

# Association Between the Polymorphism of Steroid Hormone Metabolism Genes and High-Altitude Pulmonary Edema in the Chinese Han Population

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**Purpose:** Steroid hormone metabolism plays an essential role in high-altitude pulmonary edema (HAPE) progression. This study aimed to investigate the association between polymorphism in seven steroid hormone metabolism genes (*STAR*, *HSD3B1*, *HSD3B2*, *CYP17A1*, *CYP21A2*, *CYP11B1*, and *CYP11B2*) and HAPE susceptibility among Han Chinese.

**Patients and Methods:** A total of 41 tagSNPs in the seven genes were genotyped using Sequenom MassARRAY SNP assays from 169 HAPE patients (HAPE-p) and 309 matched Han Chinese individuals resistant to HAPE (HAPE-r). The genotypic and allele frequencies, odds ratios (ORs), and 95% confidence intervals (95% CIs) were calculated.

**Results:** Four SNPs, including the allele C of rs6203 ( $p = 0.034$ , OR [95% CI] = 1.344 [1.022–1.767]) in *HSD3B1*, allele G of rs3740397 ( $p = 0.044$ , OR [95% CI] = 1.314 [1.007–1.714]) and allele C of rs10786712 ( $p = 0.039$ , OR [95% CI] = 0.751 [0.572–0.986]) in *CYP17A1*, and allele T of rs6402 ( $p = 0.006$ , OR [95% CI] = 0.504 [0.306–0.830]) in *CYP11B1*, were significantly associated with HAPE. The distribution of the genotypes of these SNPs also significantly differed between the HAPE-p and HAPE-r groups. Moreover, six haplotypes (the linkage disequilibrium block including rs10883783, rs4919686, rs3740397, rs3824755, and rs10786712) of *CYP17A1* were also significantly associated with HAPE.

**Conclusion:** The four SNPs located in *HSD3B1* (rs6203), *CYP17A1* (rs3740397 and rs10786712), and *CYP11B1* (rs6402) and the six haplotypes of *CYP17A1* are likely to have an effect on HAPE.

**Keywords:** steroid hormone metabolism gene, SNP, high-altitude pulmonary edema, susceptibility

## Introduction

High-altitude pulmonary edema (HAPE) is a serious acute mountain sickness (AMS) that is triggered by the failure to acclimatize to high altitudes and hypoxia.<sup>1</sup> The initial symptoms of HAPE include sympathetic overactivity, defective nitric oxide synthesis, exaggerated endothelin-1 synthesis, reduced fluid clearance from the alveolar space, and hypoxic pulmonary vasoconstriction, which can then develop into pulmonary hypertension, increased capillary pressure, and finally HAPE.<sup>2</sup> Although hypoxia is a major trigger factor, the exact pathogenesis of HAPE remains unclear, and individuals usually differ in their susceptibility to HAPE at the same high altitude.<sup>3</sup>

At present, HAPE is considered a multifactorial disease involving both genetic and environmental risk factors.<sup>4,5</sup> Many studies have shown that hypoxia-induced

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inflammation and steroid hormone metabolism at high altitudes may contribute to the development of HAPE.<sup>5–8</sup> For example, some studies have reported that the salivary cortisol response after awakening differs between AMS+ and AMS- both at high and low altitudes, suggesting a link between hypothalamic-pituitary-adrenal (HPA)-axis homeostasis and AMS.<sup>9</sup> In addition, high levels of plasma aldosterones have been detected in HAPE when compared with controls.<sup>10</sup> Clinical observations have revealed that the onset time for HAPE is usually in the middle of the night, which is consistent with the period during which cortical hormone secretion is low. These studies suggest that an imbalance in endogenous cortical hormone secretion in HAPE patients may be a key underlying pathophysiological mechanism. The incidence of HAPE can be reduced using conventional drug-based treatments, such as acetazolamide and dexamethasone, which play an important role in the regulation of extracellular volume homeostasis and inflammatory reactions.<sup>2</sup> This weight of evidence indicates that the adrenocortical hormone system and corresponding metabolism genes may significantly influence the pathophysiological HAPE process.

