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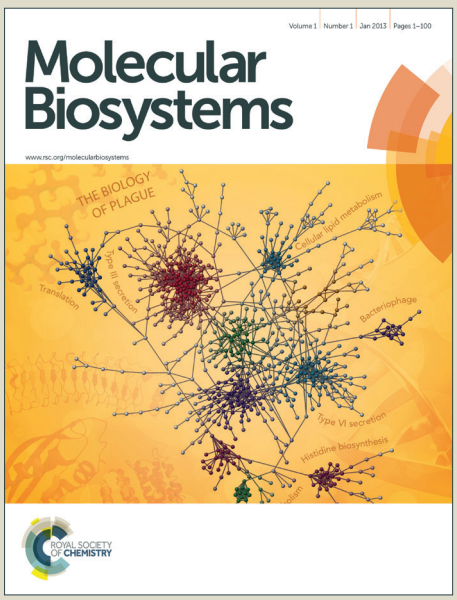

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’Ome on the range: update on high-altitude acclimatization/adaptation and disease

Yongjun Luo[1, 2, 3], Yuxiao Wang[1, 2, 3,4], Hongxiang Lu[1, 2, 3,4], Yuqi Gao [2, 3 *]

[1]Department of Military Medical Geography, Third Military Medical University, Chongqing 400038, China; [2]Key Laboratory of High Altitude Medicine (Ministry of Education), Third Military Medical University, Chongqing 400038, China; [3]Key Laboratory of High Altitude medicine (People’s Liberation Army), Third Military Medical University, Chongqing 400038, China; [4]Battalion 5 of Cadet Brigade, Third Military Medical University, Chongqing 400038, PR China

Running title: ’Omes and high altitude

Address for correspondence and reprints:

[*]Prof. Yuqi Gao, Mail address: College of High Altitude Military Medicine, Third Military Medical University, Chongqing 400038, PR China; Tel: +86 23 6875 2381; Fax: +86 23 6875 2384; E-mail: gaoy66@yahoo.com.

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Abstract

The main physiological challenge in high-altitude plateau environments is hypoxia. When people living in a plains environment migrate to the plateau, they face the threat of hypoxia. Most people can acclimatize to high altitudes; the acclimatization process mainly consists of short-term hyperventilation and long-term compensation by increased oxygen uptake, transport, and use due to increased red blood cell mass, myoglobin, and mitochondria. If individuals cannot acclimatize to high altitude, they may suffer from a high-altitude disease, such as acute mountain disease (AMS), high-altitude pulmonary edema (HAPE), high-altitude cerebral edema (HACE) or chronic mountain sickness (CMS). Because some individuals are more susceptible to high altitudes than others, the incidence of these high-altitude diseases is variable and cannot be predicted. Studying "omes" using genomics, proteomics, metabolomics, transcriptomics, lipidomics, immunomics, glycomics and RNomics can help us understand the factors that mediate susceptibility to high altitude illnesses. Moreover, analysis of the "omes" using a systems biology approach may provide a greater understanding of high-altitude illness pathogenesis and improve the efficiency of the diagnosis and treatment of high-altitude illnesses in the future. Below, we summarize the current literature regarding the role of "omes" in high-altitude acclimatization/adaptation and disease and discuss key research gaps to better understand the contribution of "omes" to high-altitude illness susceptibility.

The main characteristic of the plateau environment is hypoxia. When people living in a plains environment migrate to the plateau, they face the threat of hypoxia[1]. Most people can acclimatize to high altitudes; the acclimatization process mainly involves short-term hyperventilation and long-term compensation by increased oxygen uptake, transport, and use due to increased red blood cell mass, myoglobin, and mitochondria[2-6]. If individuals cannot acclimatize to the high altitude environment, they may suffer from a high-altitude illness, such as acute mountain disease (AMS), high-altitude pulmonary edema (HAPE), high-altitude cerebral edema (HACE) or chromic mountain sickness (CMS)[7-12]. Because some individuals are more susceptible to high altitude than others, the incidence of high-altitude diseases is variable and cannot be predicted.

