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Original Research

High-impact Genetic Variants in *EGLN1*, *EPAS1*, and Other Genes Identified in Mountaineers by Exome Sequencing

Evgeniia M. Maksiutenko[1,*,†], Valeriia A. Merkureva[1,2,†], Yury A. Barbitoff[1], Mikhail V. Aseev[1], Tatyana E. Lazareva[1], Andrey S. Glotov[1,3], Oleg S. Glotov[1,3]

[1]Department of Genomic Medicine, D.O. Ott Research Institute of Obstetrics, Gynaecology, and Reproductology, 199034 St. Petersburg, Russia
[2]CerbaLab Ltd., 199106 St. Petersburg, Russia
[3]Department of Experimental Medical Virology, Molecular Genetics and Biobanking of Pediatric Research and Clinical Center for Infectious Diseases, 197022 St. Petersburg, Russia
*Correspondence: evgeniia_maksiutenko@mail.ru (Evgeniia M. Maksiutenko)
[†]These authors contributed equally.
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Abstract

Background: Investigating the genetic basis of adaptation to environmental stresses, such as hypoxia, can enhance our understanding of human biology and resilience. High-altitude adaptation provides a valuable model for studying the genetic mechanisms of the hypoxic response. Indeed, most known loci associated with hypoxic adaptation have been identified in indigenous mountain populations; however, research on elite climbers remains limited. In our previous study, we conducted exome sequencing of experienced mountaineers and identified two pathogenic variants in the *RTEL1* and *COL6A1* genes, both of which are linked to respiratory failure. These findings encouraged this study, which conducted exome sequencing to explore genetic variation in a larger cohort. **Methods**: We performed exome sequencing for a cohort of 114 mountaineers with varying levels of experience. Variant calling was performed in the sequencing data using a pipeline based on the Genome Analysis Toolkit (GATK) v.4.1.9. Annotated variants were used to identify rare and common variants with possible effects on high-altitude adaptation. **Results**: The analysis did not identify any common adaptive variants in these individuals; however, nine variants were identified as potentially relevant to high-altitude adaptation and climbing performance. These included novel variants in the *EPAS1* and *EGLN1* genes, which may have a positive effect under hypoxic conditions, as well as variants in *TCAP*, *F5*, *GP1BA*, and other genes involved in muscle activity and blood coagulation. **Conclusions**: This study identified rare variants in the *EPAS1* and *EGLN1* genes, which had previously been associated with high-altitude adaptation. Additionally, we describe several potentially pathogenic variants in genes not previously linked to hypoxia, highlighting the value of studying elite mountaineers as a unique cohort for broader interpretation of genetic variation.

Keywords: mountaineers; genetic variants; hypoxic adaptation

1. Introduction

Extreme environmental conditions at high altitudes trigger complex adaptive responses at multiple levels, including behavioral, physiological, and molecular changes [1]. The nature of these responses is influenced by both the duration of exposure (e.g., short-term versus long-term stay at high altitude) and the severity of environmental stressors, such as elevation above sea level [2]. Populations residing in mountainous regions for generations have evolved distinct adaptations shaped by prolonged geographic isolation and consistent environmental pressures [3,4].

Recent advancements in multiomics technologies have enabled comprehensive investigations into genomic, proteomic, and metabolic changes associated with hypoxia. These studies encompass a wide range of subjects, from individuals ascending to high altitudes for the first time to acclimatized lowlanders and native high-altitude populations [3,5–7]. Over the past 25 years, studies of Andean, Tibetan, and Ethiopian populations have revealed distinct oxygen-transport patterns, providing indirect evidence of genetic adaptation to high-altitude environments [8]. Both short-term acclimatization and long-term genetic changes affect oxygen homeostasis, with the latter enhancing delivery and metabolic efficiency. At the cellular level, hypoxia induces an upregulation of the genes involved in anaerobic energy production and downregulation of genes involved in ATP consumption [9]. System-wide responses include elevated heart and respiratory rates and increased erythrocyte production [10,11]. These physiological adjustments, including higher hemoglobin levels and red blood cell counts over time, reflect the process of acclimatization [12]. More recently, proteomics has been used alongside genomics to investigate adaptive and maladaptive responses in both acclimatized lowlanders and native highlanders, although sample sizes remain limited [3]. Despite significant progress, the genetic mechanisms—especially those involving single-nucleotide polymorphisms (SNPs)—remain poorly understood [8].

