subracial categories.

Scientists agree that one of the main factors in the formation of morphophysiological signs of representatives of various adaptive types is the entire set of physical characteristics of a particular anthropogeocenosis [83]. Moreover, the discussion of adaptive types and mechanisms of their formation is inseparable from the discussion of the features of heredity and variability, which are genetically determined traits in certain human populations [84, 85].

The concept of the confinement of manifestations of human body variability to natural–climatic zones and altitudinal zonality is comprehensively formulated in studies by Alekseeva [86, 87]. In this concept, an adaptive type is understood as a reaction norm that depends on specific environmental conditions within a certain zonality and/or altitude. Consequently, adaptive types that formed in similar environmental conditions are distinguished by a similar reaction norm and, accordingly, a set of morphological traits. One or another adaptive set of traits is reflected in the variations in the size and proportions of the body, combination of body components, and physiological characteristics of the blood as an indicator of the internal environment of the body [88].

Among the four adaptive types identified by Alekseeva, namely, arctic, continental, equatorial, and high-mountain, the last one is of interest in the present study [87]. The distinctive features of people belonging to populations that are highly possible to form in high-mountain conditions are characterized by larger body sizes, owing to a more voluminous chest, large long bones, and a massive skeleton, regardless of racial and ethnic affiliation. These traits were considered to include the degree of the face flattening; however, studies of the facial skeleton did not confirm the adaptive nature of the latter trait [89].

The listed morphological features, characteristic of representatives of mountainous countries, are associated with an enlargement of blood vessels and respiratory organs that is, those changes in the physiological functions of the body that are the result of adaptation to a decrease in atmospheric pressure and a lack of oxygen. Notably, the rate of basal metabolism and oxidation-reduction processes and functioning of the adrenal glands, thyroid gland, and heart contractions slow down, whereas blood oxygenation increases because of a large amount of hemoglobin and increased erythropoiesis [86]. Moreover, researchers do not have a clear understanding of the exact altitudes above sea level the conditions for the formation of the described population features begin to be created. Thus, according to Alekseev, the air rarefaction begins to affect at an altitude of about 1000 m above sea level, whereas the conventional highland boundary adopted in the study of mountain populations is considered to be 2000 m above sea level [88].

In addition, it is crucial to note that morphologically close adaptive types can have different biochemical mechanisms of adaptation to identical conditions [90].

PHYSICO-GEOGRAPHICAL, CLIMATIC, AND ETHNOLOGICAL FEATURES OF THE CAUCASUS

The geographical, historical, ethnological, and cultural aspects of the Caucasus have aroused particular interest in the study of this region. The history of the settlement in the Caucasus and all of Europe by modern humans has many blank spots. The Caucasus was inhabited by hominids (*Homo erectus georgicus*) in the Lower Pleistocene approximately 1.8 million years ago [91, 92]. Thus, the Caucasus is the oldest area of settlement of representatives of the genus *Homo* outside Africa, which indicates favorable conditions for habitation in this territory since ancient times and the possible genetic adaptation of the autochthonous population of the region to conditions of chronic oxygen deficiency.

Determining the nature of this adaptation is complicated by the climatic conditions in which this colonization occurred. The period from 26.5 to 19,000 years ago is characterized by the maximum extent of the ice sheet on Earth (the Last Glacial Maximum) [93]. More than 60% of the territory of modern Europe was covered by ice. This served as the main factor in population dynamics 30,000–13,000 years ago [94] and could have influenced migrations in the latitudinal and altitudinal directions (in mountainous regions), which in turn could have influenced the genetic portrait of modern populations. Periods with the lowest temperatures alternated with significantly warmer time periods. Thus, approximately 14,000 years ago, a rapid Allerod warming began on Earth, which abruptly transitioned to the final stage of glaciation, the Younger Dryas (10,730–9700 BC) [95].

In connection with such abrupt climate changes, refugia are of particular interest to scientists. A refugium is a surface area where species can survive an unfavorable period of geological time. Data indicate that postglacial warming released human populations from various climatic refugia with subsequent settlement of large territories [96]. In this context, the Caucasus is considered as a possible intermediate zone for the settlement of Eastern Europe and as a refugium, where the population became a source for the repopulation of both Eastern Europe and Southwest Asia after the Last Glacial Maximum [97, 98]. Although this territory was favorable for the preservation of the human population as a species, paleoclimatological data indicate harsher climatic conditions in the region compared to the modern state. For example, the snow cover line was 600–850 m below the contemporary level [99].

Considering that the Caucasus is located on the border between Europe and Western Asia, this territory was densely populated throughout the historical period. This is confirmed by the diversity of historical and archeological cultures that inhabited the region under study in different periods [10, 100, 101]. The influence of the Near Asian community on the population of the Caucasus can be traced back to the Early Bronze Age (3 millennium BC) and is associated with the Maikop and Kura–Araxes archeological cultures [102, 103]. In parallel with the Maikop culture, archeologists distinguish the development of the catacomb cultural and historical community (25–20 centuries BC). Their burials can be found in the basins of the Baksan, Chegem, and Kuban rivers that is, in modern Kabardino-Balkarian and Karachay-Cherkess Republics [100, 104, 105]. The Maikop culture was replaced by the settled population of the North Caucasian cultural and historical community (beginning of the 3 millennium BC–beginning of the 2 millennium BC) and then by the Kuban and Koban cultural and historical communities (13–3 centuries BC) [102, 106].

In the 8–7 centuries BC, the nomadic tribes of the Cimmerians [107], displaced by the Scythians from Asia Minor, appeared in the Black Sea region, and later the Scythians, who were eventually conquered by the

Sarmatians. The link between the populations of the North Caucasus and nomadic tribes of the Alans, who appeared in the Ciscaucasia in the first century AD, requires a separate study. The influence of the Turkic-speaking populations of the Huns, Bulgars, and Khazars, who dominated the region from the 4th to the 10th centuries AD, on the population of the Caucasus should be comprehensively studied [108]. Moreover, the history of the eastern part of the North Caucasus cannot be studied in isolation from the Arab–Khazar wars, which had a significant impact on the entire region [109]. The 13th century is characterized by the transition of the territory under the control of the Tatar-Mongols [110].

The most high-mountain part of the Caucasus is its central region; hence, the ethnogenesis of the Balkars and Karachays should be evaluated. To date, several studies have been conducted on the anthropological characteristics of the Karachays and Balkars [14, 16, 111], resulting in a conclusion regarding their aboriginal origin (Caucasian) and kinship with representatives of neighboring people [15]. The modern population participated in the studies, and remains from medieval burials were investigated.

Studies conducted using various marker systems (i.e., mitochondrial DNA, Y chromosome, and autosomal markers) revealed the genetic homogeneity of the ethnically and linguistically diverse population of the North Caucasus and its predominant Middle Eastern origin with little external influence [97, 112, 113]. Moreover, the discovered East Eurasian lines of mtDNA and Y-chromosome haplogroups, in the absence of Mongoloid signs, indicate an ancient admixture and/or a founder effect against the background of a successful reproductive history of the carriers of these haplogroups [112–114].

CONCLUSION

Despite the increasing knowledge of the physiological, genetic, and epigenetic bases of high-altitude adaptation over the past decade, the ability to adapt to high-altitude conditions and its risk factors remain unclear. This is crucial because not all high-altitude regions worldwide have been studied to the necessary extent to date. The mountainous territories of Russia appear to be the most promising for researchers. In this regard, the Caucasus is of the greatest interest, because for many millennia, this region has been a place of active contact and formation of various people and cultural communities, which led to settlement in the highest mountain areas of this region. This review summarizes the contributions of genetic, epigenetic, and metabolic nature to the process of adaptation of populations to high-altitude conditions and characterizes the people of the Central Caucasus as the focus for further comprehensive study in this context.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: M.A. Dzhaubermezov — collecting a collection of biomaterials, writing the text; N.V. Ekomasova — study concept and design, text writing; R.N. Mustafin — writing the text; O.S. Chagarov — collection of biomaterials; Yu.Yu. Fedorova — study concept and design; A.Kh. Nurgalieva — text writing, literature review; L.R. Gabidullina — literature review; D.S. Prokofieva — attracting funding; E.K. Khusnutdinova— making final edits.