The "omes" are hot topics in life science research. Studying biology using genomics, proteomics, metabolomics, transcriptomics, lipidomics, immunomics, glycomics and RNomics approaches can help us understand the susceptibility to high-altitude illnesses and other conditions. Moreover, "ome" analysis using a systems biology approach (i.e., an approach that integrates genomics, epigenomics, and proteomics) may provide a greater understanding of the pathogenesis of high-altitude illness and improve the efficiency of diagnosis and treatment in the future. The current study focuses on using "omes" to provide background information about high-altitude illness and the ability of newcomers to high-altitude areas to adapt to such environments. In this study, we summarize the current literature on the role of "omes" associated with susceptibility to high-altitude illnesses and discuss key research gaps to better understand the contribution of the "omes" to high-altitude illness susceptibility.

1. Omics and high altitude acclimatization/adaptation

1.1 Haplotype

Research on the mechanisms of human adaptation to the hypoxic high-altitude environment is of great interest in the fields of human physiology and clinical medicine. In 2011, MacInnis et al. published a review covering omics, titled *Range between altitude adaptation, positive selection, and Himalayan genomics* [13]. These authors briefly reviewed recent developments in the "omic" analysis of Tibetan highland natives. Two notable factors, egl nine homolog 1 (EGLN1) and endothelial PAS domain protein 1 (EPAS1), were identified as strong candidates in the evolutionary adaptation to high altitude [14], and the time course over which this adaptation occurred was determined by one team to be remarkably brief. Human EPAS1 encodes the oxygen-sensitive alpha subunit of hypoxia-inducible factor-2 (HIF-2) transcription factor, which is a key regulator of chronic hypoxia through its regulation of a large number of genes involved in the cellular and systemic responses to hypoxia[15, 16]. After this study, Ge et al. found that one specific EPAS1 haplotype is significantly associated with an increased concentration of lactate, the product of anaerobic glycolysis[17]. Furthermore, the potentially advantageous peroxisome proliferator-activated receptor α (PPARα) haplotype is correlated with serum free fatty acid concentrations, suggesting a possible decrease in the activity of fatty acid oxidation. Although further studies are required to assess the molecular mechanisms underlying these observations, these associations suggest that the genetic adaptation to high altitude involves changes in energy utilization pathways[17]. Based on genome-wide association study (GWAS) data, Ji et al. determined that the mu-type opioid receptor 1-encoding gene (OPRM1), which has been implicated in the stimulation of respiration, is important in cardiopulmonary adaptation to high-altitude environments [18]. In addition to the Tibetan population, Deedu (DU) Mongolians, who

migrated from the Mongolian steppes to the Qinghai-Tibetan Plateau approximately 500 years ago, have also been studied. The changes that Xing et al. identified in DU Mongolians are shared with other Asian groups (e.g., the ectodysplasin A receptor gene, EDAR) and the neighboring Tibetan populations, including the high-altitude candidates EPAS1 and peroxisome proliferator-activated receptor gamma (PPARG) [19](Table 1).

1.2 Copy number variations

In addition to polymorphisms, copy number variations (CNVs) have been implicated in the pathogenesis of high-altitude diseases, including rare genetic disorders and a wide range of common diseases [20]. In addition to the pathogenic CNVs, a large number of common CNVs have been identified in healthy individuals. Zhang et al. scanned 29 Tibetan genomes using the Illumina Human-1 M high-resolution genotyping microarray and identified 139 putative copy number variable regions (CNVRs), consisting of 70 deletions, 61 duplications, and 8 multi-allelic loci. The Tibetan CNVRs are enriched for genes involved in human reproductive disease [such as the deleted in azoospermia (DAZ), BPY2 (basic charge, Y-linked, 2), CDY (chromodomain protein, Y-linked), HLA-DQ and HLA-DR gene clusters] and genes in the "response to DNA damage stimuli" and "DNA repair" gene ontology categories [such as RAD51 recombinase (RAD51), RAD52 recombinase (RAD52), and MRE11 meiotic recombination 11 (MRE11A)] [21](Table 1). These variations are related to the higher infant birth weight and darker skin tone traits of Tibetans and may be attributed to recent local adaptation.