Numerous studies utilizing whole-genome sequencing, genome-wide association studies (GWAS), and scans for DNA polymorphisms have identified multiple genomic regions under positive selection, particularly in Tibetan, Andean, and Ethiopian populations—suggesting a role in hypoxia adaptation [3,7,13,14]. One of the earliest and most prominent findings was the identification of Endothelial PAS domain-containing protein 1 (*EPAS1*), a gene that encodes the Hypoxia-inducible factor-2alpha (HIF-2α) subunit of the hypoxia-inducible factor complex, which promotes red blood cell production and increases hemoglobin concentration [15]. Interestingly, SNP variants in *EPAS1* that are more common among Tibetans were found to be linked to lower hemoglobin levels, possibly providing a protective effect against polycythemia, which can hinder tissue perfusion and oxygen transport. Similarly, Sherpa individuals carrying the rs113305133, rs116611511, and rs12467821 *EPAS1* alleles exhibit lower hemoglobin levels, higher blood oxygen saturation, increased oxygen affinity, and elevated heart rate, all of which may support high-altitude performance [16,17]. Blood is central to these adaptations, not only for its oxygen-carrying capacity but also for its roles in coagulation, immunity, and endocrine signaling. Only a few studies have examined transcriptomic changes in blood during human exposure to high altitude [12,18,19].

Another important gene, Egl-9 Family Hypoxia Inducible Factor 1 (*EGLN1*), encodes proline hydroxylase 2 (PHD2), a HIF prolyl-hydroxylase isoform. Similar to *EPAS1*, two *EGLN1* variants (rs12097901 and rs186996510) appear to be driving the selection signal and are present in both Sherpa and Tibetan individuals. Nonetheless, whether the action mechanism of these two mutations is via gain-of-function or loss-of-function remains unclear [20–22].

The vast majority of variants associated with adaptation to hypoxia and high altitudes were found in the genomes of indigenous inhabitants of mountainous regions [23]. Meanwhile, only a few studies have examined successful climbers and high-altitude athletes, focusing primarily on polymorphisms in the *angiotensin-converting enzyme* (*ACE*) gene [24]. The *ACE* genotype has been associated with enhanced metabolic efficiency, with elite mountaineers showing a higher prevalence of the I allele (insertion variant) and the I/I genotype compared to control groups [25,26]. Notably, this pattern was not observed among amateur climbers. Supporting data come from high-altitude populations in South America and India, where individuals of lowland ancestry also show increased frequencies of the I allele. Notably, while the *ACE* genotype appears to contribute to athletic performance, the genotype is only one of many influencing factors, and the underlying biological mechanisms remain largely unclear despite over a decade of investigation [25,27]. Additionally, several studies have focused on the role of polymorphisms in the Collagen, type I, alpha 1 (*COL1A1*) [28], Alpha-actinin-3 (*ACTN3*), *ACE1*, Thyrotropin-releasing hormone receptor (*TRHR*), Creatine Kinase, M-Type (*CKM*) genes in sport climbers and athletes [29,30].

Recently, we have performed exome sequencing of a limited number of experienced mountaineers. While our study did not uncover any likely adaptive common variants at high frequency in this cohort, we detected two pathogenic variants in genes associated with Mendelian conditions, Regulator of Telomere Elongation Helicase 1 (*RTEL1*) and Collagen, type VI, alpha 1 (*COL6A1*), which are linked to respiratory system failure [31]. This observation prompted us to explore the landscape of functional genetic variation in a broader cohort of 114 mountaineers with varying levels of experience. Thus, this study presents the results of our attempt to discover functionally significant genetic variation in this cohort.

2. Materials and Methods

2.1 Description of Donors

The analysis included 114 mountaineers (80 males and 34 females) with an average age of 35 years. The cohort of mountaineers comprised professional guides who frequently lead expeditions above 7000 meters, experienced climbers who have reached elevations over 8000 meters, and individuals who took part in high-altitude ascents exceeding 4000 meters as members of the Russian national team (Table 1).

Seventeen donors in our sample were not assigned to any specific group due to insufficient information. In addition to this group, we used several additional classification tags attached to the samples: “technician” (specialist in very challenging, technical climbing on lower-altitude routes, usually up to 4000 meters); “high-altitude technician” (focused on slightly less technical difficulty, with the added factor of high altitude, ranging from 4000 to 6999 meters); “high-altitude climber” (expert in generally less technical (sometimes with no technical) difficulty classic routes, at altitudes over 7000 meters).