Funding source. The work was supported by the State Assignment of the Ministry of Science and Higher Education of the Russian Federation No. 075–03–2024–123/1. This work was supported by the program for supporting bioresource collections (Collection of Human Biological Materials, Institute of Biochemistry and Genetics, Ufa Federal Research Center, Russian Academy of Sciences) and grant of the Ministry of Education and Science of the Republic of Bashkortostan No. 1 dated August 14, 2023 on the topic "Prospects of using population genetic features of mtDNA as diagnostic markers of gastric cancer" in terms of statistical data processing.

Competing interests. The authors declare that they have no competing interests.

Ethics approval. Sampling was carried out in accordance with the ethical standards of the Bioethics Committee, developed by the WMA Declaration of Helsinki "Ethical Principles for the Conduct of Medical Research Involving Human Subjects". All subjects filled out a questionnaire taking into account nationality up to three generations, year of birth. All respondents signed an informed voluntary consent to participate in the study. The work was approved by the Local Ethics Committee of the Institute of Biochemistry and Genetics of the Ufa Federal Research Center Russian Academy of Sciences (protocol No. 14 of September 15, 2016).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Личный вклад каждого автора: М.А. Джаубермезов — сбор коллекции биоматериала, написание текста; Н.В. Екомасова — концепция и дизайн исследования, написание текста; Р.Н. Мустафин — написание текста; О.С. Чагаров — сбор коллекции биоматериала и написание текста; Ю.Ю. Федорова — концепция и дизайн исследования; А.Х. Нургалиева — написание текста, обзор литературы; Л.Р. Габидуллина — обзор литературы; Д.С. Прокофьева — привлечение финансирования; Э.К. Хуснутдинова — внесение окончательной правки.

Источник финансирования. Исследование выполнено в рамках государственного задания Министерства науки и высшего образования РФ № 075-03-2024-123/1. Работа проведена при содействии программы поддержки биоресурсных коллекций

(Коллекция биологических материалов человека Института биохимии и генетики ФГБНУ «Уфимский федеральный исследовательский центр РАН») и гранта Министерства образования и науки Республики Башкортостан № 1 от 14 августа 2023 г. по теме «Перспективы использования популяционно-генетических особенностей мтДНК в качестве диагностических маркеров рака желудка» в части статистической обработки данных.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Этический комитет. Забор биоматериала проводился в соответствии с этическими стандартами Комитета по биоэтике, разработанными Хельсинкской декларацией WMA «Этические принципы проведения медицинских исследований с участием людей». Все участники заполняли анкету с учетом национальности до трех поколений и указанием года рождения. Все респонденты подписали информированное добровольное согласие на участие в исследовании. Работа одобрена локальным этическим комитетом Института биохимии и генетики УНЦ РАН (протокол № 14 от 15 сентября 2016 г.).

REFERENCES

1. Naumenko SE. *Mountain sickness: textbook*. Novosibirsk: IPC NSU; 2018. 72 p. (In Russ.)

2. Hackett PH, Roach RC. High-altitude illness. *N Engl J Med*. 2001;345(2):107–114. doi: 10.1056/NEJM200107123450206

3. Burtscher M, Hefti U, Hefti JP. High-altitude illnesses: Old stories and new insights into the pathophysiology, treatment and prevention. *Sport Med Health Sci*. 2021;3(2):59–69. doi: 10.1016/j.smhs.2021.04.001

4. Bigham AW, Lee FS. Human high-altitude adaptation: forward genetics meets the HIF pathway. *Genes Dev*. 2014;28(20):2189–2204. doi: 10.1101/gad.250167.114

5. Paralikar SJ, Paralikar JH. High-altitude medicine. *Indian J Occup Environ Med*. 2010;14(1):6–12. doi: 10.4103/0019-5278.64608

6. Tremblay JC, Ainslie PN. Global and country-level estimates of human population at high altitude. *PNAS USA*. 2021;118(18): e2102463118. doi: 10.1073/pnas.2102463118

7. Aldenderfer M. Modelling plateau peoples: The early human use of the world's high plateau. *World Archaeol*. 2007;38(3):357–370. doi: 10.1080/00438240600813285

8. Zhang XL, Ha BB, Wang SJ, et al. The earliest human occupation of the high-altitude Tibetan Plateau 40 thousand to 30 thousand years ago. *Science*. 2018;362(6418):1049–1051. doi: 10.1126/science.aat8824

9. Rademaker K, Hodgins G, Moore K, et al. Paleoindian settlement of the high-altitude Peruvian Andes. *Science*. 2014;346(6208): 466–469. doi: 10.1126/science.1258260

10. Munchayev RM. *Caucasus at the dawn of the Bronze Age*. Moscow: Nauka; 1974. 416 p. (In Russ.)

11. Semyonov PP, editor. *Picturesque Russia. Caucasus. Vol. IX*. Saint Petersburg, Moscow: Edition of the M.O. Wolf; 1883. P. II. (In Russ.)

12. Tizengausen G. *Collection of materials relating to the history of the Golden Horde. Vol. II: Extracts from Persian writings*. 1941. P. 181. (In Russ.)

13. Gvozdetsky NA. *Caucasus. Sketch of nature*. Moscow: Geografgiz; 1963. 262 p. (In Russ.)

14. Treskov IV, editor. *Materials of the scientific session on the problem of the origin of the Balkar and Karachai peoples; 1959 June 22–26*. Nalchik: Kabardino-Balkarian Book Publishing House; 1960. (In Russ.)

15. Karaketov MD, Sabanchiev H-MA, editors. *Karachais. Balkars*. Moscow: Nauka; 2014. 815 p. (In Russ.)

16. Alekseev VP. *Origin of the peoples of the Caucasus. Craniological study*. Moscow: Nauka; 1974. 317 p. (In Russ.)

17. rosstat.gov.ru [Internet]. Federal state statistics service [cited 2024 Apr 4]. Available from: https://rosstat.gov.ru/ (In Russ.)

18. topographic-map.com [Internet]. Federal state statistics service [cited 2024 Apr 1]. Available from: https://ru-ru.topographic-map.com/ (In Russ.)

19. Miziev IM. *Traces on Elbrus*. Karachaevsk: KChGPU; 2001. 184 p. (In Russ.)

20. Brutsaert TD, Kiyamu M, Elias Revollendo G, et al. Association of EGLN1 gene with high aerobic capacity of Peruvian Quechua at high altitude. *PNAS USA*. 2019;116(48):24006–24011. doi: 10.1073/pnas.1906171116

21. Heinrich EC, Wu L, Lawrence ES, et al. Genetic variants at the EGLN1 locus associated with high-altitude adaptation in Tibetans are absent or found at low frequency in highland Andeans. *Ann Hum Genet*. 2019;83(3):171–176. doi: 10.1111/ahg.12299

22. Bigham A, Bauchet M, Pinto D, et al. Identifying signatures of natural selection in Tibetan and Andean populations using dense genome scan data. *PLoS Genet*. 2010;6(9):e1001116. doi: 10.1371/journal.pgen.1001116

23. Bigham AW, Wilson MJ, Julian CG, et al. Andean and Tibetan patterns of adaptation to high altitude. *Am J Hum Biol*. 2013;25(2): 190–197. doi: 10.1002/ajhb.22358

24. Pagani L, Ayub Q, MacArthur DG, et al. High altitude adaptation in Daghestani populations from the Caucasus. *Hum Genet*. 2012;131(3):423–433. doi: 10.1007/s00439-011-1084-8

25. Lessel D, Vaz B, Halder S, et al. Mutations in SPRTN cause early onset hepatocellular carcinoma, genomic instability and progeroid features. *Nat Genet*. 2014;46(11):1239–1244. doi: 10.1038/ng.3103

26. Wu B, Guo W. The exocyst at a glance. *J Cell Sci*. 2015;128(16):2957–2964. doi: 10.1242/jcs.156398

27. Rajput C, Arif E, Vibhuti A, et al. Predominance of interaction among wild-type alleles of CYP11B2 in Himalayan natives associates with high-altitude adaptation. *Biochem Biophys Res Commun*. 2006;348(2):735–740. doi: 10.1016/j.bbrc.2006.07.116

28. Mallet RT, Burtscher J, Pialoux V, et al. Molecular mechanisms of high-altitude acclimatization. *Int J Mol Sci*. 2023;24(2):1698. doi: 10.3390/ijms24021698