The biosynthesis of steroid hormones from cholesterol involves multiple enzymes, including cytochrome P450 enzymes (CYPs), hydroxysteroid dehydrogenases (HSDs), and steroid reductases. Studies have found that the polymorphisms of these enzymes are associated with a variety of diseases.<sup>11</sup> Although many genetic association studies have identified dozens of genes associated with susceptibility to HAPE,<sup>12–19</sup> few studies have reported a relationship between the genetic characteristics of steroid hormone metabolism genes and HAPE. Thus, in this study, we conducted a case-control association analysis to investigate the correlation between seven steroid hormone metabolism genes (*STAR*, *HSD3B1*, *HSD3B2*, *CYP17A1*, *CYP21A2*, *CYP11B1*, and *CYP11B2*) and HAPE in a Chinese Han population (Figure 1).

## Materials and Methods

### Subjects

In total, 169 Han Chinese who were admitted to Yushu & Hainan People's Hospital between March 2010 and June 2020 due to the onset of HAPE 1–7 days after their arrival at the destination (>2500 m) were recruited by this study as HAPE patients (HAPE-p) and included in the final analysis. The diagnosis of HAPE was based on chest X-rays and standard diagnostic criteria.<sup>20</sup> In total, 309 healthy controls that were resistant to HAPE (HAPE-

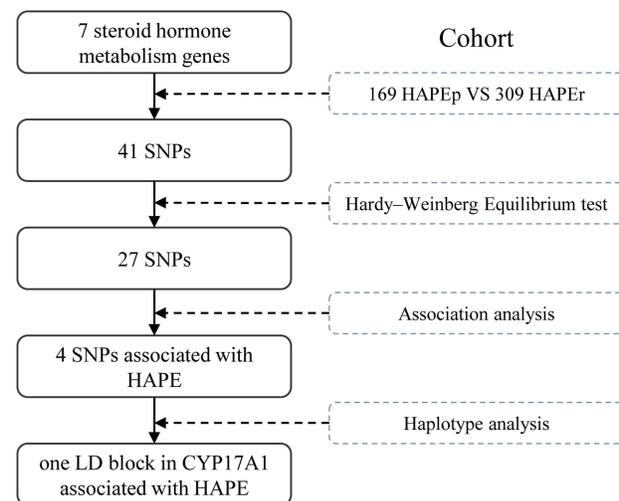


Figure 1 Flowchart for this study.

r) were randomly selected from coworkers of the HAPE-p group to match the patients in terms of age, gender, ethnicity, and working conditions. These subjects remained healthy after working at the destination (>2500 m) for at least three months and did not suffer from HAPE or other high-altitude diseases. All subjects from both groups came from the same elevation and had the same ascent profile and working conditions. The study protocols were approved by the Ethics Committee of Qinghai University (Xining, China) and were conducted in accordance with the Declaration of Helsinki. All participants in this study signed informed consent forms.

### Gene and SNP Selection and Genotyping Assays

Seven genes (*STAR*, *HSD3B1*, *HSD3B2*, *CYP17A1*, *CYP21A2*, *CYP11B1*, and *CYP11B2*) were selected because of their key roles in steroid hormone metabolism. The stellate protein encoded by the *STAR* gene is the first and rate-limiting step in cholesterol transport from the outer to the inner mitochondrial membrane.<sup>21</sup> HSD3B (*HSD3B1* and *HSD3B2*) is a key rate-limiting enzyme in the biosynthetic pathway for steroids, which produces aldosterone, estradiol, testosterone, and cortisol.<sup>11</sup> The steroid 21 hydroxylase encoded by the *CYP21* gene is a key enzyme in the synthesis of mineralocorticoid (aldosterone) and glucocorticoid (cortisol),<sup>22</sup> while 17 $\alpha$ -hydroxylase encoded by *CYP17A* is a key regulatory enzyme in the steroid hormone production pathway.<sup>23</sup> *CYP11B2* encodes aldosterone synthase, which catalyzes the final step in the biosynthesis of the major mineralocorticoid aldosterone,

and 11 $\beta$ -hydroxylase, which is encoded by *CYP11B1*, is the final step in catalyzing the synthesis of cortisol.<sup>24</sup>

