

EPAS1 and VEGFA Polymorphisms Modulate COPD Susceptibility in a High-Altitude Population: A Case-Control Study

Lin Lin^{1,*}, Yi Zhang^{1,*}, Xiang Fu¹, Yangjie Zhang¹, Yunchao Wang², Zhen Yang¹, Xiaoming Ma³, Xinhua Wang¹

¹Institute of Public Health, Gansu University of Chinese Medicine, Lanzhou, Gansu, People's Republic of China; ²Institute of Basic Medicine, Gansu University of Chinese Medicine, Lanzhou, Gansu, People's Republic of China; ³Department of Medical, Lanzhou Pulmonary Hospital, Lanzhou, Gansu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiaoming Ma, Department of Medical, Lanzhou Pulmonary Hospital, Lanzhou, Gansu, People's Republic of China, Email 383717579@qq.com; Xinhua Wang, Institute of Public Health, Gansu University of Chinese Medicine, Lanzhou, Gansu, People's Republic of China, Email Wxh@gszy.edu.cn

Background: The onset and progression of Chronic Obstructive Pulmonary Disease (COPD) are influenced by both environmental and genetic factors. Persistent hypoxia at high altitudes is a major environmental stressor. Under hypoxic conditions, *EPAS1* is stably expressed and activates its downstream target gene *VEGFA*; however, the underlying mechanisms remain unclear.

Methods: We conducted a case-control study in Gansu Province: to evaluate the association between *EPAS1* gene polymorphisms (rs4953354, rs6743991, rs7589861, rs13419896) and susceptibility to COPD in high-altitude populations, we enrolled 517 patients and 580 controls (no significant differences in ethnic distribution, no stratification was performed); To evaluate the association of *VEGFA* gene polymorphisms (rs10434, rs2010963, rs3025020, rs833070) in Tibetan and Han populations, we enrolled 397 patients (148 Tibetans, 249 Han) and 807 controls (251 Tibetans, 556 Han).

Results: For *EPAS1*, rs4953354 A>G was associated with a decreased risk of COPD (AG vs. AA: OR = 0.680, 95% CI = 0.523–0.885; AG+GG vs. AA: OR = 0.708, 95% CI = 0.551–0.910). For *VEGFA*, in Han population, rs2010963 C>G (CG vs. CC: OR = 1.619, 95% CI = 1.070–2.449; GG vs. CC: OR = 1.751, 95% CI = 1.119–2.740; CG+GG vs. CC: OR = 1.670, 95% CI = 1.133–2.462) and rs3025020 C>T (TT vs. CC: OR = 2.290, 95% CI = 1.321–3.971; TT vs. CT+CC: OR = 2.151, 95% CI = 1.276–3.626) were associated with an increased risk of COPD. Conversely, in the Tibetan population, rs3025020 C>T was associated with a decreased risk of COPD (CT vs. CC: OR = 0.530, 95% CI = 0.329–0.853; CT+TT vs. CC: OR = 0.571, 95% CI = 0.365–0.893). No significant associations were observed for other loci.

Conclusion: This study reveals that *EPAS1* and *VEGFA* gene polymorphisms are associated with susceptibility to COPD in populations residing at high altitudes.

Keywords: chronic obstructive pulmonary disease, *EPAS1*, *VEGFA*, gene polymorphism, high altitude

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disorder characterized primarily by persistent airflow limitation. Its pathological basis is mostly manifested as chronic bronchitis and emphysema.¹ COPD has a high incidence and mortality worldwide, causing over 3.3 million deaths annually, accounting for 5.8% of global deaths, and ranks as the third leading cause of death.² The disease not only severely impairs patients' quality of life but also imposes substantial economic and medical burdens on families and society.³ Studies have shown that the onset and progression of COPD are driven by a combination of environmental and genetic factors.⁴ Environmental risk factors mainly include smoking, air pollution, and occupational exposures, whereas individual susceptibility involves genetic

predisposition. Genome-wide association studies (GWAS) have identified multiple gene loci related to COPD susceptibility, such as *EGLN1*,⁵ *GSTP1*,⁶ and *EPO*.⁷ These genetic variants not only influence disease risk but also enhance individual sensitivity to harmful environmental factors. Although GWAS continues to identify new susceptibility genes, the genetic mechanisms underlying COPD remain to be further elucidated. Particularly, the regulatory mechanisms of gene–environment interactions in COPD pathogenesis under the unique hypoxic conditions of high-alt environments remain unclear.

Endothelial PAS domain protein 1 (*EPAS1*), also known as hypoxia-inducible factor 2 alpha (HIF-2 α), is a core member of the hypoxia-inducible factor (HIF) family.⁸ It forms a heterodimeric complex with the oxygen-dependent regulatory subunit HIF-2 α and the stable structural subunit HIF-1 β , playing a key role in the regulation of cellular hypoxic homeostasis.⁹ Studies have confirmed that *EPAS1* is the only critical regulatory factor consistently associated with multiple disease severity features of COPD. Yoo et al identified *EPAS1* as a unique and essential regulator among 126 key regulators of COPD.¹⁰ Its downstream target genes significantly overlap with genomic regions associated with COPD severity, indicating its deep involvement in COPD pathogenesis.¹⁰ Vascular endothelial growth factor A (*VEGFA*), a core member of the *VEGF* family, is a crucial regulator of angiogenesis and is involved in chronic inflammation,¹¹ airway remodeling,¹² and pulmonary hypertension¹³ in COPD. The transcriptional activation of *VEGFA* relies directly on the binding of HIF family members, including *EPAS1*, to hypoxia response elements (HREs) in the gene promoter region.¹⁴ This forms the “EPAS1–HIF-2 α –VEGFA” hypoxia response regulatory axis, which plays an irreplaceable role in maintaining lung function and disease development.

The sustained hypoxia in plateau environments fundamentally differs from the secondary hypoxia observed in COPD patients in lowland areas, and this environmental specificity may lead to significant differences in the genetic regulatory mechanisms of COPD between the two settings. In lowland COPD, hypoxia is typically a “secondary acute or subacute hypoxia” occurring in the late stages of disease progression, primarily relying on the HIF-1 α pathway to activate *VEGFA* expression as a compensatory response to improve local pulmonary oxygen supply.¹⁵ In contrast, populations living at high altitudes are chronically exposed to “primary chronic hypoxia,” in which the HIF pathway, especially the *EPAS1*-mediated HIF-2 α signaling axis, has undergone adaptive evolution (for example, specific *EPAS1* variants in Tibetans reduce hemoglobin concentration to adapt to hypoxia).¹⁶ This adaptive genetic background may modify the regulatory role of the *EPAS1/VEGFA* pathway in COPD. For instance, overexpression of *VEGFA* in lowland COPD patients often exacerbates pulmonary vascular fibrosis,¹⁷ whereas moderate levels of *VEGFA* expression in high-altitude populations may contribute to pulmonary vascular adaptive remodeling,¹⁸ thereby inversely affecting COPD susceptibility. Allele frequency differences in core hypoxia adaptation genes between Tibetan and Han populations may interact synergistically or antagonistically with *EPAS1/VEGFA* gene polymorphisms, resulting in ethnic-specific genetic susceptibility to COPD.

