

Unraveling the Biomarker Prospects of High-Altitude Diseases: Insights from Biomolecular Event Network Constructed using Text Mining

Supplementary Data-6

Major genes/proteins and its biological function in High altitude diseases

Gene	Function
EGLN1	Egl nine homolog 1 (C. elegans); Cellular oxygen sensor that catalyzes, under normoxic conditions, the post-translational formation of 4-hydroxyproline in hypoxia-inducible factor (HIF) alpha proteins.
EPAS1	Endothelial PAS domain protein 1; Transcription factor involved in the induction of oxygen regulated genes. Binds to core DNA sequence 5'-[AG]CGTG-3' within the hypoxia response element (HRE) of target gene promoters. Regulates the vascular endothelial growth factor (VEGF) expression and seems to be implicated in the development of blood vessels and the tubular system of lung. May also play a role in the formation of the endothelium that gives rise to the blood brain barrier. Potent activator of the Tie-2 tyrosine kinase expression.
VEGFA	Vascular endothelial growth factor A; Growth factor active in angiogenesis, vasculogenesis and endothelial cell growth. Induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces permeabilization of blood vessels
EPO	Erythropoietin; Erythropoietin is the principal hormone involved in the regulation of erythrocyte differentiation and the maintenance of a physiological level of circulating erythrocyte mass
ERMN	Ermin, ERM-like protein; Plays a role in cytoskeletal rearrangements during the late wrapping and/or compaction phases of myelinogenesis as well as in maintenance and stability of myelin sheath in the adult.
ACE	Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1; Converts angiotensin I to angiotensin II by release of the terminal His-Leu, this results in an increase of the vasoconstrictor activity of angiotensin. Also able to inactivate bradykinin, a potent vasodilator. Has also a glycosidase activity which releases GPI-anchored proteins from the membrane by cleaving the mannose linkage in the GPI moiety
AGT	Angiotensinogen (serpin peptidase inhibitor, clade A, member 8); Essential component of the renin-angiotensin system (RAS), a potent regulator of blood pressure, body fluid and electrolyte homeostasis

NOS3	Nitric oxide synthase 3 (endothelial cell); Produces nitric oxide (NO) which is implicated in vascular smooth muscle relaxation through a cGMP-mediated signal transduction pathway. NO mediates vascular endothelial growth factor (VEGF)-induced angiogenesis in coronary vessels and promotes blood clotting through the activation of platelets
REN	Renin; Renin is a highly specific endopeptidase, whose only known function is to generate angiotensin I from angiotensinogen in the plasma, initiating a cascade of reactions that produce an elevation of blood pressure and increased sodium retention by the kidney
TNF	Tumor necrosis factor; Cytokine that binds to TNFRSF1A/TNFR1 and TNFRSF1B/TNFR. It is mainly secreted by macrophages and can induce cell death of certain tumor cell lines. It is potent pyrogen causing fever by direct action or by stimulation of interleukin-1 secretion and is implicated in the induction of cachexia, Under certain conditions it can stimulate cell proliferation and induce cell differentiation
IL6	Interleukin 6 (interferon, beta 2); Cytokine with a wide variety of biological functions. It is a potent inducer of the acute phase response. Plays an essential role in the final differentiation of B-cells into Ig- secreting cells Involved in lymphocyte and monocyte differentiation. Acts on B-cells, T-cells, hepatocytes, hematopoietic progenitor cells and cells of the CNS. Required for the generation of T(H)17 cells. Also acts as a myokine. It is discharged into the bloodstream after muscle contraction and acts to increase the breakdown of fats and to improve insulin resistance.

Major genes/proteins and the connected biological pathways

<i>Pathway</i>	<i>Process</i>	<i>Genes</i>
HIF-1 signaling pathway <i>hsa04066</i>	Hypoxia-inducible factor 1 (HIF-1) is a transcription factor that functions as a master regulator of oxygen homeostasis. HIF-1 acts as a master regulator of numerous hypoxia-inducible genes under hypoxic conditions. The target genes of HIF-1 encode proteins that increase O ₂ delivery and mediate adaptive responses to O ₂ deprivation. Despite its name, HIF-1 is induced not only in response to reduced oxygen availability but also by other stimulants, such as nitric oxide, or various growth factors.	EPO erythropoietin ANGPT1 angiopoietin 1 AKT3 AKT serine/threonine kinase 3 VEGFA vascular endothelial growth factor A EDN1 endothelin 1 NOS3(eNOS) nitric oxide synthase 3 LDHA lactate dehydrogenase A PHD1 hypoxia-inducible factor prolyl hydroxylase

<p>Renin-angiotensin system(RAS)</p> <p><i>hsa04614</i></p>	<p>The renin-angiotensin system (RAS) is a peptidergic system with endocrine characteristics regarding to the regulation of the blood pressure and hydro-electrolytic balance. pLAYS IMPORTANT ROLE IN vasoconstriction, renal sodium (Na+) reabsorption, and aldosterone secretion, increasing blood pressure and contributing to the development of hypertension.</p>	<p>AGT angiotensinogen</p> <p>AGTR1 angiotensin II receptor type 1</p> <p>AGTR2 angiotensin II receptor type 2</p> <p>ACE angiotensin-converting enzyme</p> <p>REN renin</p>
<p>Vascular smooth muscle contraction</p> <p><i>hsa04270</i></p>	<p>The vascular smooth muscle cell (VSMC) is a highly specialized cell whose principal function is contraction. On contraction, VSMCs shorten, thereby decreasing the diameter of a blood vessel to regulate the blood flow and pressure.</p>	<p>AGTR1 angiotensin II receptor type 1</p> <p>EDNRA endothelin receptor type A</p> <p>MAPK1 mitogen-activated protein kinase 1</p>