2.2 DNA Library Preparation and Sequencing

Genomic DNA was isolated from peripheral blood. Sequencing libraries were prepared following the manufacturer’s instructions using the Roche Inherited Disease Panel (IDP) v2 and the KAPA HyperExome kit (details available at https://rochesequencingstore.com/catalog/kapa-hyperexome/). Prepared libraries were then sequenced on one of the following platforms: Illumina HiSeq 2500, Illumina HiSeq 4000, Illumina NovaSeq 6000 (Illumina Inc., San Diego, CA, USA), or DNBSEQ G400 (MGI Tech Co., Ltd., Shenzhen, China).

2.3 Bioinformatic Analysis

Whole-exome sequencing data were processed using a standardized workflow for the cohort-based variant

Table 1. Description of the studied cohort of mountaineers.

Characteristic	Group A	Group B	Group C
Number of donors	33	16	48
Average age	40	34	32
Physical condition	Excellent; all in top physical shape, some age-related conditions (e.g., hypertension, excess weight)	Ordinary to high-level athletes; about half are world-class athletes	Above average; physically fit, near-sports lifestyle
Experience	Professional guides with 7000+ m ascents and 8000+ m experience, national team member and professional sky runners	National team and amateur climbers, professional sky runners with exceptional performance at altitudes up to 4000 m	Professional climbers and amateurs without elite-level experience
Health status	Mostly healthy; minor age-related issues in some donors over 50 years	No health problems at time of examination; issues with altitude adaptation	Nearly healthy; no serious identified health issues
Adaptation to high altitude	Some individuals displayed signs of acute mountain sickness	Problems adapting above 5000 m. Acute mountain sickness (e.g., pulmonary or cerebral edema)	Most individuals displayed signs of acute mountain sickness

analysis. Sequencing reads were aligned to the GRCh38 human genome reference using the bwa-mem2 algorithm [32]. Alignment files were subsequently refined using the Genome Analysis Toolkit (GATK - v4.1.9.0, Broad Institute, Cambridge, MA, USA) [33,34] which included marking of duplicate reads and recalibrating base quality scores. Variant calling was performed with the GATK HaplotypeCaller in GVCF mode, followed by joint genotyping of all samples. To ensure high-quality results, variants were filtered using the Variant Quality Score Recalibration (VQSR) method [35]. Genotypes with a sequencing depth below 10 reads were designated as missing. Variant annotation was conducted using the Ensembl Variant Effect Predictor (VEP) (release 108) [36], with supplemental data including allele frequencies from the gnomAD and RUSeq databases [37], as well as clinical significance annotations from ClinVar (National Center for Biotechnology Information, Bethesda, MD, USA) [38].

The resulting variant dataset was analyzed using the Hail Python framework (https://hail.is/). Samples were quality-filtered based on the following metrics: heterozygous-to-homozygous variant ratio between 1.25 and 2.25, transition/transversion ratio between 2.35 and 2.75, and insertion/deletion ratio between 0.7 and 0.95. After sample-level filtering, additional variant-level filtering was applied to exclude multiallelic sites and variants with a call rate below 20%.

Following the initial filtering, targeted analysis of specific variant groups was performed. First, we investigated rare disease-causing genetic variants present in the studied samples. To focus our analysis on relevant groups of disease-associated genes, we used panels of genes associated with neuromuscular, pulmonary, and blood diseases. A list of 500 genes (**Supplementary Table 1**) was constructed in silico using publicly available Blueprint Genetics gene panels (i.e., Muscular Dystrophy/Myopathy Panel, https://blueprintgenetics.com/tests/panels/neurology/comprehensive-muscular-dystrophy-myopathy-panel/; Comprehensive Neuromuscular Panel, https://www.preventiongenetics.com/testInfo?val=Comprehensive-Neuromuscular-Panel; Comprehensive Hematology Panel, https://blueprintgenetics.com/tests/panels/hematology/comprehensive-hematology-panel/) and used to filter the identified variants. Following the selection of variants within the targeted gene set, those located in genes associated with autosomal dominant inheritance were organized into a tabular format and evaluated according to the ACMG Standards and Guidelines for variant classification [39]. Variant interpretations were further reviewed and confirmed using the Franklin analysis platform (https://franklin.genoox.com/clinical-db/home).