Based on the above background, we hypothesized that specific single nucleotide polymorphisms (SNPs) in the *EPAS1* and *VEGFA* genes are associated with COPD susceptibility in high-altitude hypoxic environments, and that the association involving *VEGFA* differs between Tibetan and Han populations. To test this hypothesis, we conducted a case-control study. To date, no studies have analyzed the relationship between these SNPs and COPD susceptibility in high-altitude populations. This study represents the first systematic case-control investigation of the associations between the aforementioned SNPs and COPD risk in high-altitude residents. Our objectives are to identify populations at increased genetic risk for COPD, provide a theoretical basis for early prevention and individualized interventions in this region, and lay a scientific foundation for establishing biomarker-based early screening systems, advancing tertiary prevention strategies, and developing targeted.

Methods

Study Population

According to international conventions, high altitude is defined as ranging from 1500 to 3500 meters.¹⁹ In this study, the selected regions were Tianzhu Tibetan Autonomous County in Wuwei City and the Gannan Tibetan Autonomous

Prefecture, both located in Gansu Province, China. The altitudes of these areas exceed 2500 meters. Participants who have resided in these regions for more than five years were chosen as study subjects to ensure phenotypic stability.

This study employed a case-control design. Between 2023 and 2024, we recruited an initial multi-ethnic cohort comprising 517 COPD patients and 580 healthy controls to screen four SNPs in the *EPAS1* gene (rs4953354 A>G, rs6743991 C>A, rs7589861 A>G, and rs13419896 G>A), aiming to evaluate the fundamental role of *EPAS1* as a key regulatory gene. Based on the results of the initial phase and the recognized biological significance of *VEGFA*, we hypothesized the presence of ethnicity-specific genetic effects. To test this hypothesis, we established an ethnically stratified extended cohort in the same regions, including 397 COPD patients (148 Tibetan and 249 Han) and 807 healthy controls (251 Tibetan and 556 Han). This cohort was specifically used to analyze four SNPs in the *VEGFA* gene (rs10434 A>G, rs2010963 C>G, rs3025020 C>T, and rs833070 T>C). This design allowed for a more precise evaluation of the role of *VEGFA* across different genetic backgrounds, minimizing potential confounding effects of ethnic composition present in the initial cohort. Together, the two study phases constitute a comprehensive and logical framework that progresses from upstream regulatory factors to downstream effector genes, and from generalized association analyses to ethnicity-specific investigations.

All study participants were recruited from the natural urban and rural populations in Gansu Province. This study primarily included COPD patients in a stable phase with relatively mild clinical symptoms, mainly characterized by cough, sputum production, and shortness of breath. Patients with comorbid respiratory diseases such as asthma or pulmonary fibrosis, or other conditions potentially affecting lung function, were excluded. All subjects enrolled in both the case-control and prevalence studies completed standardized pulmonary function tests and respiratory health questionnaires. The questionnaires collected key variables including sociodemographic characteristics and environmental exposure history. After obtaining written informed consent, trained medical personnel collected 5 mL of venous blood from each participant for subsequent genome-wide genotyping analyses.

Diagnostic Criteria for COPD and Pulmonary Function Testing

According to the 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,²⁰ COPD is diagnosed when a patient presents with symptoms such as dyspnea, cough, and sputum production, alongside smoking-related risk factors, and the ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) measured 30 minutes after inhalation of 400 µg salbutamol is less than 70%. Pulmonary function tests were performed using the EasyOne spirometer (NDD Medizintechnik AG, Switzerland) following the manufacturer's instructions.

SNP Selection and Genotyping

We downloaded all loci of the two genes from the National Center for Biotechnology Information (NCBI) and the 1000 Genomes Project databases. The selection criteria were as follows: SNPs located within ±2000 base pairs of the *EPAS1* and *VEGFA* genes; SNPs with a minor allele frequency (MAF) greater than 0.05 in the Chinese population and conforming to Hardy-Weinberg equilibrium (HWE); and tag SNPs with low linkage disequilibrium (LD, $r^2 < 0.8$) identified through LD analysis using Haploview 4.2. The detailed screening process is shown in [Supplementary Figure 1](#). Ultimately, we selected rs4953354 A>G, rs6743991 C>A, rs7589861 A>G, rs13419896 G>A in *EPAS1* and rs10434 A>G, rs2010963 C>G, rs3025020 C>T, rs833070 T>C in *VEGFA* for further analysis. Detailed information on each SNP is summarized in [Table 1](#). The genetic linkage disequilibrium map is shown in [Supplementary Figures 4 and 5](#).

Genomic DNA was extracted from the collected peripheral blood samples using the blood genome DNA extraction kit (DP349) provided by TianGen Biochemical Technology. Genotyping was performed using the TaqMan-MGB probe method. To ensure the reliability of PCR reactions, each plate included negative controls, and 10% of the samples were randomly selected for duplicate testing to assess reproducibility ($Kappa \geq 0.80$). The relevant experimental methods, equipment, and reagents are described in [Supplementary Figures 2–3](#) and [Supplementary Tables 1–2](#).

Methods of Statistical Analysis

Data were double-entered and verified using Epidata 3.1 to ensure accuracy. All statistical analyses were conducted with SPSS version 26.0. Categorical data were presented as counts and percentages or composition ratios. In the analysis of

Table 1 Information of tag SNPs Finally Included in the *EPAS1* and *VEGFA* Gene

SNP	Chromosomal Position ^a	Region	MAF ^b
EPAS1			
rs4953354 (A>G)	chr2:46575388	intron_variant	0.117
rs6743991 (C>A)	chr2:46583235	intron_variant	0.15
rs7589861 (A>G)	chr2:46610479	intron_variant	0.17
rs13419896 (G>A)	chr2:46556345	intron_variant	0.306
VEGFA			
rs10434 (A>G)	Chr6:43753212	3 prime UTR	0.35
rs2010963 (C>G)	Chr6:43738350	5 prime UTR	0.33
rs3025020 (C>T)	Chr6:43749110	intron variant	0.23
rs833070 (T>C)	Chr6:43742626	intron variant	0.34

Notes: ^a Human Reference Genome GRCh37 ^b Minor Allele Frequency in the 1000 Genomes Phase 3 Database.

general demographic characteristics, χ^2 -tests were applied to compare distributions of variables such as sex, age, marital status, and education level between the case and control groups, assessing differences between groups. A significance level of $\alpha = 0.05$ was used for all statistical tests.

In the genetic association analysis, we systematically evaluated the relationships between COPD risk and eight SNPs: four loci in the *EPAS1* gene (rs4953354 A>G, rs6743991 C>A, rs7589861 A>G, rs13419896 G>A) and four loci in the *VEGFA* gene (rs10434 A>G, rs2010963 C>G, rs3025020 C>T, rs833070 T>C). For each SNP, additive, dominant, and recessive genetic models were constructed to comprehensively assess genotype–disease associations. Binary logistic regression was applied for the analysis. After adjusting for potential confounders including age, sex, and smoking status, odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated to quantify the association between genotypes and the risk of developing COPD. To identify the genetic model that best fit the data, we compared the Akaike Information Criterion (AIC) values across the three models for each SNP. The model with the smallest AIC value was selected as the optimal genetic model and used for subsequent stratified analyses and interaction investigations.