DNA was isolated from the whole blood cells of the participants with the use of a Gentra Puregene Blood Kit (Qiagen, 158389, Germany) following standard procedures. A total of 41 tagSNPs (a minor allele frequency >0.05, with an  $r^2$  threshold of 0.8) in the *STAR*, *HSD3B1*, *HSD3B2*, *CYP17A1*, *CYP21A2*, *CYP11B1*, and *CYP11B2* genes have been identified in the HapMap Han Chinese population. The SNPs were genotyped using single-base extension detecting technology (iPLEX; Capital Bio Corporation, Beijing, China). The primers for PCR and single-base extension were designed using Sequenom MassARRAY Assay Design Genotyping Software and Tools (Sequenom, San Diego, CA, USA). PCR was conducted under the following thermal cycling conditions: 94°C for 4 min, followed by 94°C for 20 sec, 56°C for 30 sec, and 72°C for 1 min for 45 cycles, then 72°C for 4 min. PCR products were treated with shrimp alkaline phosphatase to remove free deoxyribonucleoside triphosphates, and the single-base extension reaction was performed in a system containing 2.0 mL of EXTEND MIX, 0.619 mL of ddH<sub>2</sub>O, 0.94 mL of Extend primer mix, 0.2 mL of iPLEX buffer plus, 0.2 mL of iPLEX terminator, and 0.041 mL of iPLEX enzyme (Sequenom, San Diego, CA, USA). The thermal cycling conditions were as follows: 94°C for 30 sec, followed by 94°C for 5 sec, 52°C for 5 sec, and 80°C for 5 sec for 40 cycles, then 72°C for 3 min. The purified extension products were dispensed onto a 384-element SpectroCHIP bioarray (Sequenom, San Diego, CA, USA), and mass spectrometric analysis was conducted using matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF; Sequenom, San Diego, CA, USA). The results were analyzed using TYPER 4.0 software (Sequenom, San Diego, CA, USA).

## Statistical Analysis

SPSS software (version 17.0, SPSS, Inc., Chicago, USA) was used for the statistical analysis. Student's *t*-tests and Fisher's exact tests were used to assess the differences in the mean and frequency distributions of the demographic and clinical characteristics between the HAPE-p and HAPE-r groups, while the Hardy-Weinberg equilibrium (HWE) was used to assess the representativeness of the participants. Allele frequencies were calculated based on the genotype frequencies in the HAPE-p and HAPE-r groups, and the intergroup differences were estimated using  $\chi^2$  tests. Haplotype frequencies and the expected number of haplotypes for each individual were calculated using SHEsis software (<http://analysis.bio-x.cn>).<sup>25</sup>

Differences were deemed significant at  $p < 0.05$  for all comparisons.

## Results

### Basic Characteristics of the Study Population

A total of 169 patients with HAPE and 309 healthy controls were included in the study (Table 1). No significant differences were noted in the demographic characteristics (ie, gender or age) of the HAPE-r and HAPE-p groups, and no significant differences were observed in their clinical characteristics (ie, HR, SaO<sub>2</sub>, HGB, or Hct).