In addition to the genes in the Tibetan population, Scheinfeldt et al. investigated several candidate genes that are involved in high-altitude adaptation in Ethiopia, including mitochondrial calcium uptake 1 (CBARA1), vav 3 guanine nucleotide

exchange factor (VAV3), aryl-hydrocarbon receptor nuclear translocator 2 (ARNT2) and thyroid hormone receptor beta (THRB). In their study, they found that THRB and ARNT2 function in the hypoxia-inducible factor 1 (HIF-1) pathway and demonstrated significantly different hemoglobin levels between high- and low-altitude populations in Ethiopia(Table 1). These combined results suggest that adaptation to high altitude arose independently through convergent evolution in the high-altitude Amhara populations in Ethiopia[22].

1.3 Proteomics

Chen et al. detected protein expression levels in the mitochondrial fractions of Wistar rats that were exposed to hypobaric hypoxia using proteomic methods. These authors identified eight mitochondrial proteins that were differentially expressed in the hypoxic group compared to the normoxic control group[23]. These proteins included chain A of F1-ATPase, voltage dependent anion channel 1 (VDAC), hydroxyacyl-coenzyme A dehydrogenase α-subunit, mitochondrial F1 complex γ-subunit, androgen-regulated protein and tripartite motif protein 50. Two of the identified proteins, corresponding to VDAC and the α-subunit of ATP synthase, were confirmed by Western blot analysis. The authors concluded that exposure to hypoxia for 30 days affects the expression of mitochondrial proteins that are involved in ATP production and lipid metabolism, decreases the stability of the mitochondrial membrane, and affects the mitochondrial electron transport chain(Table 1).

1.4 Transcriptomics

With regard to high altitude acclimatization, Chen et al. studied the transcriptome and network changes in climbers at extreme altitudes. They followed four climbers on an expedition up Mount Xixiabangma (8,012 m) and collected blood samples at four stages during the climb for miRNA expression analysis. They computationally

predicted and experimentally validated that increased expression of the OCT4 protein at extreme altitudes can directly elevate the expression of hemoglobin genes[24] (Table 1) .

2. Omics and acute mountain sickness

2.1 Haplotype

Altitude exposure in non-acclimatized subjects can lead to acute mountain sickness (AMS), which has become a significant environmental health issue due to air travel or relocation to higher-altitude settlements[8, 25]. In 2011, MacInnis et al. reviewed the evidence for inherited susceptibility to acute mountain sickness[26]. A large number of candidate genes have been associated with AMS susceptibility, including genes encoding angiotensin-converting enzyme (ACE), angiotensin II type 1 receptor (AGTR1), beta-2 adrenergic receptor (ADRB2), bradykinin receptor-B2 (BDKRB2), heat shock protein 70 (Hsp70), HIF1α, endothelial nitric oxide synthase (eNOS), and vascular endothelial growth factor (VEGF) [8] (Table 2).

Following this report, 2 articles reported data regarding omics research and AMS. Buroker et al. compared 85 patients with AMS to 79 healthy Han individuals. Arterial oxygen saturation (SaO_2) of the Han patients with AMS was found to be significantly associated with the EGLN1 rs480902 SNP and the EGLN1 rs480902 SNP[27]. In another study, Buroker et al. studied the associations of AKT3 (v-akt murine thymoma viral oncogene homolog 3), angiopoietin-like 4 (ANGPTL4), NOS3, and vascular endothelial growth factor (VEGFA) with AMS. These authors found that heart rate (HR) was significantly associated with the NOS3 rs1799983 SNP and that SaO_2 was significantly associated with two VEGFA SNPs (rs13207351 and rs1570360) in Han AMS patients, indicating that these nucleotide alterations have a physiological effect