In the stratified analysis, subgroup analyses were conducted according to gender, age, BMI, education level, marital status, and smoking history. The Breslow-Day test was employed to assess the homogeneity of association effects across subgroups. Furthermore, the Cochran-Mantel-Haenszel test was applied to adjust for potential confounding factors and to compare the strength of the association between genetic polymorphisms and COPD risk across the population.

In the interaction analysis, multiplicative interaction models were constructed based on logistic regression to investigate whether there exist multiplicative interactions between the genotypes of each SNP locus in *EPAS1* and *VEGFA* genes and population characteristics (such as gender, age, and smoking) in relation to COPD risk.

To control the risk of Type I errors arising from testing multiple SNP loci and genetic models, we applied the Benjamini-Hochberg False Discovery Rate (FDR) method to correct the results of the main genetic association analyses. For each SNP, we selected the p-value corresponding to the best-fitting genetic model with the lowest AIC value to calculate the FDR q-value. Corrected q-values less than 0.05 were considered statistically significant. To ensure the reliability of statistical inferences, a post-hoc power analysis was conducted in this study to assess the ability of the current sample size to detect the observed effect size.

Prior to establishing the final analytical model, the distribution of ethnicity between case and control groups was first assessed. In the *EPAS1* study cohort, no significant difference in ethnic distribution was observed between groups ($P = 0.593$). Accordingly, ethnicity was not considered a major confounding factor in the genetic association analysis of *EPAS1* in this study. Therefore, subsequent analyses of *EPAS1* were conducted without ethnic stratification to preserve maximal statistical power for detecting its main effects. However, based on the biological rationale that *VEGFA*, as a downstream effector, may exhibit more population-specific regulatory patterns, a novel hypothesis was proposed. To test this, ethnic stratification was deliberately incorporated into the *VEGFA* analysis ($P = 0.032$).

Results

Association Between EPAS1 Genetic Polymorphisms and COPD in a High-Altitude Population

Demographic Characteristics Analysis

As shown in Table 2, among the included general population, the distribution of age differed significantly between the case and control groups ($P < 0.001$). In contrast, no statistically significant differences were observed in the distribution of gender ($P = 0.406$), ethnicity ($P = 0.593$), BMI ($P = 0.374$), education level ($P = 0.099$), marital status ($P = 0.107$), or smoking status ($P = 0.559$) between cases and controls. The complete table can be found in the [Supplementary Tables 3](#).

Association Analysis Between EPAS1 Genetic Polymorphisms and COPD Risk

Statistical analyses of the association between the *EPAS1* gene polymorphisms rs4953354 (A>G), rs6743991 (C>A), rs7589861 (A>G), and rs13419896 (G>A) and susceptibility to COPD were conducted under three different genetic models: additive, dominant, and recessive. The additive model compared the statistical associations among wild-type, heterozygous, and homozygous mutant genotypes. The dominant model compared wild-type genotypes with combined heterozygous plus homozygous mutant genotypes, while the recessive model compared combined wild-type plus heterozygous genotypes with homozygous mutant genotypes. Binary logistic regression was employed to analyze the association between each SNP and COPD susceptibility, adjusting for potential confounders including sex, age, and

Table 2 Basic Demographic Characteristics of the Study Population

Variables	Total	Case Group, n (%)	Control Group, n (%)	χ^2	P
EPAS1					
Age				63.521	<0.001*
≤60	528	183(35.4)	345(59.5)		
>60	569	334(64.6)	235(40.5)		
VEGFA (TOTAL)				4.582	0.032*
Ethnic Groups					
Tibetan	399	148(37.3)	251(31.1)		
Han	805	249(62.7)	556(68.9)		
VEGFA (Tibetan)				6.898	0.009*
Gender					
Male	179	79(53.4)	100(39.8)		
Female	220	69(46.6)	151(60.2)		
Age				18.676	<0.001*
≤60	241	69(46.6)	172(68.5)		
>60	158	79(53.4)	79(31.5)		
Smoking				10.771	<0.001*
Yes	115	57(38.5)	58(23.1)		
No	284	91(61.5)	193(76.9)		
VEGFA (HAN)				20.029	<0.001*
Gender					
Male	403	154(61.8)	249(44.8)		
Female	402	95(38.2)	307(55.2)		
Age				60.289	<0.001*
≤60	508	108(43.4)	400(71.9)		
>60	297	141(56.6)	156(28.1)		
Smoking				12.752	<0.001*
Yes	311	119(47.8)	192(34.5)		
No	494	130(52.2)	364(65.5)		

Note: *Statistically significant parameters.

smoking status. Finally, the model with the lowest Akaike information criterion (AIC) value was selected as the optimal model.

rs4953354 A>G

As shown in [Table 3](#), after adjusting for confounding factors, logistic regression analysis indicated that, Under the additive model, individuals carrying the AG genotype was associated with a 32% decreased risk of COPD compared to those with the AA genotype (AG vs. AA: OR = 0.680, 95% CI = 0.523–0.885, $P = 0.004$). Under the dominant model, individuals with the AG+GG genotypes were associated with a 29.2% decreased risk of COPD compared to those with the AA genotype (AG+GG vs. AA: OR = 0.708, 95% CI = 0.551–0.910, $P = 0.007$). However, the recessive model analysis indicated no statistically significant association between the rs4953354 A>G polymorphism and COPD susceptibility ($P > 0.05$).

rs6743991 C>A, rs7589861 A>G and rs13419896 G>A

In the high-altitude population included in this study, no statistically significant association with the risk of COPD was observed for the three *EPAS1* loci (rs6743991 C>A, rs7589861 A>G, and rs13419896 G>A) under any of the three genetic models—additive, dominant, or recessive ($P > 0.05$). The complete table can be found in the [Supplementary Tables 4](#).

Stratified Analysis and Interaction Analysis of EPAS1 Gene SNP Loci and COPD Risk

As shown in [Supplementary Table 5](#), The Breslow-Day test for homogeneity of the rs4953354 A>G genotype demonstrated no statistically significant differences in the effect of this genetic variant across subgroups stratified by sex, ethnicity, marital status, education level, BMI, and smoking status ($P > 0.05$). This indicates that the influence of the