2.4 Hematological Profile Analysis

Hematological profiling was performed in a certified private diagnostic laboratory “INVITRO”. According to details provided by the laboratory, erythropoietin (EPO) levels were measured using chemiluminescent immunoassay technology on the UniCelDxi800 analyzer (Beckman Coulter, Brea, CA, USA). Complete blood count (CBC) analysis was conducted using automated hematology analyzers: SYSMEX XN-9000 (SYSMEX Corporation, Kobe, Japan) and BC-6800 Plus (Mindray, Shenzhen, China). Hemoglobin concentration was determined by a colorimetric method employing sodium lauryl sulfate (SLS). Erythrocyte, leukocyte, and platelet counts, and hematocrit, were obtained by cell-specific lysis followed by automated cell counting using conductometry and hydrodynamic focusing. Red blood cell indices (e.g., mean corpuscular volume, MCV) were calculated based on measured parameters.

3. Results

This study identified 210,474 variants in 114 exome samples from climbers, of which 120,062 were found in fewer than 5% of cases and 66,991 were found in a single

sample within the entire cohort. Among the detected variants, 108,164 were located in non-coding regions, 51,852 substitutions exhibited a weak effect on the structure and function of the protein, 47,623 variants demonstrated an impact on protein sequence (i.e., missense variants, in-frame insertions and deletions), and 2834 variants can potentially lead to a loss of protein function.

To identify variants that may contribute to the adaptation of athletes to altitude and hypoxic conditions, we performed several types of analysis for different groups of variants (see **Supplementary Note** for details). Having observed no signs of common variant-mediated adaptation (**Supplementary Tables 2,3**), we mostly focused on searching for rare variants. To this end, we filtered substitutions that were not presented in the local allele frequency RUSeq database [37], were observed no more than 3 times across the gnomAD database and may lead to a loss of protein function. This analysis identified 9 variants in potentially relevant genes, which were then interpreted according to the ACMG standards and guidelines for variant interpretation.

All discovered variants (Table 2) were divided into three groups according to their ACMG classification: 1 pathogenic variant in Titin-Cap (*TCAP*) gene (P), 7 likely pathogenic (LP) variants in *F5*, *EGLN1*, Titin (*TTN*), Dystrobrevin alpha (*DTNA*), Glycoprotein Ib (*GP1BA*), Signal recognition particle 72 (*SRP72*), Sodium channel epithelial 1 subunit alpha (*SCNN1A*) genes and 1 variant of uncertain significance (VUS) in *EPAS1*. The most intriguing and important of these findings were the high-impact genetic variants in the *EPAS1* and *EGLN1* genes, which are known to be crucial for hypoxic response and high-altitude adaptation.

3.1 High-impact Genetic Variants in the EGLN1 and EPAS1 Genes

As mentioned in the Introduction, *EPAS1* and *EGLN1* are two of the best-studied genes involved in adaptation to high altitudes. One of the donors in our cohort was found to be heterozygous for the *EGLN1* nonsense variant c.381T>A (p.Cys127*), which leads to a protein truncation upstream of the oxygen-dependent degradation domain in PHD2. The variant was identified in a professional mountain guide who regularly leads tourist groups to high altitudes and does not experience significant altitude sickness. The individual is classified in Group A and holds the title of Master of Sports in technical mountaineering.

To validate the physiological effect of this variant, as well as to identify the associated mechanism of high-altitude adaptation, we have examined the hematological profile (Table 3) of the respective donor, as well as his plasma erythropoietin (EPO) levels. This analysis showed a hemoglobin level of 16.0 g/dL, a hematocrit value of 45.1%, and an erythrocyte count of 5.62 $\times$ 10^6/µL, which are slightly above the normal range, along with a MCV of 80.2 fL (slightly reduced). Importantly, the EPO level was 6.8 mIU/mL, remaining within the physiological reference range. These results indicate a very mild erythrocytosis in the donor, consistent with the effects of other previously reported *EGLN1* variants (see Discussion).