on the development of AMS[28]. At the same time, Buroker et al. conducted genetic analyses of seven single-nucleotide polymorphisms in the promoter region of the VEGFA gene in lowland (Han) and highland (Tibetan) Chinese populations. SaO_2 was found to be significantly associated with the rs699947, rs34357231, rs13207351, and rs1570360 SNPs in Han patients with AMS; the rs2010963 SNP was found to approach significance in the AMS study group and was significantly associated with the normal Tibetan study group. All these SNPs were found in transcription factor binding sites (TFBS), and their potential roles in gene regulation were evaluated with regard to mountain sickness[29](Table 2).

3. Omics and high-altitude pulmonary edema

3.1 Haplotype

High-altitude pulmonary edema (HAPE) is a life-threatening condition resulting from a rapid ascent to altitudes greater than 2,500 m[30-33]. In 2012, Luo et al. reviewed the genetic polymorphisms associated with HAPE susceptibility and suggested that polymorphisms in nitric oxide synthase 3 (NOS3), angiotensin-converting enzyme (ACE), CYP11B2 (cytochrome P450, family 11, subfamily B, polypeptide 2), Hsp70, endothelin-1 (ET-1) and pulmonary surfactant proteins A1 and A2 are associated with the incidence of HAPE. Additional associations of tyrosine hydroxylase (TH) and VEGF with HAPE remain to be fully elucidated [34]. Subsequently, Mishra et al. studied the CYBA (cytochrome b-245, alpha polypeptide) and glutathione S-transferase pi 1 (GSTP1) variants associated with HAPE and found that the CYBA G-C (-930A/G) and H72Y (C/T) haplotypes and the GSTP1 G-C and G-T changes of I105V (A/G) and A114V (C/T) genotypes were over-represented in HAPE patients[35]. This suggests that the risk alleles of CYBA and GSTP1, their haplotypes, and

gene-gene interactions are associated with imbalanced oxidative stress, influencing the development of HAPE(Table 3).

The renin-angiotensin-aldosterone system (RAAS) pathway also plays a key role in the regulation of vascular tone and circulatory homeostasis. Srivastava et al. studied the associations of polymorphisms in the angiotensin and aldosterone synthase genes of the RAAS pathway with HAPE and found that the abundance of the T174M polymorphism in AGT was significantly different between the HAPE individuals and controls. Additionally, genotyping in the CYP11B2 T-344C promoter region showed a significant difference between HAPE individuals and controls. Through their investigation, Srivastava et al. demonstrated a possible association between polymorphisms in the RAAS pathway (AGT T174M and CYP11B2 C-344T) and the susceptibility of an individual to HAPE[36] (Table 3).

EGLN1 plays a pivotal role in the HIF pathway and has emerged as one of the most intriguing genes with respect to the physiology of high altitudes. Mishra A et al. screened 30 polymorphisms in EGLN1, evaluated the expression of this gene and performed association analyses in 250 HAPE patients, 210 controls and 430 healthy Ladakhi highland natives. The genotypes of seven polymorphisms (rs1538664, rs479200, rs2486729, rs2790879, rs480902, rs2486736 and rs973252) differed significantly between the HAPE patients and controls ($P<0.008$). The genotypes AA, TT, AA, GG, CC, AA and GG of rs1538664, rs479200, rs2486729, rs2790879, rs480902, rs2486736 and rs973252 were prevalent in HAPE and were identified as risk genotypes; the opposite homozygotes, prevalent in healthy highland controls, were identified as protective. EGLN1 expression was up-regulated 4.56-fold in HAPE patients. Yang et al. reported that the EPAS1 polymorphism is associated with susceptibility to HAPE in a Han Chinese population [37]. Similarly, a regression

analysis showed that the risk alleles and susceptible haplotypes were associated with decreased SaO_2 levels in the three groups, which contributed to uncovering the molecular mechanisms underlying hypobaric hypoxic adaptation and maladaptation [38](Table 3).