Table 3 Association of SNPs in *EPAS1* and *VEGFA* with COPD Susceptibility

Models	Genotypes	Case Group n (%)	Control Group n (%)	Adjusted OR ^a (95% CI)	P ^a	FDR q ^b	AIC
EPAS1 rs4953354A>G	AA	329(63.6)	322(55.5)				
	AG	158(30.6)	227(39.1)	0.680(0.523–0.885)	0.004*	0.016	1427.920
	GG	30(5.8)	31(5.3)	0.909(0.529–1.562)	0.730		
	Additive			0.708(0.551–0.910)	0.007*		
	Dominant	AG+GG vs. AA	258(44.5)	1.048(0.615–1.784)	0.864		
	Recessive	GG vs. AA+AG	549(94.7)				1437.577
VEGFA rs2010963C>G (HAN)	CC	60(24.1)	93(16.7)				
	CG	116(46.6)	277(49.8)	1.619(1.070–2.449)	0.022*	0.028	989.857
	GG	73(29.3)	186(33.5)	1.751(1.119–2.740)	0.014*		
	Additive			1.670(1.133–2.462)	0.010*		
	Dominant	CG+GG vs. CC	463(83.3)	1.246(0.884–1.756)	0.209		
	Recessive	GG vs. CC+CG	370(66.5)				994.509
rs3025020C>T (Tibetan)	CC	47(31.8)	107(42.6)				
	CT	76(51.4)	102(40.6)	0.530(0.329–0.853)	0.009*	0.036	520.952
	TT	25(16.9)	42(16.7)	0.695(0.372–1.298)	0.253		
	Additive			0.571(0.365–0.893)	0.014*		
	Dominant	CT+TT vs. CC	144(57.4)	0.985(0.562–1.727)	0.959		
	Recessive	TT vs. CT+CC	209(83.3)				521.538
rs3025020C>T (HAN)	CC	114(45.8)	212(38.1)				
	CT	114(45.8)	253(45.5)	1.127(0.805–1.578)	0.485	0.012	984.896
	TT	21(8.4)	91(16.4)	2.290(1.321–3.971)	0.003*		
	Additive			1.306(0.948–1.799)	0.102		
	Dominant	CT+TT vs. CC	344(61.9)	2.151(1.276–3.626)	0.004*		
	Recessive	TT vs. CT+CC	465(83.6)				991.715
							986.089

Notes: *Statistically significant parameters. ^a Logistic regression after correction gender, age, smoking status. ^b FDR q-values were calculated using the Benjamini-Hochberg procedure.

Abbreviations: OR, Odds Ratio; CI, confidence interval; AIC, Akachi Information Criterion.

rs4953354 A>G polymorphism on COPD susceptibility is consistent among different stratified groups. Further stratified analysis using the Cochran–Mantel–Haenszel (CMH) test to combine effects showed that the differences between the subgroup-specific CMH OR values and the original OR value (0.689) were all less than 0.1, supporting the consistency of OR values after controlling for confounding factors.

Additionally, interaction analysis between rs4953354 A>G and factors including sex, age, ethnicity, marital status, education level, BMI, and smoking status showed no statistically significant differences between cases and controls ($P > 0.05$).

Stratified Analysis and Interaction Analysis of VEGFA Gene SNP Loci and COPD Risk Demographic Characteristics Analysis of Tibetan and Han Populations

As shown in Table 2, within the Tibetan natural population, the distributions of sex ($P = 0.009$), age ($P < 0.001$), and smoking status ($P < 0.001$) differed significantly between the case and control groups; however, no statistically significant differences were observed for BMI ($P = 0.986$), education level ($P = 0.317$), or marital status ($P = 0.063$). Similarly, in the Han natural population, significant differences between cases and controls were found for sex ($P < 0.001$), age ($P < 0.001$), and smoking ($P < 0.001$), while no significant differences were detected for BMI ($P = 0.146$), education level ($P = 0.652$), or marital status ($P = 0.118$). The complete table can be found in the [Supplementary Tables 6 and 7](#).

Association Analysis of VEGFA Gene Polymorphisms with COPD Risk in Tibetan and Han Populations

Statistical analyses were conducted to assess the association between *VEGFA* gene polymorphisms (rs10434 A>G, rs2010963 C>G, rs3025020 C>T, and rs833070 T>C) and susceptibility to COPD using three genetic models: additive, dominant, and recessive. The additive model compared the effects among wild-type, heterozygous, and homozygous mutant genotypes; the dominant model assessed the association between wild-type versus combined heterozygous and homozygous mutant genotypes; and the recessive model compared wild-type plus heterozygous genotypes against homozygous mutants. Binary logistic regression was applied to analyze the relationship between each SNP and COPD susceptibility, adjusting for potential confounders including sex, age, and smoking status. The model with the lowest Akaike Information Criterion (AIC) value was ultimately selected as the best-fitting model.

rs2010963C>G

As shown in Table 3, In the Han population, after adjusting for confounding factors, logistic regression analysis indicated that under the additive model, individuals carrying the CG genotype was associated with a 61.9% increased risk of COPD compared to those with the CC genotype (CG vs. CC: OR = 1.619, 95% CI = 1.070–2.449, $P = 0.022$), and those with the GG genotype was associated with a 75.1% increased risk compared with CC carriers (GG vs. CC: OR = 1.751, 95% CI = 1.119–2.740, $P = 0.014$). Under the dominant model, individuals with the combined CG+GG genotypes were associated with a 67% increased risk of COPD compared with the CC genotype (CG+GG vs. CC: OR = 1.670, 95% CI = 1.133–2.462, $P = 0.010$). However, under the recessive model, no statistically significant association was found between rs2010963 C>G and COPD susceptibility ($P > 0.05$). In the Tibetan population, analyses based on all three genetic models showed no statistically significant association between rs2010963 C>G and COPD risk ($P > 0.05$).

rs3025020C>T

As shown in Table 3, In the Tibetan population, after adjusting for confounding factors, logistic regression analysis showed that under the additive model, individuals carrying the CT genotype was associated with a 47% decreased risk of COPD compared to those with the CC genotype (CT vs. CC: OR = 0.530, 95% CI = 0.329–0.853, $P = 0.009$). Under the dominant model, individuals with the combined CT+TT genotypes were associated with a 42.9% decreased risk of COPD compared with the CC genotype (CT+TT vs. CC: OR = 0.571, 95% CI = 0.365–0.893, $P = 0.014$). However, no statistically significant association was observed between rs3025020 C>T and COPD susceptibility under the recessive model ($P > 0.05$).

In the Han population, after adjusting for confounding factors, logistic regression analysis indicated that under the additive model, individuals carrying the TT genotype was associated with a 129% increased risk of COPD compared to

those with the CC genotype (TT vs. CC: OR=2.290, 95% CI=1.321–3.971, $P=0.003$). The dominant model showed no statistically significant association between rs3025020 C>T and COPD susceptibility ($P > 0.05$). Under the recessive model, individuals with the TT genotype was associated with a 115.1% increased risk of COPD compared to those with CT or CC genotypes combined (TT vs. CT+CC: OR=2.151, 95% CI=1.276–3.626, $P=0.004$).

rs10434A>G and rs833070T>C

Among both Tibetan and Han populations living at high altitudes, no statistically significant association was observed between the *VEGFA* rs10434 A>G and rs833070 T>C loci and the risk of COPD under additive, dominant, or recessive genetic models ($P > 0.05$). The complete table can be found in the [Supplementary Tables 8 and 9](#).