Another intriguing finding was a heterozygous mutation in the *EPAS1* gene (c.2613A>G; p.Ter871TrpfsTer64), which was identified in a 47-year-old male mountaineer, a master of sports with over 30 years of experience. A versatile and highly skilled mountain guide, he regularly leads groups on both high-altitude and technical routes. Known as a strong climber who experiences no difficulties at high altitudes, he has frequently ascended peaks between 5000 and 6000 meters, reaching a maximum of 7134 meters. Although he ascended without supplemental oxygen, he reported experiencing only mild symptoms, such as headaches and slight weakness. Meanwhile, observed variants in the *EPAS1* gene are usually associated with four of eight known types of familial erythrocytosis, a congenital condition characterized by elevated red blood cell counts, as well as hemoglobin and hematocrit levels [40,41]. Although the *EPAS1* gene is associated with erythrocytosis, loss-of-function mutations are not always associated with elevated red blood cell counts, hemoglobin levels, or hematocrit values [42].

The hematological evaluation of our donor revealed a hemoglobin concentration of 15.9 g/dL and a hematocrit level of 45.6%, both within normal physiological limits. Similar to the donor carrying the *EGLN1* variant, the donor carrying the *EPAS1* variant had a normal serum EPO level of 8.9 mIU/mL. The only notable deviation in the hematological profile of this individual was a slightly reduced platelet count at 142 $\times$ 10^3/µL. While these results do not allow us to draw a definitive conclusion about the impact of the identified *EPAS1* variant, these data may suggest a mechanism through which this mutation can confer adaptation (see Discussion for more details).

3.2 Variants in Genes Previously not Associated With High-altitude Adaptation

In addition to variants in the highly important *EPAS1* and *EGLN1* genes, we identified seven additional variants that could be classified as pathogenic or likely pathogenic if detected in an individual with a Mendelian disease. While we are unable to provide further evidence regarding the functional impact of these variants on acute hypoxic adaptation, these variants warrant a specific mention due to their potential relevance for altitude-associated phenotypes.

A heterozygous pathogenic variant (rs1555606976; c.90_91del; p.Ser31Hisfs*11) was identified in the *TCAP* gene, which is exclusively expressed in striated and cardiac muscle. The donor, currently 71 years old, is an Honored Master of Sports of Russia in mountaineering. He reached an altitude of 8848 meters (Everest) and was classified as an "A" group high-altitude climber for his exceptional skills. Pre-existing high blood pressure was noted, for which he

Table 2. Variants found in genes associated with hypoxia, neuromuscular diseases, and blood diseases.

Variant location	Allele	Gene name	Substitution (HGVS)	Variant consequence	gnomAD AF	Pathogenicity*	Diseases associated with the gene	Inheritance
				Whole exomes				
chr1:169542404	[‘G’, ‘A’]	*F5*	NM_000130.5:c.2686C>T	Stop gained	-	LP	Thrombophilia and 5 more	AD, AR
chr1:231421508	[‘A’, ‘T’]	*EGLN1*	NM_022051.3:c.381T>A	Stop gained	-	LP	Hemoglobin, high altitude adaptation, Erythrocytosis, familial, 3	AD
chr2:46384660	[‘A’, ‘G’]	*EPAS1*	NM_001430.5:c.2613A>G	Stop lost	-	VUS	Erythrocytosis, familial, 4	AD
chr2:178669592	[‘CT’, ‘C’]	*TTN*	NM_001267550.2:c.35469del	Frameshift variant & splice region variant	-	LP	Various types of cardiomyopathy, muscular dystrophy, myopathy	AD, AR
chr17:4932933	[‘T’, ‘A’]	*GP1BA*	NM_000173.7: c.329T>A	Stop gained	-	LP	Bernard–Soulier syndrome, type A1 (recessive) and A2 (dominant) von Willebrand disease, platelet-type	AD, AR
				Clinical exomes				
chr4:56478475	[‘C’, ‘T’]	*SRP72*	NM_006947.4: c.739C>T	Stop_gained	-	LP	Bone marrow failure syndrome 1	AD
chr12:6363461	[‘C’, ‘T’]	*SCNN1A*	NM_001038.6: c.666G>A	Stop_gained	0.000001879	LP	Bronchiectasis with or without elevated sweat chloride 2, Pseudohypoaldosteronism, type IB1, Liddle syndrome 3	AD, AR
chr17:39665447	[‘CTG’, ‘C’]	*TCAP*	NM_003673.4: c.90_91del	Frameshift_variant	-	P	Cardiomyopathy, hypertrophic, 25	AD
chr18:34829399	[‘GGTTACCTGA GGGAATAAGT’, ‘G’]	*DTNA*	NM_001386795.1: c.1087_1105del	Frameshift_variant & splice_region_variant	-	LP	Left ventricular noncompaction 1, with or without congenital heart defects	AD

* - pathogenicity class was assigned assuming the variant is observed in an individual affected with the respective disorder. P, pathogenic; LP, likely pathogenic; VUS, variant of uncertain significance; AD, autosomal dominant; AR, autosomal recessive; AF, allele frequency.