Mitochondria are the energy metabolism centers of the cell and are related to oxidative stress. More than 95% of cellular energy is produced by mitochondrial oxidative phosphorylation. Mitochondrial function can be affected by variations in mitochondrial DNA such as polymorphisms, content changes, and deletions [39]. Luo et al. found that mitochondrial DNA haplogroup D4 is associated with resistance to HAPE, while haplogroup B is a genetic risk factor for this condition. Haplogroup D4 (which is identified by the 3010A SNP) may enhance the stability of 16S rRNA, resulting in reduced oxidative stress and protection against HAPE. Within haplogroup B, the subhaplogroup B4c (which is identified by the 15436A and 1119C SNPs) was associated with an increased risk for HAPE, while subhaplogroup B4b may protect against HAPE [12]. In addition to the above mtDNA variants, Luo et al. found that the frequency of mtDNA 3397G in the HAPE group (2.3%) was significantly higher than that of the control group (0%). The frequency of mtDNA 3552A in the HAPE group (6.8%) was also significantly higher than that in the control group (1.7%)[10](Table 3). These studies suggest that mitochondria are involved in adverse reactions to acute hypoxic exposure; differences in susceptibility as a function of mitochondrial DNA haplotype may shed light on the pathogenesis of other disorders associated with hypoxia, such as chronic obstructive pulmonary disease.

3.2 Proteomics

Genomic variation can cause protein changes[40]. Ahmad et al. identified that haptoglobin and apolipoprotein A-I are biomarkers for HAPE by investigating the

plasma proteome using 2D gel electrophoresis and matrix-assisted laser desorption/ionization tandem time of flight [41]. In another study, Luo et al. investigated proteomic variations in the plasma of HAPE patients and found that the K1 immunoglobulin light chain, serum transferrin protein precursor, and α-trypsin inhibitor heavy chain-related protein expression were increased in HAPE patients and that the human fibrin glue coagulation protein 3 was decreased in these patients(Table 3). These changes may be related to the occurrence of HAPE and may be used as potential targets for predicting HAPE [42].

3.3 Metabolomics

Proteomic variation can cause metabolomic variation [43]. Luo et al. studied the metabolomic variation in the plasma of HAPE patients using 1H NMR and found that HAPE patients had significant increases in valine, lysine, leucine, isoleucine, glycerol phosphoryl choline, glycine, glutamine, glutamic acid, creatinine, citrate, and methyl histidine. These increases were accompanied by decreases in α- and β-glucose, trimethylamine, and the metabolic products of lipids[11](Table 3). Therefore, the data generated by omics research may be effective for the diagnosis of high-altitude illnesses in the future and may be used to improve our understanding of the pathogenesis of illnesses.

4. Omics and high altitude cerebral edema

High altitude cerebral edema (HACE) is one of the most serious high altitude illnesses[44]. Zhang et al. analyzed the plasma proteome and identified six different proteins from the comparison between HACE and HAPE patients and another six proteins that varied from the plasma of HACE patients compared to that of AMS patients [45]. Apolipoprotein E was identified in the two groups of comparative maps,

and the enzyme-linked immunosorbent assay results were consistent with the 2-DE results. Based on the results of their study, Zhang et al. offered clues to improve our understanding of HACE for prevention, diagnosis and treatment.

5. Omics and chronic mountain sickness

5.1 Transcriptomics

Chronic mountain sickness (CMS) is a major public health problem in mountainous regions of the world[46]. CMS is a hypobaric, hypoxia-related illness that presents with polycythemia leading to cardiac failure or neurological disorders. CMS seriously affects the health of highland immigrants and often results in significant declines in productivity and quality of life[47]. CMS patients usually experience decreased exercise tolerance, loss of memory, headache, dizziness, and fatigue[48, 49]. Compared to their Tibetan counterparts, Han Chinese suffer from significantly higher rates of CMS when they reside in highland areas [48]. However, the pathogenesis of HAPC is poorly understood.