Stratified Analysis and Interaction Analysis of VEGFA Gene SNPs and COPD Risk

As shown in [Supplementary Table 10](#), in the Han population, stratified analysis of rs2010963 C > G under the dominant model used the CC genotype as the reference. Stratification by sex, age, body mass index (BMI), education level, and smoking status showed homogeneity among groups ($P > 0.05$). However, stratification by marital status revealed significant heterogeneity between groups ($P < 0.05$). In the multiplicative interaction analysis of rs2010963 C>G in the Han population under the dominant model, no significant multiplicative interactions were observed between rs2010963 C > G and sex, age, BMI, education, marital status, or smoking status ($P > 0.05$).

[Supplementary Table 11](#) presents the stratified analysis of rs3025020 C>T in the Tibetan population. Using the CC genotype as the reference under the dominant model, stratification by smoking status, sex, age, BMI, education level, and marital status showed homogeneity across all groups ($P > 0.05$). In the multiplicative interaction analysis of rs3025020 C>T within the Tibetan population under the dominant model, no significant multiplicative interactions were detected between rs3025020 C>T and smoking, sex, age, BMI, education, or marital status ($P > 0.05$).

[Supplementary Table 12](#) presents the stratified analysis of rs3025020 C>T in the Han population. Under the recessive model, using the combined CC+CT genotypes as the reference, stratification by smoking status, sex, age, BMI, education level, and marital status demonstrated homogeneity among groups ($P > 0.05$). The multiplicative interaction analysis under the recessive model showed no significant interactions between rs3025020 C>T and smoking, sex, age, BMI, education, or marital status ($P > 0.05$).

Analysis of the Relationship Between COPD Severity and SNPs

To investigate whether the identified susceptibility loci (*EPAS1* rs4953354, *VEGFA* rs2010963, and *VEGFA* rs3025020) are associated with the clinical severity of COPD, we stratified the patients and analyzed disease severity according to GOLD stages 1–4. Key pulmonary function parameters for the case and control groups are shown in [Table 4](#).

As shown in [Table 5](#), for the rs4953354 locus of the *EPAS1* gene, there was no statistically significant difference in the distribution of the AA, AG, and GG genotypes across GOLD stages 1–4 in the COPD patient cohort ($P = 0.061$). For the rs2010963 locus of the *VEGFA* gene, no significant statistical association was observed between the distributions of the CC, CG, and GG genotypes and the respective GOLD stages in Han Chinese patients ($P = 0.869$). Similarly, for the rs3025020 locus, the distributions of the CC, CT, and TT genotypes did not show statistically significant associations with GOLD classifications in either Tibetan ($P = 0.586$) or Han Chinese ($P = 0.579$) patients. The complete table can be found in [Supplementary Table 13](#).

Table 4 Comparison of Pulmonary Function Parameters Among EPAS1 and VEGFA Genotype Groups

Indicators	EPAS1		VEGFA (Tibetan)		VEGFA (HAN)	
	Case Group	Control Group	Case Group	Control Group	Case Group	Control Group
FEV1	2.091±0.698	2.648±0.665	2.150±0.630	2.448±0.587	2.280±0.660	2.572±0.646
FVC	3.327±0.976	3.502±0.868	3.481±0.945	3.252±0.756	3.667±0.916	3.418±0.848
FEV1/FVC (%)	62.343±8.657	75.777±5.991	61.742±7.015	75.236±5.855	61.906±8.045	75.472±6.110
FEV1%pred (%)	76.955±21.529	93.617±17.318	82.669±18.348	93.332±14.641	80.219±20.243	91.460±16.325

Table 5 Association Analysis Between COPD Severity and SNPs

Genotypes	GOLD 1 n (%)	GOLD 2 n (%)	GOLD 3 n (%)	GOLD 4 n (%)	χ^2	P
EPAS1						
rs4953354						
AA	133(56.8)	155(68.0)	32(71.1)	9(90.0)	11.469	0.061
AG	88(37.6)	59(25.9)	10(22.2)	1(10.0)		
GG	13(5.6)	14(6.1)	3(6.7)	0(0.0)		
VEGFA						
rs2010963 (HAN)						
CC	26(22.4)	27(25.7)	5(25.0)	2(25.0)	2.636	0.869
CG	57(49.1)	44(41.9)	10(50.0)	5(62.5)		
GG	33(28.5)	34(32.4)	5(25.0)	1(12.5)		
rs3025020 (Tibetan)						
CC	29(32.2)	16(32.7)	1(12.5)	1(100.0)	4.804	0.586
CT	48(53.3)	23(46.9)	5(62.5)	0(0.0)		
TT	13(14.5)	10(20.4)	2(25.0)	0(0.0)		
rs3025020 (HAN)						
CC	54(46.6)	44(41.9)	10(50.0)	6(75.0)	4.536	0.579
CT	51(44.0)	51(48.6)	10(50.0)	2(25.0)		
TT	11(9.4)	10(9.5)	0(0.0)	0(0.0)		

Notes: Both the χ^2 and P values were obtained using Fisher's exact test.

Discussion

Association of EPAS1 Gene Polymorphisms with COPD at High Altitude

The relationship between *EPAS1* and COPD is complex. In COPD patients, hypoxic states frequently accompany airway obstruction and diminished pulmonary function,²¹ with such hypoxia exacerbated at high altitudes. This hypoxic state may activate *EPAS1* and its downstream signaling pathways, thereby influencing the pathophysiological processes of COPD.²² Research indicates that *EPAS1* may participate in inflammatory responses and pulmonary tissue remodeling, playing a significant role in the pathogenesis and progression of COPD.^{23,24} Our study investigated four *EPAS1* single nucleotide polymorphisms to evaluate their association with COPD risk in Tibetan and Han populations living at high altitude.

rs4953354A>G

Under the additive genetic model, individuals carrying the AG genotype exhibited a 32% reduced risk of developing COPD compared to those with the wild-type homozygous AA genotype. Similarly, under the dominant model (AG+GG vs. AA), the overall risk was decreased by 29.2%. However, no significant association was observed between the rs4953354 A>G variant and COPD risk under the recessive model. Stratified analysis further indicated that this protective association showed consistent trends across all subgroups, and no multiplicative interactions were observed. We hypothesize that the protective effect of the G allele at rs4953354 may stem from its function as an expression quantitative trait locus (eQTL) that downregulates *EPAS1* expression. It is also plausible that this variant may synergistically affect mRNA splicing or microRNA regulation. In the context of chronic hypoxia characteristic of high-altitude environments, moderated *EPAS1* activity could help maintain a balanced HIF-2 α signaling pathway, thereby preventing excessive activation of downstream target genes involved in pathological pulmonary vascular remodeling and inflammation. This regulatory effect may ultimately confer reduced susceptibility to COPD in individuals harboring the rs4953354 G allele.