29. Ahsan A, Norboo T, Baig MA, Qadar Pasha MA. Simultaneous selection of the wild-type genotypes of the G894T and 4B/ 4A polymorphisms of NOS3 associate with high-altitude adaptation. *Ann Hum Genet*. 2005;69(3):260–267. doi: 10.1046/j.1529-8817.2005.00158.x
30. Droma Y, Hanaoka M, Basnyat B, et al. Genetic contribution of the endothelial nitric oxide synthase gene to high altitude adaptation in Sherpas. *High Alt Med Biol*. 2006;7(3):209–220. doi: 10.1089/ham.2006.7.209
31. Liu L, Zhang Y, Zhang Z, et al. Associations of high altitude polycythemia with polymorphisms in EPHA2 and AGT in Chinese Han and Tibetan populations. *Oncotarget*. 2017;8(32):53234–53243. doi: 10.18632/oncotarget.18384
32. Dijkstra AE, Postma DS, van Ginneken B, et al. Novel genes for airway wall thickness identified with combined genome-wide association and expression analyses. *Am J Respir Crit Care Med*. 2015;191(5):547–556. doi: 10.1164/rccm.201405-0840OC
33. Oshima N, Onimaru H, Yamagata A, et al. Erythropoietin, a putative neurotransmitter during hypoxia, is produced in RVLM neurons and activates them in neonatal Wistar rats. *Am J Physiol Regul Integr Comp Physiol*. 2018;314(5):R700–R708. doi: 10.1152/ajpregu.00455.2017
34. Silverman EK. Genetics of COPD. *Annu Rev Physiol*. 2020;82:413–431. doi: 10.1146/annurev-physiol-021317-121224
35. Dmytriiev K, Mostovoy Y, Slepchenko N, Smereka Y. Clinical course of COPD in patients with Arg16Gly (rs1042713) polymorphism of ADRB2 gene. *Monaldi Arch Chest Dis*. 2022;93(2):2314. doi: 10.4081/monaldi.2022.2314
36. Wang Y, Li Z, Zhang X, et al. EPO rs1617640 A>C is a protective factor for chronic obstructive pulmonary disease: A case control study. *Front Biosci (Landmark Ed)*. 2023;28(9):215. doi: 10.31083/j.fbl2809215
37. Young JM, Williams DR, Thompson AAR. Thin air, thick vessels: historical and current perspectives on hypoxic pulmonary hypertension. *Front Med (Lausanne)*. 2019;6:93. doi: 10.3389/fmed.2019.00093
38. Wang N, Hua J, Fu Y, et al. Updated perspective of EPAS1 and the role in pulmonary hypertension. *Front Cell Dev Biol*. 2023;11:1125723. doi: 10.3389/fcell.2023.1125723
39. Yi X, Liang Y, Huerta-Sanchez E, et al. Sequencing of 50 human exomes reveals adaptation to high altitude. *Science*. 2010;329(5987):75–78. doi: 10.1126/science.1190371
40. Huerta-Sánchez E, Casey FP. Archaic inheritance: Supporting high-altitude life in Tibet. *J Appl Physiol (1985)*. 2015;119(10):1129–1134. doi: 10.1152/japplphysiol.00322.2015
41. Zhang X, Witt KE, Bañuelos MM, et al. The history and evolution of the Denisovan-EPAS1 haplotype in Tibetans. *PNAS USA*. 2021;118(22):e2020803118. doi: 10.1073/pnas.2020803118
42. Döring F, Onur S, Fischer A, et al. A common haplotype and the Pro582Ser polymorphism of the hypoxia-inducible factor-1alpha (HIF1A) gene in elite endurance athletes. *J Appl Physiol (1985)*. 2010;108(6):1497–500. doi: 10.1152/japplphysiol.01165.2009
43. Malczewska-Lenczowska J, Orysiak J, Majorczyk E, et al. HIF-1α and NFIA-AS2 polymorphisms as potential determinants of total hemoglobin mass in endurance athletes. *J Strength Cond Res*. 2022;36(6):1596–1604. doi: 10.1519/JSC.0000000000003686
44. Ipekoglu G, Cetin T, Apaydin N, et al. The role of AGT, AMPD1, HIF1α, IL-6 gene polymorphisms in the athletes' power status: A meta-analysis. *J Hum Kinet*. 2023;89:77–87. doi: 10.5114/jhk/169262
45. Vadapalli S, Rani HS, Sastry B, Nallari P. Endothelin-1 and endothelial nitric oxide polymorphisms in idiopathic pulmonary arterial hypertension. *Int J Mol Epidemiol Genet*. 2010;1(3):208–213. doi: 10.1007/s12041-011-0008-7
46. Tobe SW, Baker B, Hunter K, et al. The impact of endothelin-1 genetic analysis and job strain on ambulatory blood pressure. *J Psychosom Res*. 2011;71(2):97–101. doi: 10.1016/j.jpsychores.2011.01.003
47. Ahmed M, Rghigh A. Polymorphism in Endothelin-1 gene: An overview. *Curr Clin Pharmacol*. 2016;11(3):191–210. doi: 10.2174/1574884711666160701000900
48. Yu J, Liu C, Zhang C, et al. EDN1 gene potentially involved in the development of acute mountain sickness. *Sci Rep*. 2020;10(1):5414. doi: 10.1038/s41598-020-62379-z
49. Scheinfeldt LB, Soi S, Thompson S, et al. Genetic adaptation to high altitude in the Ethiopian highlands. *Genome Biol*. 2012;13(1):R1. doi: 10.1186/gb-2012-13-1-r1
50. Alkorta-Aranburu G, Beall CM, Witonsky DB, et al. The genetic architecture of adaptations to high altitude in Ethiopia. *PLoS Genet*. 2012;8(12):e1003110. doi: 10.1371/journal.pgen.1003110
51. Getu A. Ethiopian native highlander's adaptation to chronic high-altitude hypoxia. *Biomed Res Int*. 2022;2022:5749382. doi: 10.1155/2022/5749382
52. Hirsilä M, Koivunen P, Günzler V, et al. Characterization of the human prolyl 4-hydroxylases that modify the hypoxia-inducible factor. *Biol Chem*. 2003;278(33):30772–30780. doi: 10.1074/jbc.M304982200
53. Epstein AC, Gleadle JM, McNeill LA, et al. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. *Cell*. 2001;107(1):43–54. doi: 10.1016/s0092-8674(01)00507-4
54. Metzen E, Berchner-pfannschmidt U, Stengel P, et al. Intracellular localisation of human HIF-1 alpha hydroxylases: implications for oxygen sensing. *Cell Sci*. 2002;116(7):1319–1326. doi: 10.1242/jcs.00318
55. Cioffi CL, Liu XQ, Kosinski PA, et al. Differential regulation of HIF-1 alpha prolyl-4-hydroxylase genes by hypoxia in human cardiovascular cells. *Biochem Biophys Res Commun*. 2003;303(3):947–953. doi: 10.1016/s0006-291x(03)00453-4
56. Naranjo-Suárez S, Castellanos MC, Alvarez-Tejado M, et al. Down-regulation of hypoxia-inducible factor-2 in PC12 cells by nerve growth factor stimulation. *J Biol Chem*. 2003;278(34):31895–31901. doi: 10.1074/jbc.M304079200
57. Lopez-Mosqueda J, Maddi K, Prgomet S, et al. SPRTN is a mammalian DNA-binding metalloprotease that resolves DNA-protein crosslinks. *Elife*. 2016;5:e21491. doi: 10.7554/eLife.21491
58. Julian CG, Pedersen BS, Salmon CS, et al. Unique DNA methylation patterns in offspring of hypertensive pregnancy. *Clin Transl Sci*. 2015;8(6):740–745. doi: 10.1111/cts.12346
59. Julian CG. Epigenomics and human adaptation to high altitude. *J Appl Physiol*. 2017;123(5):1362–1370. doi: 10.1152/japplphysiol.00351.2017