### Genotype and Allele Distribution

We calculated the genotypic distributions and allelic frequencies of 41 SNPs in the seven steroid hormone metabolism genes. The HWE was analyzed for the HAPE-p and HAPE-r groups using PLINK 2.0, and the 14 SNPs that did not conform to the HWE (corrected  $p < 0.05$ ) were excluded (Table S1). The allele and genotype distributions of the remaining SNPs in the HAPE-p and HAPE-r groups are presented in Table S2. Of these, four were significantly associated with HAPE (Table 2). The minor allele C of rs6203 ( $p = 0.034$ , OR [95% CI] = 1.344 [1.022–1.767]) in *HSD3B1* was significantly associated with the risk of HAPE. The distribution of the genotype between the HAPE-p and HAPE-r groups was also significantly different for this allele ( $p = 0.019$ , OR [95% CI] = 2.051 [1.117–3.767]). The minor allele G of rs3740397 ( $p = 0.044$ , OR [95% CI] = 1.314 [1.007–1.714]) and minor allele C of rs10786712 ( $p = 0.039$ , OR [95% CI] = 0.751 [0.572–0.986]) in *CYP17A1* were significantly associated with

**Table 1** Demographic and Clinical Characteristics of the Study Subjects

	HAPE-r	HAPE-p	p
Gender			
Male	260	156	0.997
Female	49	13	
Age (years)	36.40±9.54	33.85±9.85	0.151
HR	80.63±12.06	79.58±11.85	0.224
SaO <sub>2</sub> (%)	90.34±2.89	90.68±7.21	0.687
HGB (g/L)	168.58±15.12	162.71±18.48	0.113
Hct (%)	49.96±5.50	48.13±5.71	0.325

**Table 2** Minor Allele and Genotype Frequencies for the SNPs Associated with HAPE in the Chinese Han Population

Gene	SNP	Type	Genotype/ Allele	HAPE-p (n %)	HAPE-r (n %)	OR (95% CI)	X <sup>2</sup>	p
<b>HSD3B1</b>	rs6203	Genotype	TT	59(0.349)	130(0.421)			
			TC	83(0.491)	150(0.485)	1.219(0.811–1.834)	0.907	0.341
			CC	27(0.160)	29(0.094)	2.051(1.117–3.767)	5.479	<b>0.019</b>
		Allele	T	201(0.595)	410(0.663)			
			C	137(0.405)	208(0.337)	1.344(1.022–1.767)	4.478	<b>0.034</b>
			Dominant model	TT	59(0.349)	130(0.421)		
			TC+CC	110(0.651)	179(0.579)	1.354(0.918–1.997)	2.343	0.126
<b>CYP17A1</b>	rs3740397	Genotype	CC	48(0.284)	72(0.233)			
			CG	84(0.497)	143(0.463)	1.135(0.721–1.787)	0.299	0.585
			GG	37(0.219)	94(0.304)	1.694(1.000–2.870)	3.865	<b>0.049</b>
		Allele	C	180(0.533)	287(0.464)			
			G	158(0.467)	331(0.536)	1.314(1.007–1.714)	4.061	<b>0.044</b>
			Dominant model	CC	48(0.284)	72(0.233)		
			CG+GG	121(0.716)	237(0.767)	0.766(0.500–1.172)	1.512	0.219
<b>CYP17A1</b>	rs10786712	Genotype	TT	65(0.385)	103(0.333)			
			TC	82(0.485)	139(0.450)	0.935(0.618–1.413)	0.102	0.749
			CC	22(0.130)	67(0.217)	0.520(0.293–0.923)	5.072	<b>0.024</b>
		Allele	T	212(0.627)	345(0.558)			
			C	126(0.373)	273(0.442)	0.751(0.572–0.986)	4.274	<b>0.039</b>
			Dominant model	TT	65(0.385)	103(0.333)		
			TC+CC	104(0.615)	206(0.667)	0.800(0.542–1.181)	1.26	0.262
<b>CYP11B1</b>	rs6402	Genotype	GG	137(0.811)	276(0.893)			
			TG	30(0.178)	33(0.107)	0.546(0.320–0.932)	5.009	<b>0.025</b>
			TT	2(0.012)	0(0.000)	–	3.99	<b>0.046</b>
		Allele	G	304(0.899)	585(0.947)			
			T	34(0.101)	33(0.053)	0.504(0.306–0.830)	7.467	<b>0.006</b>
			Dominant model	GG	137(0.811)	276(0.893)		
			<b>TG+TT</b>	<b>32(0.189)</b>	<b>33(0.107)</b>	<b>1.954(1.153–3.311)</b>	<b>6.337</b>	<b>0.012</b>

**Notes:** Data are presented as the odds ratio (OR), 95% confidence interval (CI), and p-values in the comparison between HAPE patients and the control group. A bolded p-value indicates statistical significance.