Oxidative-nitrosative stress plays an important role in the pathogenesis of CMS. Bailey et al. studied oxidative-nitrosative stress[examining ascorbate radicals (A•-) using electron paramagnetic resonance spectroscopy, nitrite (NO^{2-}) levels, and ozone-based chemiluminescence] in the venous blood of 25 male highlanders living at 3,600 m with and without CMS. Compared to lowlanders, oxidative-nitrosative stress was moderately increased in CMS as indicated by elevated A•- and lower NO^{2-}, and vascular function was preserved [50]. In addition to oxidative-nitrosative stress, Ge et al. studied the B-type natriuretic peptide, vascular endothelial growth factor, endothelin-1, and nitric oxide synthase in patients with chronic mountain sickness and found severe chronic hypoxemia and consequent pulmonary hypertension in patients with CMS;

they also found that CMS may stimulate the release of natriuretic peptides and angiogenic cytokines[51]. Regarding the human immune response, Jiang et al. studied the gene expression profiling of high-altitude polycythemia in Han Chinese migrating to the Qinghai-Tibetan plateau and identified a total of 9 differentially expressed genes in HAPC patients using microarrays; 5 of these genes were up-regulated and 4 were down-regulated. A functional analysis of the array data revealed that cell division cycle 42 (CDC42) and the human immune response may be key features underlying the mechanism and development of HAPC[52](Table 4).

5.2 Haplotype

Buroker et al. studied the associations between CMS and EPAS1 and EGLN1 in Han and Tibetan Chinese living on the Qinghai-Tibetan Plateau. These authors found that the EGLN1 rs480902 SNP was significantly correlated with hematocrit (HCT)[27]. In another study, Buroker et al. studied the associations between AKT3, ANGPTL4, eNOS3, and VEGFA and CMS on the Qinghai-Tibetan Plateau. Hemoglobin (Hb), hematocrit (Hct), and red blood cell count (RBC) were found to be significantly associated with the AKT3 rs4590656 SNP, Hb was found to be associated with the eNOS3 rs1007311 SNP, and RBC was found to be significantly associated with the VEGFA rs1570360 SNP in Tibetan patients with CMS. CMS patients were found to diverge significantly for both eNOS3 SNPs and the VEGFA rs28357093 SNP as measured by genetic distance[28](Table 4).

Buroker et al. studied the association of several genetic loci with CMS, including ACE I/D (rs4340), AGT M235T (rs699), AGTR1 A1166C (rs5186), GNB3 [guanine nucleotide binding protein (G protein), beta polypeptide 3] A(-350)G (rs2071057) and apolipoprotein B (APOB) A/G (rs693). The ACE D and AGT 235M alleles were found to be significantly associated with CMS. ACE (I/D) was significantly

associated with HR in CMS patients. APOB A/G was significantly associated with HR in CMS patients. Furthermore, the authors suggested that the ACE I/D and AGT M235T polymorphisms had an effect on CMS[53]. From the above study, we can conclude that these vasoactive peptides may play an important role in the pathogenesis and clinical expression of CMS, have prognostic value for CMS, and serve as targets for therapeutic trials or clinical decision-making. In another study, Jiang et al found the mtDNA 8414T, 10609T (WT) was significantly associated with an increased risk of HAPC ($P<0.01$, OR=2.558, 95% CI: 1.250-5.236) [54](Table 4).