60. Childebayeva A, Jones TR, Goodrich JM, et al. LINE-1 and EPAS1 DNA methylation associations with high-altitude exposure. *Epigenetics*. 2019;14(1):1–15. doi: 10.1080/15592294.2018.1561117
61. Childebayeva A, Goodrich JM, Leon-Velarde F, et al. Genome-wide epigenetic signatures of adaptive developmental plasticity in the Andes. *Genome Biol Evol*. 2021;13(2):evaa239. doi: 10.1093/gbe/evaa239
62. Peng Y, Cui C, He Y, et al. Down-regulation of EPAS1 transcription and genetic adaptation of Tibetans to high-altitude hypoxia. *Mol Biol Evol*. 2017;34(4):818–830. doi: 10.1093/molbev/msw280
63. Gonzales GF, Chaupis D. Higher androgen bioactivity is associated with excessive erythrocytosis and chronic mountain sickness in Andean Highlanders: a review. *Andrologia*. 2015;47(7):729–743. doi: 10.1111/and.12359
64. West JB. Physiological effects of chronic hypoxia. *N Engl J Med*. 2017;376(20):1965–1971. doi: 10.1056/NEJMra1612008
65. Gao Y-M, Han G-X, Xue C-H, et al. Expression of key enzymes in glucose metabolism in chronic mountain sickness and its correlation with phenotype. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2023;31(1):197–202. doi: 10.19746/j.cnki.issn.1009-2137.2023.01.031
66. Zhang P, Li Z, Yang F, et al. Novel insights into plasma biomarker candidates in patients with chronic mountain sickness based on proteomics. *Biosci Rep*. 2021;41(1):BSR20202219. doi: 10.1042/BSR20202219
67. Villafuerte FC, Corante N. Chronic mountain sickness: Clinical aspects, etiology, management, and treatment. *High Alt Med Biol*. 2016;17(2):61–69. doi: 10.1089/ham.2016.0031
68. León-Velarde F, Richalet JP. Respiratory control in residents at high altitude: physiology and pathophysiology. *High Alt Med Biol*. 2006;7(2):125–137. doi: 10.1089/ham.2006.7.125
69. Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. *PNAS USA*. 2007;104(S1):8655–8660. doi: 10.1073/pnas.0701985104
70. Tremblay JC, Hoiland RL, Carter HH, et al. UBC-Nepal expedition: upper and lower limb conduit artery shear stress and flow-mediated dilation on ascent to 5,050 m in lowlanders and Sherpa. *Am J Physiol Heart Circ Physiol*. 2018;315(6):H1532–H1543. doi: 10.1152/ajpheart.00345.2018
71. Richalet J-P, Hermand E, Lhuissier FJ. Cardiovascular physiology and pathophysiology at high altitude. *Nat Rev Cardiol*. 2024;21(2):75–88. doi: 10.1038/s41569-023-00924-9
72. León-Velarde F, Villafuerte FC, Richalet JP. Chronic mountain sickness and the heart. *Prog Cardiovasc Dis*. 2010;52(6):540–549. doi: 10.1016/j.pcad.2010.02.012
73. Doutreleau S, Ulliel-Roche M, Hancco I, et al. Cardiac remodelling in the highest city in the world: effects of altitude and chronic mountain sickness. *Eur J Prev Cardiol*. 2022;29(17):2154–2162. doi: 10.1093/eurjpc/zwac166
74. Bailey DM, Brugniaux JV, Filipponi T, et al. Exaggerated systemic oxidative-inflammatory-nitrosative stress in chronic mountain sickness is associated with cognitive decline and depression. *J Physiol*. 2019;597(2):611–629. doi: 10.1113/JP276898
75. Shanjun Z, Shenwei X, Bin X, et al. Individual chronic mountain sickness symptom is an early warning sign of cognitive impairment. *Physiol Behav*. 2020;214:112748. doi: 10.1016/j.physbeh.2019.112748
76. Thiersch M, Swenson ER. High altitude and cancer mortality. *High Alt Med Biol*. 2018;19(2):116–123. doi: 10.1089/ham.2017.0061
77. San Martin R, Brito J, Siques P, León-Velarde F. Obesity as a conditioning factor for high-altitude diseases. *Obes Facts*. 2017;10(4):363–372. doi: 10.1159/000477461
78. Ortiz-Prado E, Portilla D, Mosquera-Moscoso J, et al. Hematological parameters, lipid profile, and cardiovascular risk analysis among genotype-controlled indigenous Kiwcha men and women living at low and high altitudes. *Front Physiol*. 2021;12:749006. doi: 10.3389/fphys.2021.749006
79. Kang J-G, Sung HJ, Amar MJ, et al. Low ambient oxygen prevents atherosclerosis. *J Mol Med (Berl)*. 2016;94(3):277–286. doi: 10.1007/s00109-016-1386-3
80. Beall CM. Tibetan and Andean patterns of adaptation to high-altitude hypoxia. *Hum Biol*. 2000;72(1):201–228.
81. Yao H, Zhao H, Wang J, Haddad GG. Intracellular pH regulation in iPSCs-derived astrocytes from subjects with chronic mountain sickness. *Neuroscience*. 2018;375:25–33. doi: 10.1016/j.neuroscience.2018.02.008
82. Liu H, Tang F, Su J, et al. EPAS1 regulates proliferation of erythroblasts in chronic mountain sickness. *Blood Cells Mol Dis*. 2020;84:102446. doi: 10.1016/j.bcmd.2020
83. Tegako LI, Kmetinsky E. *Anthropology: Textbook*. Moscow: New Knowledge; 2004. (In Russ.)
84. Alekseev VP. *Geography of human races*. Moscow: Mysl; 1974. 351 p. (In Russ.)
85. Rychkov YuG. *Anthropology and genetics of isolated populations (ancient isolates of the Pamirs)*. Moscow: MSU Publishing House; 1969. 222 p. (In Russ.)
86. Alekseeva TH. *Adaptive processes in human populations*. Moscow: MSU Publishing House; 1986. 215 p. (In Russ.)
87. Alekseeva TH. *Human adaptation in different ecological niches (biological aspects)*. Moscow: MNEPU Publishing House; 1998. 283 p. (In Russ.)
88. Alekseev VP. *Essays on human ecology*. Moscow: Nauka; 1993. 191 p. (In Russ.)
89. Bunak VV. Climato-zonal and ethnic differences in facial and head structure in the indigenous population of North Asia (in connection with the problem of adaptation). In: Barbashova ZI, Likhnitska AI, editors. *Human adaptation*. Leningrad: Nauka; 1972. (In Russ.)
90. Spitsyn VA. *Ecological genetics*. Moscow: Nauka; 2008. 502 p. (In Russ.)
91. Lordkipanidze D, Jashashvili T, Vekua A, et al. Postcranial evidence from early Homo from Dmanisi, Georgia. *Nature*. 2007;449(7160):305–310. doi: 10.1038/nature06134
92. Adler DS, Bar-Yosef O, Belfer-Cohen A, et al. Dating the demise: neandertal extinction and the establishment of modern humans in the Southern Caucasus. *J Hum Evol*. 2008;55(5):817–833. doi: 10.1016/j.jhevol.2008.08.010
93. Yeakel JD, Guimarães PR, Bocherens H, Koch PL. The impact of climate change on the structure of Pleistocene food webs across the mammoth steppe. *Proc R Soc B*. 2013;280(1762):20130239. doi: 10.1098/rspb.2013.0239