Table 3. Haematological profile of the donors with variants in the *EGLN1* and *EPAS1* genes.

Parameters	Reference levels	*EGLN1* variant carrier	*EPAS1* variant carrier
EPO level	2.59–18.5	6.8 mIU/mL	8.9 mIU/mL
Hematocrit	39–50	45.1%	45.6%
Hemoglobin	13.1–17.2	16.0 g/dL	15.9 g/dL
Erythrocytes	4.2–5.6	**5.62 × 10^6/µL**	5.01 × 10^6/µL
MCV (medium erythrocytes volume)	81–101	**80.2 fL**	91.0 fL
Thrombocytes	150–400	214 × 10^3/µL	**142 × 10^3/µL**
Leukocytes	4.5–11	4.76 × 10^3/µL	6.24 ×10^3/µL

Values outside of the reference intervals are highlighted in bold. EPO, erythropoietin.

regularly received medication to manage critically elevated levels. Mutations in *TCAP* are associated with limb-girdle muscular dystrophy, a disease with a wide geographic distribution, although genotype-phenotype relationships remain unclear [43,44]. Previous studies have also linked *TCAP* missense mutations to hypertrophic cardiomyopathy-25 in two Japanese patients [45] and to late-onset hypertrophic cardiomyopathy in a Portuguese family [46].

Among the likely pathogenic variants a heterozygous variant (c.2686C>T; p.Gln896*) in the *F5* gene was identified in a 35-year-old male who has been mountaineering for over 12 years. This individual has reached an altitude of 7134 meters without supplemental oxygen and has worked extensively as a technical climber on 5000-meter peaks. The presence of the factor V Leiden variant in one or both copies of the *F5* gene can lead to thrombophilia [47].

The donor carrying a heterozygous *TTN* gene variant (c.35469del; p.Val11824Phefs*35) is a candidate Master of Sport and a physically robust mountaineer who has an altitude of 7134 meters without supplemental oxygen, but began experiencing symptoms of acute mountain sickness above 4000 meters. Heterozygous mutations in *TTN* are associated with cardiomyopathies, and *TTN* is the most commonly implicated gene in these conditions [48].

Another likely pathogenic variant was identified in the glycoprotein Ib (*GP1BA*/*GP Ib*) gene, which serves as a receptor for von Willebrand factor [49]. A heterozygous variant (c.329T>A; p.Leu110*) in this gene was found in the exome of a 41-year-old woman included in Group B. She attempted to conquer Lenin Peak (7134 meters) for two consecutive years, reaching a maximum altitude of 5300 meters each time before needing assistance to descend. Mutations in *GP1BA* are known to cause Bernard-Soulier syndrome (BSS), a condition where patients with classical BSS exhibit a severe bleeding tendency, especially following childbirth or surgery. Heterozygous carriers are generally asymptomatic with normal platelet counts, although some may display slightly enlarged platelets and reduced expression of the platelet glycoprotein GPIb-IX-V complex [50].

Yet another likely pathogenic, heterozygous variant (p.Gln247*; c.739C>T) in the *SRP72* gene was identified in the clinical exome of a 59-year-old man from Group B. This individual has dedicated over 30 years to mountaineering, completed more than ten ascents above 5000 meters, and reached a maximum height of 7000 meters. There is only one study that describes heterozygous *SRP72* mutations in two families with autosomal-dominant familial aplastic anemia and myelodysplasia [51].