6. Conclusion

Multiple studies have examined experimental hypoxia in humans and animals and have demonstrated connections between omics and high-altitude acclimatization/adaptation[55-57]. Other investigations have also shown that the human urinary peptidome contains different proteins that could serve as biomarkers for HAPE and HACE, as determined by proteomics[11, 58]. Wu et al. also showed that EPAS1 and EGLN1 were correlated with a low Hb concentration in Tibetans that prevents development of HAPC[59]. The goal of all the described studies was to make a concerted omics effort to model and further characterize human physiology at high altitudes. The essential requirement now is the development of a computational framework that can unify these disparate data[58]. While much work remains to be done, an initial list of high-altitude illness susceptibility genes is emerging. Care should be taken when evaluating these studies, however, because phenotypic and cohort definitions may limit our ability to merge studies. It is not likely that a single “ome” will be identified as the sole determinant of any high-altitude illness; instead, the pathogenesis of each illness is likely to be polygenic, with multiple genes and the

interactions between these genes contributing to the complete high-altitude illness phenotype. Whether there is an association between any single "ome" and high-altitude illness is unclear. More sophisticated investigations are needed to study the genetics and epigenetics of high-altitude illness, including genomics, proteomics, metabolomics, transcriptomics, lipidomics, immunomics, glycomics, RNomics, and others. Due to the rarity of large high-altitude population sample sizes, a variety of ethnic populations are needed to fully test for associations between the "omes" and high-altitude illness susceptibility[60]. An improved understanding of the role that genetics plays in the development and severity of high-altitude illnesses will enhance our ability to prevent, diagnose, and treat these conditions[13, 26].

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Declaration of Interests

The authors declare no conflicts of interest and are solely responsible for the content of the paper.

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Table 1 Omics and high altitude acclimatization/adaptation

	Gene symbol	Name	Location
Haplotypes related to high altitude acclimatization/adaptation	EGLN1[14]	egl nine homolog 1	Chromosome 1, NC_000001.11
	EPAS1[15, 17]	Endothelial PAS domain protein 1	Chromosome 2, NC_000002.12
	PPARA[17]	peroxisome proliferator-activated receptor α	Chromosome 22, NC_000022.11
	OPRM1[18]	opioid receptor, mu 1	Chromosome 6, NC_000006.12
	EDAR [19]	the ectodysplasin A receptor	Chromosome 2, NC_000002.12
	PPARG [19]	peroxisome proliferator-activated receptor gamma	Chromosome 3, NC_000003.1
CNVs related to high altitude acclimatization/adaptation	DAZ[21]	deleted in azoospermia	Chromosome Y, NC_000024.10
	BPY2[21]	basic charge, Y-linked, 2	Chromosome Y, NC_000024.10
	CDY[21]	chromodomain protein, Y-linked	
		HLA-DQ and -DR gene clusters	
	RAD51[21]	RAD51 recombinase	Chromosome 15, NC_000015.10
	RAD52[21]	RAD52 recombinase	Chromosome XIII, NC_001145.3
	MRE11A[21]	MRE11 meiotic recombination 11 homolog A	Chromosome 11, NC_000011.10
	CBARA1[22]	mitochondrial calcium uptake 1	Chromosome 28, NC_022320.1
	VAV3[22]	vav 3 guanine nucleotide exchange factor	Chromosome 1, NC_000001.11
	ARNT2[22]	aryl-hydrocarbon receptor nuclear translocator 2	Chromosome 15, NC_000015.10
	THRB[22]	thyroid hormone receptor, beta	Chromosome 3, NC_000003.12
Proteins related to high altitude acclimatization/adaptation	(VDAC)[23]	Chain A of F1-ATPase[23] voltage dependent anion	

		channel 1 hydroxyacyl-coenzyme A dehydrogenase α-subunit[23] mitochondrial F1 complex γ-subunit[23] androgen-regulated protein[23] tripartite motif protein 50[23]
Transcriptomes related to high altitude acclimatization/adaptation	OCT4[24]	OCT4 protein