Research has demonstrated that the rs4953354 polymorphism is associated with susceptibility to lung adenocarcinoma in non-smoking Japanese women, with the G allele increasing the risk of developing the disease.²⁵ Jin Xu et al²⁶ reported that the rs4953354 polymorphism is related to susceptibility to high-altitude polycythemia among Tibetans residing on the Qinghai-Tibet Plateau. Shen Yang et al²⁷ found that the rs4953354 G allele is associated with high-

altitude headache in the Han Chinese population. Research by Percy et al²⁸ indicated that individuals homozygous for the rs4953354 mutation in Tibetans exhibited lower hemoglobin concentrations compared to wild-type carriers. Additionally, another study²⁹ suggested that in high-altitude regions, the correlation between hemoglobin concentration and the rs4953354 SNP in the Naxi population appears less pronounced than that reported in Tibetans. The present study results show significant differences in the distribution of the wild-type genotype AA, heterozygous genotype AG, and mutant genotype GG between the case and control groups, indicating that the G allele may be associated with risk of COPD.

rs6743991C>A, rs7589861A>G and rs13419896G>A

The association analysis results indicate that in the studied population, the loci rs6743991 C>A, rs7589861 A>G, and rs13419896 G>A showed no significant association with COPD risk under various genetic models. Several factors may account for this observation. First, MAF of these loci are relatively low; combined with the total sample size of this study ($n = 1097$), the statistical power in stratified analyses may be limited, potentially hindering the detection of subtle associations. Second, all these loci are located within intronic regions, which restricts their functional interpretation; they may not directly participate in the regulation of *EPAS1* gene expression or the activation of its protein function. The influence of *EPAS1* on COPD risk might primarily be driven by other functional variants, such as rs4953354, which could further diminish the detectable effects of these loci. Moreover, population-specific factors cannot be overlooked. For instance, our previous research³⁰ demonstrated that *EPAS1* rs13419896 G>A significantly reduces COPD susceptibility in the South China population, yet no association was observed for this locus with COPD in the high-altitude population examined in the present study. This suggests that the disease association of this locus is modulated by a combination of genetic background and environmental exposure, underscoring marked population heterogeneity.

Association of VEGFA Gene Polymorphisms with COPD in Tibetan and Han Populations at High Altitude

A complex relationship also exists between *VEGFA* and COPD. During the body's hypoxic response, hypoxia-inducible factor (HIF-1 α) occupies a central regulatory position, with *VEGFA* serving as a key downstream target gene.³¹ Genetic variations in the *VEGFA* gene may modulate susceptibility to COPD by influencing multiple biological processes, including angiogenesis, inflammatory responses, and hypoxic stress. The present study selected four SNP loci within the *VEGFA* gene for comprehensive analysis.

rs2010963C>G

In the Han Chinese population, association analysis revealed that compared with the wild-type homozygous CC genotype, individuals carrying the CG and GG genotypes exhibited a 61.9% and 75.1% increased risk of developing COPD, respectively. Under the dominant model (CG+GG vs. CC), the overall risk increased by 67%. Stratified analysis further indicated that this association was not influenced by factors such as sex, age, BMI, education level, or smoking status, suggesting that rs2010963 C>G may serve as a risk factor for COPD in the Han population. The underlying mechanism may involve reduced expression or impaired function of *VEGFA*, which weakens the repair and maintenance capacity of the pulmonary vascular network and compromises the body's adaptation and regulation in response to chronic hypoxia, thereby increasing susceptibility to COPD. However, in the Tibetan population, no significant association between rs2010963 C>G and COPD risk was observed. This ethnic difference may be attributed to the unique genetic background shaped by long-term adaptation of Tibetans living on the Qinghai-Tibet Plateau. Previous studies have reported¹⁸ that the frequencies of *VEGFA* rs2010963 SNP and haplotypes differ genetically between Sherpa highlanders and non-Sherpa lowlanders, suggesting that such genetic variation may result from natural selection driven by adaptation to high-altitude environments. Another study on altitude sickness indicated significant differences in the distribution of *VEGFA* rs2010963 alleles between Tibetan and Han populations residing long-term on the Qinghai-Tibet Plateau ($F_{\text{stat}} = 0.054$, $P < 0.05$).³²

rs3025020C>T

In the Tibetan population, the T allele of the rs3025020 locus exhibited a protective effect. Compared to the CC genotype, individuals with the CT genotype had a 47% reduced risk of developing COPD; under the dominant model

(CT+TT vs. CC), the risk was reduced by 42.9%. Stratified analyses further confirmed that this association remained stable across different subgroups and was not evidently influenced by common confounding factors. In a Spanish cohort,³³ the T allele of rs3025020 was also suggested to confer a protective effect against COPD susceptibility in the Spanish population (OR=0.60; 95% CI=0.39–0.93; $P = 0.023$), and COPD patients homozygous for the T allele demonstrated higher lung function values. Therefore, we hypothesize that in the Tibetan population, the C>T variation at this locus may reduce COPD risk by downregulating *VEGFA* expression, thereby alleviating airway inflammation and remodeling driven by its overexpression.

However, in the Han Chinese population, the genetic effect of rs3025020 C>T is diametrically opposed. Compared with the CC genotype, individuals carrying the TT genotype have a 129% increased risk of disease, and under the recessive model (TT vs. CT+CC), the risk increases by 115.1%, indicating that the T allele is a risk factor in the Han population. In a cohort from Lahore, Pakistan,³⁴ individuals carrying the T allele of rs3025020 exhibited a significantly increased risk of severe asthma. Regarding the effect of this locus on *VEGF* expression, existing studies report inconsistent results: some have found that the TT genotype is associated with elevated *VEGF* levels,³⁵ while others report associations with lower levels.³⁶ Such discrepancies may be attributable to differences in studied populations, environmental backgrounds, or detection methods.

One of the most important findings of this study is that *VEGFA* rs3025020 exhibits opposite disease association effects in Tibetan and Han populations, strongly suggesting that the functional consequence of this locus is highly dependent on population-specific genetic backgrounds. Tibetans carry unique adaptive haplotypes in key genes of the HIF pathway, such as *EPAS1* and *EGLN1*, which attenuate HIF-2 α signaling activity by disrupting hypoxia-sensitive enhancers like ENH5, thereby optimizing physiological adaptation to hypoxia and maintaining relatively low hemoglobin concentrations and pulmonary artery pressure.^{37,38} Under this regulatory context, the rs3025020 T allele may synergistically fine-tune *VEGFA* expression to an appropriate level, exerting a protective effect; in contrast, in the Han population lacking such adaptive genetic background, the same allele may manifest its potential risk. This phenomenon may also arise from epistatic effects with high-altitude adaptation genes or from eQTL effects modulated by haplotype background at this locus.³⁹ These findings further emphasize the critical importance of fully accounting for population specificity and evolutionary geographic background in genetic association studies.

rs10434A>G and rs833070T>C

The association analysis results showed that in the studied Tibetan and Han populations, the rs10434 A>G and rs833070 T>C loci did not exhibit significant associations with COPD risk under various genetic models. This outcome may suggest several points: first, although the total sample size of this study reached 1,204 subjects (399 Tibetans and 805 Han Chinese), stratification by ethnicity reduced the statistical power, which may have been insufficient to detect small genetic effects; second, these two loci are located in the 3'UTR and an intronic region, and existing functional evidence does not support their involvement in the transcriptional regulation, mRNA stability, or protein expression of *VEGFA*, thus they may not participate in pathological mechanisms related to angiogenesis, airway inflammation, or pulmonary vascular remodeling in COPD; furthermore, adaptive characteristics to high-altitude hypoxia differ between Tibetan and Han populations, with Tibetans generally exhibiting lower hemoglobin concentrations while Han individuals might rely on alternative compensatory mechanisms to cope with hypoxia.⁴⁰ Such population-specific adaptive responses may partially mask the potential effects of these loci on COPD. Nevertheless, a cohort study indicated that rs833070 T>C was associated with COPD risk in the Mongolian population.⁴¹

Study Limitations

This study has several limitations: the case-control design may be subject to recall bias; the sample was limited to high-altitude regions in Gansu, so caution is warranted when generalizing the findings; the reduced sample size following stratification led to decreased statistical power in some subgroups; and there is a lack of quantitative data on individual-level hypoxic exposure and functional experiments to substantiate the underlying mechanisms. Future studies should further validate these findings by expanding the sample size and incorporating functional genomics approaches.