The carrier of the heterozygous *SCNN1A* variant (rs1200270245; p.Trp222*) was a 31-year-old man with three ascents who had been included in Group B, having reached a maximum altitude of 6200 meters. He worked as a high-altitude cook on Lenin Peak, stationed at 4400 meters, and after extended acclimatization at that height, attempted to climb Lenin Peak several times. However, these attempts were unsuccessful due to worsening mountain sickness, which prevented him from continuing. *SCNN1A* variants are known to cause several distinct conditions, with different inheritance patterns, including Liddle syndrome, multisystem pseudohypoaldosteronism (PHA), and a cystic fibrosis-like disease (a condition with polygenic inheritance, associated with both hypo- and hyperactive alleles of the gene). While the autosomal dominant Liddle syndrome occurs when mutations in the gene's extracellular domain lead to channel activation, loss-of-function *SCNN1A* alleles tend to be recessive, causing multisystem PHA [52–54].

A heterozygous variant (c.1087_1105del; p.Leu363Hisfs*12) in the *DTNA* gene was identified in a 28-year-old woman from Group B. She is an amateur mountaineer with over 10 years of experience, having reached a peak altitude of 7134 meters without the use of supplemental oxygen. A recent study described 12 individuals from four unrelated families with dominantly inherited missense variants in *DTNA*. These individuals exhibited a range of phenotypes, including hyperCKemia—characterized by clinical symptoms such as muscle weakness, rhabdomyolysis, elevated serum creatine kinase (CK) levels, exercise intolerance, and/or myalgias—along with a mild form of muscular dystrophy [55].

4. Discussion

Identification of the genetic factors that confer adaptation to environmental stresses, such as extreme temperatures, malnutrition, or hypoxia, is a very important step

toward understanding human biology and enhancing stress resistance. High-altitude adaptation is of particular interest to researchers, as it provides a useful model for investigating the genetic and physiological determinants of the hypoxic response and hypoxic resistance.

A total of 64 distinct genetic variants (across 72 families) have been documented in various studies since the discovery of the first *EGLN1* variant, including missense, frameshift, and nonsense mutations [56]. Nearly all patients with erythrocytosis due to an *EGLN1* mutation are heterozygous, except for two siblings who were reported as homozygous for p.Cys42Arg [57]. The main phenotype for these patients is typically erythrocytosis, with complications, including thrombosis, hypertension, renal cysts, angiomas, and, in rare cases, paraganglioma or pheochromocytoma also potentially occurring [58]. Nevertheless, according to available literature, the effects of the *EGLN1* variants on hematological parameters are variable. For example, as shown in [56], individuals carrying the *EGLN1* variant p.Gln134* may display mild to moderate erythrocytosis; however, EPO levels remain normal. In contrast, in [59], the presence of the p.Gln134* variant was not consistently associated with elevated EPO or hemoglobin levels. Notably, in a cohort study of patients with *EGLN1* variants, including p.Cys127Ser [21,60], only a subset developed erythrocytosis, while others had normal EPO levels and un-elevated hemoglobin levels.

Given the combination of a mild increase in erythrocyte count and excellent high-altitude performance, we hypothesize that the p.Cys127* variant may confer an adaptive advantage in the carrier individual from our cohort, enhancing oxygen transport efficiency without triggering excessive erythropoiesis or EPO elevation. This is consistent with previous reports suggesting that some *EGLN1* variants—while not always associated with overt clinical phenotypes—may contribute to beneficial modulation of hypoxia responses in extreme environments.

A modest reduction in platelet count—similar to the mild thrombocytopenia observed in another donor carrying the *EPAS1* variant—may confer protective benefits against the prothrombotic changes seen during prolonged high-altitude exposure. It was shown that chronic hypoxia typically causes increased platelet reactivity and aggregation, leading to a prothrombotic phenotype at altitude [61].

Conversely, long-term high-altitude residency often shows decreased platelet counts [62], coupled with increased mean platelet volume—suggestive of a reduction in thrombocyte number due to consumption or redistribution. This natural counterbalance appears to protect inhabitants from excessive clot formation despite sustained hypoxia. In line with these observations, lower platelets in our *EPAS1* mutant donor may reflect a similar protective adaptation—dampening hypercoagulability and thus reducing the risk of altitude-induced thrombosis. Although we lack longitudinal or functional clotting data, this mechanism aligns with broader physiological responses seen in well-acclimatized high-altitude populations.

EPAS1 (HIF-2α) is expressed in platelets and becomes stabilized under hypoxic conditions, promoting the production of prothrombotic factors such as PAI-1 and contributing to increased thrombogenesis. Previously it was shown that individuals exposed to chronic hypoxia, including high-altitude residents, exhibit elevated HIF-2α activity in platelets and associated thrombogenic markers [63]. Therefore, we hypothesize that the *EPAS1*:c.2613A>G variant in our donor may reduce HIF-2α activity, leading to a mild antithrombotic effect. This could represent an adaptive mechanism that helps mitigate the risk of thrombosis during high-altitude exposure.