94. Tallavaara M, Luoto M, Korhonen N, et al. Human population dynamics in Europe over the Last Glacial Maximum. *PNAS*. 2015;112(27):8232–8237. doi: 10.1073/pnas.1503784112
95. Mongait AL. *Archaeology of Western Europe. Stone Age*. Moscow: Nauka; 1973. 355 p. (In Russ.)
96. Stewart JR, Stringer CB. Human evolution out of Africa: The role of refugia and climate change. *Science*. 2012;335(6074):1317–1321. doi: 10.1126/science.1215627
97. Yunusbayev B, Metspalu M, Jarve M, et al. The Caucasus as an asymmetric semipermeable barrier to ancient human migrations. *Mol Biol Evol*. 2012;29(1):359–365. doi: 10.1093/molbev/msr221
98. Platt DE, Haber M, Dagher-Kharrat MB, et al. Mapping postglacial expansions: The peopling of Southwest Asia. *Sci Rep*. 2017;6(7):40338. doi: 10.1038/srep40338
99. Burnley C, Lang D. *The Ancient Caucasus. From the prehistoric settlements of Anatolia to the Christian Kingdoms of the Early Middle Ages*. Saint Petersburg: Centerpoligraf; 2016. (In Russ.)
100. Miziev IM. *History of Balkaria and Karachay from the most ancient times to the campaigns of Timur*. Nalchik: El-Fa; 1996. (In Russ.)
101. Yanin VL, editor. *Archaeology: Textbook*. Moscow: MSU Publishing House; 2006. 608 p. (In Russ.)
102. Martynov AI. *Archaeology*. Moscow: Vyshaya Shkola; 2005. 447 p. (In Russ.)
103. Ryndina NV, Ravich IG. On metal production of the Maikop tribes of the North Caucasus (on the data of chemical-technological studies). *Vestnik arheologii, antropologii i etnografii*. 2012;(2):4–20. (In Russ.) EDN: PBHERF
104. Erdniev UE. The main results of the archaeological study of Southern Kalmykia. In: Erdniev UE, editor. *Theses of reports of IX Krupnov readings on archeology of the Caucasus*. Elista: Kalmyk State University; 1979. (In Russ.)
105. Batchaev VM. *Burial monuments near the villages of Lechinkai and Bylym. Archaeological research on new buildings in Kabardino-Balkaria*. Nalchik; 1984. (In Russ.)
106. Markovin VI. *Culture of the tribes of the North Caucasus in the Bronze Age (II millennium BC)*. Moscow: Publishing House of the Academy of Sciences of the USSR; 1960. 148 p. (In Russ.)
107. Ivanchik AI. *Cimmerians. Ancient Eastern Civilizations and Steppe Nomads in the VIII–VII centuries B.C*. Moscow: Institute of General History; 1996. 324 p. (In Russ.)
108. Artamonov MI. *History of the Khazars*. Saint Petersburg: Faculty of Philosophy, SPbSU; 2002. 549 p. (In Russ.)
109. Brook KA. *The jews of Khazaria. 2nd edit*. Plymouth: Rowman and Littlefield Publishers; 2006. 315 p.
110. Tishkov VA, editor. *Socio-political history of the North Caucasus (before the collapse of the USSR)*. Moscow: IEA RAS; 2015. 89 p. (In Russ.)
111. Khit GL. Dermatoglyphics and the Rasogenesis of the Caucasian Population. Ancient Caucasus: retrospection of cultures. In: *XXIV Krupnov Readings on the Archaeology of the North Caucasus*. Moscow; 2004. P. 198–200. (In Russ.)
112. Dzhaubermezov MA, Ekomasova NV, Khusainova RI, et al. Genetic characterization of Balkars and Karachays according to the variability of the Y chromosome. *Russian Journal of Genetics*. 2017;53(10): 1224–1231. EDN: ZIDOIL doi: 10.7868/S0016675817100034
113. Dzhaubermezov MA, Ekomasova NV, Gabidullina LR, et al. Genetic characterization of Bbalkars and Karachays using MTDNA data. *Russian Journal of Genetics*. 2019;55(1):110–120. EDN: YUBAFF doi: 10.1134/S0016675819010053
114. Kutuev IA, Khusnutdinova EK. *Genetic structure and molecular phylogeography of the peoples of Eurasia*. Ufa: Gilem; 2011. 240 p. (In Russ.)

СПИСОК ЛИТЕРАТУРЫ

1. Науменко С.Е. Горная болезнь: учебное пособие. Новосибирск: ИПЦ НГУ, 2018. 72 с.
2. Hackett P.H., Roach R.C. High-altitude illness // N Engl J Med. 2001. Vol. 345, N 2. P. 107–114. doi: 10.1056/NEJM200107123450206
3. Burtscher M., Hefti U., Hefti J.P. High-altitude illnesses: Old stories and new insights into the pathophysiology, treatment and prevention // Sport Med Health Sci. 2021. Vol. 3, N 2. P. 59–69. doi: 10.1016/j.smhs.2021.04.001
4. Bigham A.W., Lee F.S. Human high-altitude adaptation: forward genetics meets the HIF pathway // Genes Dev. 2014. Vol. 28, N 20. P. 2189–2204. doi: 10.1101/gad.250167.114
5. Paralikar S.J., Paralikar J.H. High-altitude medicine // Indian J Occup Environ Med. 2010. Vol. 14, N 1. P. 6–12. doi: 10.4103/0019-5278.64608
6. Tremblay J.C., Ainslie P.N. Global and country-level estimates of human population at high altitude // PNAS USA. 2021. Vol. 118, N 18. ID e2102463118. doi: 10.1073/pnas.2102463118
7. Aldenderfer M. Modelling plateau peoples: The early human use of the world's high plateau // World Archaeol. 2007. Vol. 38, N 3. P. 357–370. doi: 10.1080/00438240600813285
8. Zhang X.L., Ha B.B., Wang S.J., et al. The earliest human occupation of the high-altitude Tibetan Plateau 40 thousand to 30 thousand years ago // Science. 2018. Vol. 362, N 6418. P. 1049–1051. doi: 10.1126/science.aat8824
9. Rademaker K., Hodgins G., Moore K., et al. Paleoindian settlement of the high-altitude Peruvian Andes // Science. 2014. Vol. 346, N 6208. P. 466–469. doi: 10.1126/science.1258260
10. Мунчаев Р.М. Кавказ на заре бронзового века. Москва: Наука, 1974. 416 с.
11. Живописная Россия. Кавказ. Т. IX / под ред. П.П. Семенова. Санкт-Петербург, Москва: Издание Т-ва М.О. Вольф, 1883. С. II.
12. Сборник материалов, относящихся к истории Золотой Орды. Т. II: Извлечения из персидских сочинений / под ред. Г. Тизенгаузена. 1941. С. 181.
13. Гвоздецкий Н.А. Кавказ. Очерк природы. Москва: Географгиз, 1963. 262 с.
14. Материалы научной сессии по проблеме происхождения балкарского и карачаевского народов; Июнь 22–26, 1959 г. / под