Conclusion

This study found a significant association between specific SNPs in the EPAS1 and VEGFA genes and susceptibility to COPD in a population from high-altitude regions of Gansu. Within the EPAS1 gene, the rs4953354 A>G variant was associated with COPD risk, where carriers of the G allele showed a reduced risk of developing the disease. Regarding the VEGFA gene, the rs2010963 C>G variant was linked to an increased COPD risk in the Han population; however, the rs3025020 C>T variant displayed opposing effect directions between Tibetan and Han populations. These findings collectively indicate that genetic variants in the hypoxic response pathway genes EPAS1 and VEGFA are associated with individual differences in susceptibility to COPD in high-altitude environments. The observed ethnic heterogeneity highlights the potential importance of population-specific genetic backgrounds in regulating disease risk. This study advances the understanding of COPD pathogenesis in the context of gene-environment interactions under high-altitude hypoxic conditions, providing novel insights into the genetic mechanisms of COPD in plateau regions and establishing a foundation for subsequent molecular marker identification.

Abbreviations

COPD, Chronic obstructive pulmonary disease; *EPAS1*, Endothelial PAS domain protein 1; FEV1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GWAS, Genome-wide association analysis; HIF, Hypoxia-inducible factor; LD, Linkage disequilibrium; MAF, Minor allele frequency; PCR, TaqMan real-time polymerase chain reaction.; SNP, Single nucleotide polymorphism; *VEGF*, Vascular endothelial growth factor; *VEGFA*, Vascular endothelial growth factor A.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of Xi'an Jiaotong University, Faculty of Medicine (Approval No.: XJTU 2016-411) and Guangzhou Medical University (Approval No.: 202405010). In addition, we explained the purpose of the study to all participants at the time of the study and obtained their signed informed consent.

Acknowledgment

We thank the Institute of Public Health, Gansu University of Traditional Chinese Medicine. We thank the researchers in our laboratory for their guidance on experimental techniques.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the following grants: Major Project of the Gansu Provincial Joint Research Fund: 23JRR1520 (Xinhua Wang); Lanzhou City Major Projects: HXLH-JBGS03 (Xinhua Wang); Project Approval by the Northwest Collaborative Innovation Center for Traditional Chinese Medicine Prevention and Control: ZYXT-25-09 (Zhen Yang).

Disclosure

The authors report no conflicts of interest in this work.