In addition to the *EPAS1* and *EGLN1* gene variants previously described in the context of adaptation to high altitude conditions, exome sequencing in the cohort of climbers revealed a pathogenic variant in the *TCAP* gene and six likely pathogenic variants in *F5*, *TTN*, *DTNA*, *GP1BA*, *SRP72*, and *SCNN1A*. Although these variants are intriguing in the context of physiological performance under extreme environmental stress, we acknowledge that these variants most likely represent incidental findings. Thus, expanding the sample size could plausibly reveal additional variants of a similar nature. Nevertheless, we believe documenting these observations is important, as these findings contribute to the growing body of knowledge on genetic variation in rare populations with exceptional physical capabilities. Recent studies have increasingly focused on the impact of genetic factors on endurance, strength, and even injury susceptibility in athletes [64,65]. Some pathogenic variants may carry dual effects, potentially enhancing physical performance early in life, while subsequently predisposing to clinical complications [66]. This underscores the complexity of interpreting rare genetic findings in athletic individuals. While our analysis did not detect a clear adaptive signature across the group, the identification of these variants underscores the value of comprehensive genetic screening in elite populations and may help refine variant interpretation frameworks for future studies. However, notably, our analysis may have missed several potentially adaptive variants located in non-coding regions of the genome or in genes not included in standard clinical exome panels.

Proving the positive impact of the detected variants on high-altitude adaptation, even outside extreme-altitude environments, presents significant challenges for two key reasons. First, it is nearly impossible to find a suitable control group that can clearly distinguish between the environmental effects, such as those caused by exercise, and genetic influences on fitness. The ideal control group would require individuals with similar experiences and at least partially matching genotypes. Second, to demonstrate the impact of these variants on the phenotype, a larger number of individuals carrying these variants is needed to produce

statistically reliable conclusions. However, because these variants are extremely rare in the population (with an allele frequency in gnomAD of less than 10^{-5}), finding additional carriers is both difficult and time-consuming. We suppose that future functional validation of these genes, combined with proteomics-assisted insights into biological pathways, could provide valuable information regarding inter-individual differences in key proteins, thereby enriching research on high-altitude adaptation. We are convinced that future studies should focus on diverse populations, including high-altitude groups such as Sherpas and Central Asian highlanders, similar to the Kyrgyz and Andean populations, as well as lowland populations that ascend to high altitudes, including mountaineers and athletes. This broader perspective could shed light on the mechanisms underlying hypoxia adaptation.

Despite these challenges, detecting a range of functionally significant variants in high-altitude mountaineers adds to a growing body of research reporting pathogenic alleles in individuals who exhibit increased resilience to altitude-related stress. Although direct evidence of their positive role in high-altitude adaptation is difficult to obtain, the discovery of new variants in the *EPAS1* and *EGLN1* genes could contribute to our understanding of genetic resilience in extreme environments.

5. Conclusions

In summary, our study contributes to the growing understanding of genetic variation potentially involved in high-altitude adaptation among non-indigenous individuals. We identified several functionally significant variants in genes involved in cardiovascular physiology, muscle function, and the hypoxic response. Among them, the rare loss-of-function variants in *EPAS1* and *EGLN1* are of particular interest given their established roles in oxygen sensing and previous associations with high-altitude adaptation in native populations. While these findings are intriguing, their functional impact remains to be validated and should be interpreted with caution.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

VAM, ASG, MVA, and OSG conceived and designed research, VAM performed experiments, EMM, TEL and YAB analyzed data, all authors interpreted results of experiments, EMM and YAB prepared tables, EMM and YAB drafted the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the D.O. Ott Research Institute of Obstetrics, Gynaecology, and Reproductology, protocol number 117 dated 19.04.2022. All study participants or their legal guardians provided their written informed consent, including consent for publication. The study was carried out in accordance with the guidelines of the Declaration of Helsinki.

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Conflict of Interest

All authors declare no conflicts of interest. Valeriia A. Merkureva are employed by CerbaLab Ltd., but her affiliation did not influence the interpretation of data or the writing of the manuscript.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBS38966.

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