ред. И.В. Трескова. Нальчик: Кабардино-Балкарское книжное издательство, 1960.
15. Карачаевцы. Балкарцы / под ред. М.Д. Каракетова, Х.-М.А. Сабанчиева. Москва: Наука, 2014. 815 с.
16. Алексеев В.П. Происхождение народов Кавказа. Краниологическое исследование. Москва: Наука, 1974. 317 с.
17. rosstat.gov.ru [Электронный ресурс]. Федеральная служба государственной статистики [дата обращения: 04.04.2024]. Режим доступа: https://rosstat.gov.ru/
18. topographic-map.com [Электронный ресурс]. Федеральная служба государственной статистики [дата обращения: 01.04.2024]. Режим доступа: https://ru-ru.topographic-map.com/
19. Мизиев И.М. Следы на Эльбрусе. Карачаевск: КЧГПУ, 2001. 184 с.
20. Brutsaert T.D., Kiyamu M., Elias Revollendo G., et al. Association of EGLN1 gene with high aerobic capacity of Peruvian Quechua at high altitude // PNAS USA. 2019. Vol. 116, N 48. P. 24006–24011. doi: 10.1073/pnas.1906171116
21. Heinrich E.C., Wu L., Lawrence E.S., et al. Genetic variants at the EGLN1 locus associated with high-altitude adaptation in Tibetans are absent or found at low frequency in highland Andeans // Ann Hum Genet. 2019. Vol. 83, N 3. P. 171–176. doi: 10.1111/ahg.12299
22. Bigham A., Bauchet M., Pinto D., et al. Identifying signatures of natural selection in Tibetan and Andean populations using dense genome scan data // PLoS Genet. 2010. Vol. 6, N 9. ID e1001116. doi: 10.1371/journal.pgen.1001116
23. Bigham A.W., Wilson M.J., Julian C.G., et al. Andean and Tibetan patterns of adaptation to high altitude // Am J Hum Biol. 2013. Vol. 25, N 2. P. 190–197. doi: 10.1002/ajhb.22358
24. Pagani L., Ayub Q., MacArthur D.G., et al. High altitude adaptation in Daghestani populations from the Caucasus // Hum Genet. 2012. Vol. 131, N 3. P. 423–433. doi: 10.1007/s00439-011-1084-8
25. Lessel D., Vaz B., Halder S., et al. Mutations in SPRTN cause early onset hepatocellular carcinoma, genomic instability and progeroid features // Nat Genet. 2014. Vol. 46, N 11. P. 1239–1244. doi: 10.1038/ng.3103
26. Wu B., Guo W. The exocyst at a glance // J Cell Sci. 2015. Vol. 128, N 16. P. 2957–2964. doi: 10.1242/jcs.156398
27. Rajput C., Arif E., Vibhuti A., et al. Predominance of interaction among wild-type alleles of CYP11B2 in Himalayan natives associates with high-altitude adaptation // Biochem Biophys Res Commun. 2006. Vol. 348, N 2. P. 735–740. doi: 10.1016/j.bbrc.2006.07.116
28. Mallet R.T., Burtscher J., Pialoux V., et al. Molecular mechanisms of high-altitude acclimatization // Int J Mol Sci. 2023. Vol. 24, N 2. ID 1698. doi: 10.3390/ijms24021698
29. Ahsan A., Norboo T., Baig M.A., Qadar Pasha M.A. Simultaneous selection of the wild-type genotypes of the G894T and 4B/4A polymorphisms of NOS3 associate with high-altitude adaptation // Ann Hum Genet. 2005. Vol. 69, N 3. P. 260–267. doi: 10.1046/j.1529-8817.2005.00158.x
30. Droma Y., Hanaoka M., Basnyat B., et al. Genetic contribution of the endothelial nitric oxide synthase gene to high altitude adaptation in Sherpas // High Alt Med Biol. 2006. Vol. 7, N 3. P. 209–220. doi: 10.1089/ham.2006.7.209
31. Liu L., Zhang Y., Zhang Z., et al. Associations of high altitude polycythemia with polymorphisms in EPHA2 and AGT in Chinese Han and Tibetan populations // Oncotarget. 2017. Vol. 8, N 32. P. 53234–53243. doi: 10.18632/oncotarget.18384
32. Dijkstra A.E., Postma D.S., van Ginneken B., et al. Novel genes for airway wall thickness identified with combined genome-wide association and expression analyses // Am J Respir Crit Care Med. 2015. Vol. 191, N 5. P. 547–556. doi: 10.1164/rccm.201405-0840OC
33. Oshima N., Onimaru H., Yamagata A., et al. Erythropoietin, a putative neurotransmitter during hypoxia, is produced in RVLM neurons and activates them in neonatal Wistar rats // Am J Physiol Regul Integr Comp Physiol. 2018. Vol. 314, N 5. P. R700–R708. doi: 10.1152/ajpregu.00455.2017
34. Silverman E.K. Genetics of COPD // Annu Rev Physiol. 2020. Vol. 82. P. 413–431. doi: 10.1146/annurev-physiol-021317-121224
35. Dmytriiev K., Mostovoy Y., Slepchenko N., Smereka Y. Clinical course of COPD in patients with Arg16Gly (rs1042713) polymorphism of ADRB2 gene // Monaldi Arch Chest Dis. 2022. Vol. 93, N 2. ID 2314. doi: 10.4081/monaldi.2022.2314
36. Wang Y., Li Z., Zhang X., et al. EPO rs1617640 A>C is a protective factor for chronic obstructive pulmonary disease: A case control study // Front Biosci (Landmark Ed). 2023. Vol. 28, N 9. ID 215. doi: 10.31083/j.fbl2809215
37. Young J.M., Williams D.R., Thompson A.A.R. Thin air, thick vessels: historical and current perspectives on hypoxic pulmonary hypertension // Front Med (Lausanne). 2019. Vol. 6. ID 93. doi: 10.3389/fmed.2019.00093
38. Wang N., Hua J., Fu Y., et al. Updated perspective of EPAS1 and the role in pulmonary hypertension // Front Cell Dev Biol. 2023. Vol. 11. ID 1125723. doi: 10.3389/fcell.2023.1125723
39. Yi X., Liang Y., Huerta-Sanchez E., et al. Sequencing of 50 human exomes reveals adaptation to high altitude // Science. 2010. Vol. 329, N 5987. P. 75–78. doi: 10.1126/science.1190371
40. Huerta-Sánchez E., Casey F.P. Archaic inheritance: Supporting high-altitude life in Tibet // J Appl Physiol (1985). 2015. Vol. 119, N 10. P. 1129–1134. doi: 10.1152/japplphysiol.00322.2015
41. Zhang X., Witt K.E., Bañuelos M.M., et al. The history and evolution of the Denisovan-EPAS1 haplotype in Tibetans // PNAS USA. 2021. Vol. 118, N 22. ID e2020803118. doi: 10.1073/pnas.2020803118
42. Döring F., Onur S., Fischer A., et al. A common haplotype and the Pro582Ser polymorphism of the hypoxia-inducible factor-1alpha (HIF1A) gene in elite endurance athletes // J Appl Physiol (1985). 2010. Vol. 108, N 6. P. 1497–500. doi: 10.1152/japplphysiol.01165.2009
43. Malczewska-Lenczowska J., Orysiak J., Majorczyk E., et al. HIF-1α and NFIA-AS2 polymorphisms as potential determinants of total hemoglobin mass in endurance athletes // J Strength Cond Res. 2022. Vol. 36, N 6. P. 1596–1604. doi: 10.1519/JSC.0000000000003686
44. Ipekoglu G., Cetin T., Apaydin N., et al. The role of AGT, AMPD1, HIF1α, IL-6 gene polymorphisms in the athletes' power status: A meta-analysis // J Hum Kinet. 2023. Vol. 89. P. 77–87. doi: 10.5114/jhk/169262
45. Vadapalli S., Rani H.S., Sastry B., Nallari P. Endothelin-1 and endothelial nitric oxide polymorphisms in idiopathic pulmonary arterial hypertension // Int J Mol Epidemiol Genet. 2010. Vol. 1, N 3. P. 208–213. doi: 10.1007/s12041-011-0008-7