Table 2 Omics and acute mountain sickness

	Gene symbol	Name	Location
Haplotypes related to acute mountain sickness	ACE[8]	angiotensin-converting enzyme	Chromosome 17, NC_000017.11
	AGTR1[8]	angiotensin II type 1 receptor	Chromosome 3, NC_000003.12
	ADRB2[8]	beta-2 adrenergic receptor	Chromosome 5, NC_000005.10
	BDKRB2[8]	bradykinin receptor-B2	Chromosome 14, NC_000014.9
	Hsp70[8]	heat shock protein 70	Chromosome 3, NC_007114.5
	HIF1α[8]	hypoxia-inducible factor 1 alpha	Chromosome 14, NC_000014.9
	eNOS[8, 28]	endothelial nitric oxide synthase	Chromosome 7, NC_000007.14
	VEGF[8, 28]	vascular endothelial growth factor	Chromosome 4, NC_013899.1
	EGLN1[8, 28]	egl nine homolog 1	Chromosome 1, NC_000001.11

Table 3 Omics and high-altitude pulmonary edema

	Gene symbol	Name	Location
Haplotypes related to high-altitude pulmonary edema	NOS3[34]	nitric oxide synthase 3	Chromosome 7, NC_000007.14
	ACE[34]	angiotensin-converting enzyme	Chromosome 17, NC_000017.11
	CYP11B2[34, 36]	cytochrome P450, family 11, subfamily B, polypeptide 2	Chromosome 8, NC_000008.11
	Hsp70[34]	heat shock protein 70	Chromosome 3, NC_007114.5
	ET-1[34]	endothelin-1	Chromosome 12, NC_013680.1
	TH[34]	tyrosine hydroxylase	Chromosome 7, NC_000073.6
	VEGF[34]	vascular endothelial growth factor	Chromosome 4, NC_013899.1
	AGT[36]	angiotensin	Chromosome 1, NC_000001.11
		pulmonary surfactant proteins A1 and A2	
	CYBA[35]	cytochrome b-245, alpha polypeptide	Chromosome 16, NC_000016.10
	GSTP1[35]	glutathione S-transferase pi 1	Chromosome 11, NC_000011.10
	EGLN1[16]	egl nine homolog 1	Chromosome 1, NC_000001.11
	mt3397G[10]		mtDNA
	mt3352A[10]		mtDNA
	mt3010A[12]		mtDNA
	EPAS1[27]	endothelial PAS domain protein 1	endothelial PAS domain protein 1
Proteins related to high-altitude pulmonary edema		haptoglobin[41]	
		apolipoprotein A-I[41]	
		K1 immunoglobulin light chain[42]	
		serum transferrin protein precursor[42]	
		α-trypsin inhibitor heavy chain-related protein[42]	
		human fibrin glue coagulation protein 3[42]	

Metabolites related to high-altitude pulmonary edema	Valine[11] Lysine[11] Leucine[11] Isoleucine[11] glycerol phosphoryl choline[11] glycine[11] glutamine[11] glutamic acid[11] creatinine[11] citrate[11] methyl histidine[11] α- and β-glucose[11] trimethylamine[11] the metabolic products of lipids[11]

Table 4 Omics and chronic mountain sickness

	Gene symbol	Gene name	Location
Transcriptomes related to chronic mountain sickness	CDC42[52]	cell division cycle 42	Chromosome 1, NC_000001.11
Haplotypes related to chronic mountain sickness	EPAS1[27]	endothelial PAS domain protein 1	endothelial PAS domain protein 1
	EGLN1[27]	egl nine homolog 1	Chromosome 1, NC_000001.11
	AKT3[28]	v-akt murine thymoma viral oncogene homolog 3	Chromosome 1, NC_000001.11
	VEGFA[28]	vascular endothelial growth factor A	Chromosome 6, NC_000006.12
	AGT[53]	angiotensin	Chromosome 1, NC_000001.11
	ACE[53]	angiotensin-converting enzyme	Chromosome 17, NC_000017.11
	mt8414T[54]		mtDNA
	mt10609T[54]		mtDNA