References

- de Oca MM, Perez-Padilla R, Celli B, et al. The global burden of COPD: epidemiology and effect of prevention strategies. *Lancet Respir Med*. 2025;13(8):709–724. doi:10.1016/s2213-2600(24)00339-4
- Momtazmanesh S, Moghaddam SS, Ghamari SH, et al. Global burden of chronic respiratory diseases and risk factors, 1990–2019: an update from the Global Burden of Disease Study 2019. *EClinicalMedicine*. 2023;59:101936. doi:10.1016/j.eclinm.2023.101936
- Hurst JR, Skolnik N, Hansen GJ, et al. Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life. *Eur J Intern Med*. 2020;73:1–6. doi:10.1016/j.ejim.2019.12.014
- Agustí A, Melén E, DeMeo DL, Breyer-Kohansal R, Faner R. Pathogenesis of chronic obstructive pulmonary disease: understanding the contributions of gene-environment interactions across the lifespan. *Lancet Respir Med*. 2022;10(5):512–524. doi:10.1016/s2213-2600(21)00555-5
- Li X, Zhang P, Yu J, et al. A case-control study of the associations between EGLN1 gene polymorphisms and COPD. *Front Biosci*. 2024;29(1):18. doi:10.31083/j.fbl2901018
- Li H, Wang R, Wei X, et al. GSTP1 rs4147581 C>G and NLRP3 rs3806265 T>C as risk factors for chronic obstructive pulmonary disease: a Case-Control Study. *Int J Chron Obstruct Pulmon Dis*. 2024;19:489–500. doi:10.2147/copd.S445680
- 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*. 2023;28(9):215. doi:10.31083/j.fbl2809215
- Moya EA. EPAS1/HIF-2 α : a key regulator for chronic hypoxia across species. *J Physiol*. 2022;600(18):4053–4054. doi:10.1113/jp283554
- Van Patot MC, Gassmann M. Hypoxia: adapting to high altitude by mutating EPAS-1, the gene encoding HIF-2 α . *High Alt Med Biol*. 2011;12(2):157–167. doi:10.1089/ham.2010.1099
- Yoo S, Takikawa S, Geraghty P, et al. Integrative analysis of DNA methylation and gene expression data identifies EPAS1 as a key regulator of COPD. *PLoS Genet*. 2015;11(1):e1004898. doi:10.1371/journal.pgen.1004898
- Valipour A, Schreder M, Wolzt M, et al. Circulating vascular endothelial growth factor and systemic inflammatory markers in patients with stable and exacerbated chronic obstructive pulmonary disease. *Clin Sci*. 2008;115(7):225–232. doi:10.1042/cs20070382
- Lee CG, Link H, Baluk P, et al. Vascular endothelial growth factor (VEGF) induces remodeling and enhances TH2-mediated sensitization and inflammation in the lung. *Nat Med*. 2004;10(10):1095–1103. doi:10.1038/nm1105
- Voelkel NF, Gomez-Arroyo J. The role of vascular endothelial growth factor in pulmonary arterial hypertension. The angiogenesis paradox. *Am J Respir Cell Mol Biol*. 2014;51(4):474–484. doi:10.1165/rcmb.2014-0045TR
- Bartoszewski R, Moszyńska A, Serocki M, et al. Primary endothelial cell-specific regulation of hypoxia-inducible factor (HIF)-1 and HIF-2 and their target gene expression profiles during hypoxia. *FASEB J*. 2019;33(7):7929–7941. doi:10.1096/fj.201802650RR
- Xu YR, Wang AL, Li YQ. Hypoxia-inducible factor 1- α is a driving mechanism linking chronic obstructive pulmonary disease to lung cancer. *Front Oncol*. 2022;12:984525. doi:10.3389/fonc.2022.984525
- Tashi T, Scott Reading N, Wuren T, et al. Gain-of-function EGLN1 prolyl hydroxylase (PHD2 D4E:C127S) in combination with EPAS1 (HIF-2 α) polymorphism lowers hemoglobin concentration in Tibetan highlanders. *J Mol Med*. 2017;95(6):665–670. doi:10.1007/s00109-017-1519-3
- Barratt SL, Blythe T, Ourradi K, et al. Effects of hypoxia and hyperoxia on the differential expression of VEGF-A isoforms and receptors in Idiopathic Pulmonary Fibrosis (IPF). *Respir Res*. 2018;19(1):9. doi:10.1186/s12931-017-0711-x
- Droma Y, Hanaoka M, Kinjo T, et al. The blunted vascular endothelial growth factor-A (VEGF-A) response to high-altitude hypoxia and genetic variants in the promoter region of the VEGFA gene in Sherpa highlanders. *PeerJ*. 2022;10:e13893. doi:10.7717/peerj.13893
- Pollard AJ, Murdoch DR. *The High Altitude Medicine Handbook*. Radcliffe Publishing; 2003.
- Venkatesan P. GOLD COPD report: 2024 update. *Lancet Respir Med*. 2024;12(1):15–16. doi:10.1016/s2213-2600(23)00461-7
- Shakeel I, Ashraf A, Afzal M, et al. The molecular blueprint for Chronic Obstructive Pulmonary Disease (COPD): a new paradigm for diagnosis and therapeutics. *Oxid Med Cell Longev*. 2023;2023:2297559. doi:10.1155/2023/2297559
- Myronenko O, Foris V, Crnkovic S, et al. Endotyping COPD: hypoxia-inducible factor-2 as a molecular “switch” between the vascular and airway phenotypes? *Eur Respir Rev*. 2023;32(167). doi:10.1183/16000617.0173-2022
- Evans CE. Hypoxia-Inducible factor signaling in inflammatory lung injury and repair. *Cells*. 2022;11(2). doi:10.3390/cells11020183
- Ahmad A, Ahmad S, Malcolm KC, et al. Differential regulation of pulmonary vascular cell growth by hypoxia-inducible transcription factor-1 α and hypoxia-inducible transcription factor-2 α . *Am J Respir Cell Mol Biol*. 2013;49(1):78–85. doi:10.1165/rcmb.2012-0107OC
- Iwamoto S, Tanimoto K, Nishio Y, et al. Association of EPAS1 gene rs4953354 polymorphism with susceptibility to lung adenocarcinoma in female Japanese non-smokers. *J Thorac Oncol*. 2014;9(11):1709–1713. doi:10.1097/jto.0000000000000309
- Xu J, Yang YZ, Tang F, Ga Q, Tana W, Ge RL. EPAS1 gene polymorphisms are associated with high altitude polycythemia in tibetans at the qinghai-tibetan plateau. *Wilderness Environ Med*. 2015;26(3):288–294. doi:10.1016/j.wem.2015.01.002
- Shen Y, Zhang J, Yang J, et al. Association of EPAS1 and PPARG gene polymorphisms with high-altitude headache in chinese han population. *Biomed Res Int*. 2020;2020:1593068. doi:10.1155/2020/1593068
- Percy MJ, Furlow PW, Lucas GS, et al. A gain-of-function mutation in the HIF2A gene in familial erythrocytosis. *N Engl J Med*. 2008;358(2):162–168. doi:10.1056/NEJMoa073123
- Sh X. *Correlation Between EPAS1 Gene Polymorphism and Hemoglobin in Naxi Ethnic Group Across Cross-Plateau Regions*. Dali University; 2023.
- Wang Y, Lin A, He R, et al. The role of EPAS1 polymorphisms on COPD susceptibility in southern Chinese. *Heliyon*. 2023;9(10):e20226. doi:10.1016/j.heliyon.2023.e20226
- Yu ZG, Wang BZ, Cheng ZZ. The association of genetic polymorphisms of hypoxia inducible factor-1 α and vascular endothelial growth factor with increased risk of chronic obstructive pulmonary disease: a case-control study. *Kaohsiung J Med Sci*. 2017;33(9):433–441. doi:10.1016/j.kjms.2017.05.014
- Buroker NE, Ning XH, Zhou ZN, et al. VEGFA SNPs and transcriptional factor binding sites associated with high altitude sickness in Han and Tibetan Chinese at the Qinghai-Tibetan Plateau. *J Physiol Sci*. 2013;63(3):183–193. doi:10.1007/s12576-013-0257-8
- Baz-Dávila R, Espinoza-Jiménez A, Rodríguez-Pérez Mdel C, et al. Role of HIF1A, VEGFA and VEGFR2 SNPs in the susceptibility and progression of COPD in a Spanish population. *PLoS One*. 2016;11(5):e0154998. doi:10.1371/journal.pone.0154998

34. Aslam A, Vijverberg SJH, Zee AM, Sabar MF. Genetic variations on chromosome 6p21 are associated with asthma risk and disease severity: a Case-Control Study from Pakistan. *Genes*. 2024;15(12). doi:10.3390/genes15121608
35. Al-Habboubi HH, Sater MS, Almawi AW, Al-Khateeb GM, Almawi WY. Contribution of VEGF polymorphisms to variation in VEGF serum levels in a healthy population. *Eur Cytokine Netw*. 2011;22(3):154–158. doi:10.1684/ecn.2011.0289
36. Villani L, Rosti V, Massa M, et al. VEGFA rs3025020 polymorphism contributes to CALR -mutation susceptibility and is associated with low risk of deep vein thrombosis in primary myelofibrosis. *TH Open*. 2021;5(4):e513–e520. doi:10.1055/s-0041-1739293
37. Gray OA, Yoo J, Sobreira DR, et al. A pleiotropic hypoxia-sensitive EPAS1 enhancer is disrupted by adaptive alleles in Tibetans. *Sci Adv*. 2022;8(47):eade1942. doi:10.1126/sciadv.ade1942
38. Deng L, Zhang C, Yuan K, et al. Prioritizing natural-selection signals from the deep-sequencing genomic data suggests multi-variant adaptation in Tibetan highlanders. *Natl Sci Rev*. 2019;6(6):1201–1222. doi:10.1093/nsr/nwz108
39. Gray OA, Witonsky DB, Jousma J, et al. Transcriptomic analysis of iPSC-derived endothelium reveals adaptations to high altitude hypoxia in energy metabolism and inflammation. *PLoS Genet*. 2025;21(2):e1011570. doi:10.1371/journal.pgen.1011570
40. Mathieson I. Human genetics: an extreme fitness landscape. *Curr Biol*. 2023;33(20):R1064–r1066. doi:10.1016/j.cub.2023.09.023
41. Gao X, Wang X, Jiao N, Chen J, Sun D. Association of VEGFA polymorphisms with chronic obstructive pulmonary disease in Chinese Han and Mongolian populations. *Exp Physiol*. 2021;106(8):1839–1848. doi:10.1113/ep089523

International Journal of Chronic Obstructive Pulmonary Disease

Publish your work in this journal

The International Journal of COPD is an international, peer-reviewed journal of therapeutics and pharmacology focusing on concise rapid reporting of clinical studies and reviews in COPD. Special focus is given to the pathophysiological processes underlying the disease, intervention programs, patient focused education, and self management protocols. This journal is indexed on PubMed Central, MedLine and CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-journal>

Dovepress
Taylor & Francis Group