46. Tobe S.W., Baker B., Hunter K., et al. The impact of endothelin-1 genetic analysis and job strain on ambulatory blood pressure // J Psychosom Res. 2011. Vol. 71, N 2. P. 97–101. doi: 10.1016/j.jpsychores.2011.01.003
47. Ahmed M., Rghigh A. Polymorphism in Endothelin-1 gene: An overview // Curr Clin Pharmacol. 2016. Vol. 11, N 3. P. 191–210. doi: 10.2174/1574884711666160701000900
48. Yu J., Liu C., Zhang C., et al. EDN1 gene potentially involved in the development of acute mountain sickness // Sci Rep. 2020. Vol. 10, N 1. ID 5414. doi: 10.1038/s41598-020-62379-z
49. Scheinfeldt L.B., Soi S., Thompson S., et al. Genetic adaptation to high altitude in the Ethiopian highlands // Genome Biol. 2012. Vol. 13, N 1. ID R1. doi: 10.1186/gb-2012-13-1-r1
50. Alkorta-Aranburu G., Beall C.M., Witonsky D.B., et al. The genetic architecture of adaptations to high altitude in Ethiopia // PLoS Genet. 2012. Vol. 8, N 12. ID e1003110. doi: 10.1371/journal.pgen.1003110
51. Getu A. Ethiopian native highlander's adaptation to chronic high-altitude hypoxia // Biomed Res Int. 2022. Vol. 2022. ID 5749382. doi: 10.1155/2022/5749382
52. Hirsilä M., Koivunen P., Günzler V., et al. Characterization of the human prolyl 4-hydroxylases that modify the hypoxia-inducible factor // Biol Chem. 2003. Vol. 278, N 33. P. 30772–30780. doi: 10.1074/jbc.M304982200
53. Epstein A.C., Gleadle J.M., McNeill L.A., et al. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation // Cell. 2001. Vol. 107, N 1. P. 43–54. doi: 10.1016/s0092-8674(01)00507-4
54. Metzen E., Berchner-Pfannschmidt U., Stengel P., et al. Intracellular localisation of human HIF-1 alpha hydroxylases: implications for oxygen sensing // Cell Sci. 2002. Vol. 116, N 7. P. 1319–1326. doi: 10.1242/jcs.00318
55. Cioffi C.L., Liu X.Q., Kosinski P.A., et al. Differential regulation of HIF-1 alpha prolyl-4-hydroxylase genes by hypoxia in human cardiovascular cells // Biochem Biophys Res Commun. 2003. Vol. 303, N 3. P. 947–953. doi: 10.1016/s0006-291x(03)00453-4
56. Naranjo-Suárez S., Castellanos M.C., Alvarez-Tejado M., et al. Down-regulation of hypoxia-inducible factor-2 in PC12 cells by nerve growth factor stimulation // J Biol Chem. 2003. Vol. 278, N 34. P. 31895–31901. doi: 10.1074/jbc.M304079200
57. Lopez-Mosqueda J., Maddi K., Prgomet S., et al. SPRTN is a mammalian DNA-binding metalloprotease that resolves DNA-protein crosslinks // Elife. 2016. Vol. 5. ID e21491. doi: 10.7554/eLife.21491
58. Julian C.G., Pedersen B.S., Salmon C.S., et al. Unique DNA methylation patterns in offspring of hypertensive pregnancy // Clin Transl Sci. 2015. Vol. 8, N 6. P. 740–745. doi: 10.1111/cts.12346
59. Julian C.G. Epigenomics and human adaptation to high altitude // J Appl Physiol. 2017. Vol. 123, N 5. P. 1362–1370. doi: 10.1152/japplphysiol.00351.2017
60. Childebayeva A., Jones T.R., Goodrich J.M., et al. LINE-1 and EPAS1 DNA methylation associations with high-altitude exposure // Epigenetics. 2019. Vol. 14, N 1. P. 1–15. doi: 10.1080/15592294.2018.1561117
61. Childebayeva A., Goodrich J.M., Leon-Velarde F., et al. Genome-wide epigenetic signatures of adaptive developmental plasticity in the Andes // Genome Biol Evol. 2021. Vol. 13, N 2. ID evaa239. doi: 10.1093/gbe/evaa239
62. Peng Y., Cui C., He Y., et al. Down-regulation of EPAS1 transcription and genetic adaptation of Tibetans to high-altitude hypoxia // Mol Biol Evol. 2017. Vol. 34, N 4. P. 818–830. doi: 10.1093/molbev/msw280
63. Gonzales G.F., Chaupis D. Higher androgen bioactivity is associated with excessive erythrocytosis and chronic mountain sickness in Andean Highlanders: a review // Andrologia. 2015. Vol. 47, N 7. P. 729–743. doi: 10.1111/and.12359
64. West J.B. Physiological effects of chronic hypoxia // N Engl J Med. 2017. Vol. 376, N 20. P. 1965–1971. doi: 10.1056/NEJMra1612008
65. Gao Y.-M., Han G.-X., Xue C.-H., et al. Expression of key enzymes in glucose metabolism in chronic mountain sickness and its correlation with phenotype // Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2023. Vol. 31, N 1. P. 197–202. doi: 10.19746/j.cnki.issn.1009-2137.2023.01.031
66. Zhang P., Li Z., Yang F., et al. Novel insights into plasma biomarker candidates in patients with chronic mountain sickness based on proteomics // Biosci Rep. 2021. Vol. 41, N 1. ID BSR20202219. doi: 10.1042/BSR20202219
67. Villafuerte F.C., Corante N. Chronic mountain sickness: Clinical aspects, etiology, management, and treatment // High Alt Med Biol. 2016. Vol. 17, N 2. P. 61–69. doi: 10.1089/ham.2016.0031
68. León-Velarde F., Richalet J.P. Respiratory control in residents at high altitude: physiology and pathophysiology // High Alt Med Biol. 2006. Vol. 7, N 2. P. 125–137. doi: 10.1089/ham.2006.7.125
69. Beall C.M. Two routes to functional adaptation: Tibetan and Andean high-altitude natives // PNAS USA. 2007. Vol. 104, N S1. P. 8655–8660. doi: 10.1073/pnas.0701985104
70. Tremblay J.C., Hoiland R.L., Carter H.H., et al. UBC-Nepal expedition: upper and lower limb conduit artery shear stress and flow-mediated dilation on ascent to 5,050 m in lowlanders and Sherpa // Am J Physiol Heart Circ Physiol. 2018. Vol. 315, N 6. P. H1532–H1543. doi: 10.1152/ajpheart.00345.2018
71. Richalet J.-P., Hermand E., Lhuissier F.J. Cardiovascular physiology and pathophysiology at high altitude // Nat Rev Cardiol. 2024. Vol. 21, N 2. P. 75–88. doi: 10.1038/s41569-023-00924-9
72. León-Velarde F., Villafuerte F.C., Richalet J.P. Chronic mountain sickness and the heart // Prog Cardiovasc Dis. 2010. Vol. 52, N 6. P. 540–549. doi: 10.1016/j.pcad.2010.02.012
73. Doutreleau S., Ulliel-Roche M., Hancco I., et al. Cardiac remodelling in the highest city in the world: effects of altitude and chronic mountain sickness // Eur J Prev Cardiol. 2022. Vol. 29, N 17. P. 2154–2162. doi: 10.1093/eurjpc/zwac166
74. Bailey D.M., Brugniaux J.V., Filipponi T., et al. Exaggerated systemic oxidative-inflammatory-nitrosative stress in chronic mountain sickness is associated with cognitive decline and depression // J Physiol. 2019. Vol. 597, N 2. P. 611–629. doi: 10.1113/JP276898
75. Shanjun Z., Shenwei X., Bin X., et al. Individual chronic mountain sickness symptom is an early warning sign of cognitive impairment // Physiol Behav. 2020. Vol. 214. ID 112748. doi: 10.1016/j.physbeh.2019.112748
76. Thiersch M., Swenson E.R. High altitude and cancer mortality // High Alt Med Biol. 2018. Vol. 19, N 2. P. 116–123. doi: 10.1089/ham.2017.0061
77. San Martin R., Brito J., Siques P., León-Velarde F. Obesity as a conditioning factor for high-altitude diseases // Obes Facts. 2017. Vol. 10, N 4. P. 363–372. doi: 10.1159/000477461

78. Ortiz-Prado E., Portilla D., Mosquera-Moscoso J., et al. Hematological parameters, lipid profile, and cardiovascular risk analysis among genotype-controlled indigenous Kiwcha men and women living at low and high altitudes // Front Physiol. 2021. Vol. 12. ID 749006. doi: 10.3389/fphys.2021.749006
79. Kang J.-G., Sung H.J., Amar M.J., et al. Low ambient oxygen prevents atherosclerosis // J Mol Med (Berl). 2016. Vol. 94, N 3. P. 277–286. doi: 10.1007/s00109-016-1386-3
80. Beall C.M. Tibetan and Andean patterns of adaptation to high-altitude hypoxia // Hum Biol. 2000. Vol. 72, N 1. P. 201–228.
81. Yao H., Zhao H., Wang J., Haddad G.G. Intracellular pH regulation in iPSCs-derived astrocytes from subjects with chronic mountain sickness // Neuroscience. 2018. Vol. 375. P. 25–33. doi: 10.1016/j.neuroscience.2018.02.008
82. Liu H., Tang F., Su J., et al. EPAS1 regulates proliferation of erythroblasts in chronic mountain sickness // Blood Cells Mol Dis. 2020. Vol. 84. ID 102446. doi: 10.1016/j.bcmd.2020
83. Тегако Л.И., Кметинский Е. Антропология: Учебное пособие. Москва: Новое знание, 2004.
84. Алексеев В.П. География человеческих рас. Москва: Мысль, 1974. 351 с.
85. Рычков Ю.Г. Антропология и генетика изолированных популяций (древние изоляты Памира). Москва: Издательство МГУ, 1969. 222 с.
86. Алексеева Т.И. Адаптивные процессы в популяциях человека. Москва: Издательство МГУ, 1986. 215 с.
87. Алексеева Т.И. Адаптация человека в различных экологических нишах (биологические аспекты). Москва: Издательство МНЭПУ, 1998. 283 с.
88. Алексеев В.П. Очерки экологии человека. Москва: Наука, 1993. 191 с.
89. Бунак В.В. Климато-зональные и этнические различия в строении лица и головы у коренного населения Северной Азии (в связи с проблемой адаптации). В кн.: Адаптация человека / под ред. З.И. Барбашовой, И.И. Лихницкой. Ленинград: Наука, 1972.
90. Спицын В.А. Экологическая генетика. Москва: Наука, 2008. 502 с.
91. Lordkipanidze D., Jashashvili T., Vekua A., et al. Postcranial evidence from early Homo from Dmanisi, Georgia // Nature. 2007. Vol. 449, N 7160. P. 305–310. doi: 10.1038/nature06134
92. Adler D.S., Bar-Yosef O., Belfer-Cohen A., et al. Dating the demise: neandertal extinction and the establishment of modern humans in the Southern Caucasus // J Hum Evol. 2008. Vol. 55, N 5. P. 817–833. doi: 10.1016/j.jhevol.2008.08.010
93. Yeakel J.D., Guimarães P.R., Bocherens H., Koch P.L. The impact of climate change on the structure of Pleistocene food webs across the mammoth steppe // Proc R Soc B. 2013. Vol. 280, N 1762. ID 20130239. doi: 10.1098/rspb.2013.0239
94. Tallavaara M., Luoto M., Korhonen N., et al. Human population dynamics in Europe over the Last Glacial Maximum // PNAS. 2015. Vol. 112, N 27. P. 8232–8237. doi: 10.1073/pnas.1503784112
95. Монгайт А.Л. Археология Западной Европы. Каменный век. Москва: Наука, 1973. 355 с.
96. Stewart J.R., Stringer C.B. Human evolution out of Africa: The role of refugia and climate change // Science. 2012. Vol. 335, N 6074. P. 1317–1321. doi: 10.1126/science.1215627
97. Yunusbayev B., Metspalu M., Jarve M., et al. The Caucasus as an asymmetric semipermeable barrier to ancient human migrations // Mol Biol Evol. 2012. Vol. 29, N 1. P. 359–365. doi: 10.1093/molbev/msr221
98. Platt D.E., Haber M., Dagher-Kharrat M.B., et al. Mapping postglacial expansions: The peopling of Southwest Asia // Sci Rep. 2017. Vol. 6, N 7. ID 40338. doi: 10.1038/srep40338
99. Бернли Ч., Лэнг Д. Древний Кавказ. От доисторических поселений Анатолии до христианских царств раннего Средневековья. Санкт-Петербург: Центрполиграф, 2016.
100. Мизиев И.М. История Балкарии и Карачая с древнейших времен до походов Тимура. Нальчик: Эль-Фа, 1996.
101. Археология: Учебник / под ред. В.Л. Янина. Москва: Издательство МГУ, 2006. 608 с.
102. Мартынов А.И. Археология. Москва: Высшая школа, 2005. 447 с.
103. Рындина Н.В., Равич И.Г. О металлопроизводстве майкопских племен Северного Кавказа (по данным химико-технологических исследований) // Вестник археологии, антропологии и этнографии. 2012. № 2. С. 4–20. EDN: PBHERF
104. Эрдниев У.Э. Основные итоги археологического изучения Южной Калмыкии. В кн.: Тезисы докладов IX Крупновских чтений по археологии Кавказа / под ред. У.Э. Эрдниева. Элиста: Калмыцкий государственный университет, 1979.
105. Батчаев В.М. Погребальные памятники у селений Лечинкай и Былым. Археологические исследования на новостройках Кабардино-Балкарии. Нальчик, 1984.
106. Марковин В.И. Культура племен Северного Кавказа в эпоху бронзы (II тыс. до н. э.). Москва: Изд-во Академии наук СССР, 1960. 148 с.
107. Иванчик А.И. Киммерийцы. Древневосточные цивилизации и степные кочевники в VIII–VII вв. до н. э. Москва: Институт всеобщей истории, 1996. 324 с.
108. Артамонов М.И. История хазар. Санкт-Петербург: Философский факультет СПбГУ, 2002. 549 с.
109. Brook K.A. The jews of Khazaria. 2nd edit. Plymouth: Rowman and Littlefield Publishers, 2006. 315 p.
110. Социально-политическая история Северного Кавказа (до распада СССР) / под ред. В.А. Тишкова. Москва: ИЭА РАН, 2015. 89 с.
111. Хить Г.Л. Дерматоглифика и расогенез населения Кавказа. Древний Кавказ: ретроспекция культур. В кн.: XXIV Крупновские чтения по археологии Северного Кавказа. Москва, 2004. С. 198–200.
112. Джаубермезов М.А., Екомасова Н.В., Литвинов С.С., и др. Генетическая характеристика балкарцев и карачаевцев по данным об изменчивости Y-хромосомы // Генетика. 2017. Т. 53, № 10. С. 1224–1231. EDN: ZIDOIL doi: 10.7868/S0016675817100034
113. Джаубермезов М.А., Екомасова Н.В., Рейдла М., и др. Генетическая характеристика балкарцев и карачаевцев по данным об изменчивости митохондриальной ДНК // Генетика. 2019. Т. 55, № 1. С. 110–120. EDN: YUBAFF doi: 10.1134/S0016675819010053
114. Кутуев И.А., Хуснутдинова Э.К. Генетическая структура и молекулярная филогеография народов Евразии. Уфа: Гилем, 2011. 240 с.

AUTHORS' INFO

***Murat A. Dzhaubermezov,** Cand. Sci. (Biology);
address: 32 Zaky Validi st., Ufa, 450076, Russia;
ORCID: 0000-0003-1570-3174; eLibrary SPIN: 1066-3369;
e-mail: murat-kbr@mail.ru

Natalia V. Ekomasova, Cand. Sci. (Biology);
ORCID: 0000-0003-3996-5734; eLibrary SPIN: 6528-4117;
e-mail: trofimova_nata_@mail.ru

Rustam N. Mustafin, Cand. Sci. (Biology);
ORCID: 0000-0002-4091-382X; eLibrary SPIN: 4810-2535;
e-mail: ruji79@mail.ru

Ongar S. Chagarov; ORCID: 0000-0002-1857-4163;
eLibrary SPIN: 1455-0797; e-mail: chagarov89@gmail.com

Yuliya Yu. Fedorova, Cand. Sci. (Biology);
ORCID: 0000-0002-9344-828X; eLibrary SPIN: 5497-0441;
e-mail: fedorova-y@yandex.ru

Liliya R. Gabidullina; ORCID: 0009-0007-1575-2642;
eLibrary SPIN: 2799-0206; e-mail: liliya.gab@gmail.com

Alfiya Kh. Nurgalieva, Cand. Sci. (Biology);
ORCID: 0000-0001-6077-9237; eLibrary SPIN: 9658-8010;
e-mail: alfiyakh83@gmail.com

Darya S. Prokofyeva, Cand. Sci. (Biology);
ORCID: 0000-0003-0229-3188; eLibrary SPIN: 7918-4737;
e-mail: dager-glaid@yandex.ru

Elza K. Khusnutdinova, Dr. Sci. (Biology);
ORCID: 0000-0003-2987-3334; eLibrary SPIN: 7408-9797;
e-mail: elzakh@mail.ru

ОБ АВТОРАХ

***Мурат Алиевич Джаубермезов,** канд. биол. наук;
адрес: Россия, 450076, Уфа, ул. Заки Валиди, д. 32;
ORCID: 0000-0003-1570-3174; eLibrary SPIN: 1066-3369;
e-mail: murat-kbr@mail.ru

Наталья Вадимовна Екомасова, канд. биол. наук;
ORCID: 0000-0003-3996-5734; eLibrary SPIN: 6528-4117;
e-mail: trofimova_nata_@mail.ru

Рустам Наилевич Мустафин, канд. биол. наук;
ORCID: 0000-0002-4091-382X; eLibrary SPIN: 4810-2535;
e-mail: ruji79@mail.ru

Онгар Салихович Чагаров; ORCID: 0000-0002-1857-4163;
eLibrary SPIN: 1455-0797; e-mail: chagarov89@gmail.com

Юлия Юрьевна Федорова, канд. биол. наук;
ORCID: 0000-0002-9344-828X; eLibrary SPIN: 5497-0441;
e-mail: fedorova-y@yandex.ru

Лилия Рафисовна Габидуллина; ORCID: 0009-0007-1575-2642;
eLibrary SPIN: 2799-0206; e-mail: liliya.gab@gmail.com

Альфия Хаматьяновна Нургалиева, канд. биол. наук;
ORCID: 0000-0001-6077-9237; eLibrary SPIN: 9658-8010;
e-mail: alfiyakh83@gmail.com

Дарья Симоновна Прокофьева, канд. биол. наук;
ORCID: 0000-0003-0229-3188; eLibrary SPIN: 7918-4737;
e-mail: dager-glaid@yandex.ru

Эльза Камилевна Хуснутдинова, д-р биол. наук;
ORCID: 0000-0003-2987-3334; eLibrary SPIN: 7408-9797;
e-mail: elzakh@mail.ru

* Corresponding author / Автор, ответственный за переписку