**Abbreviations:** HAPE-p, high-altitude pulmonary edema patients; HAPE-r, high-altitude pulmonary edema resistant (ie, the control).

HAPE. The distribution of the genotypes between the HAPE-p and HAPE-r groups was also significantly different for these two alleles (genotype GG of rs3740397:  $p = 0.049$ , OR [95% CI] = 1.694 [1.000–2.870]; genotype CC

of rs10786712:  $p = 0.024$ , OR [95% CI] = 0.520 [0.293–0.923]). The minor allele T of rs6402 ( $p = 0.006$ , OR [95% CI] = 0.504 [0.306–0.830]) in *CYP11B1* was significantly associated with a lower risk of HAPE. The

distribution of the genotype between the HAPE-p and HAPE-r groups was also significantly different for this allele ( $p = 0.025$ , OR [95% CI] = 0.546 [0.320–0.932]).

## Haplotype Analysis

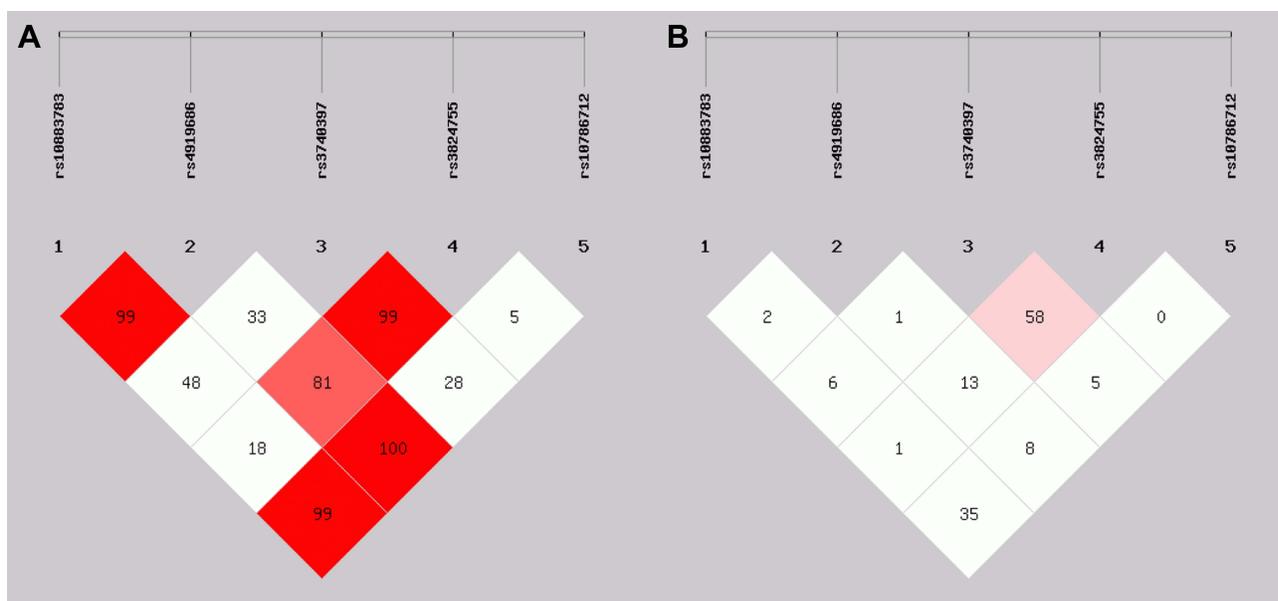
As shown in Figure 2, rs10883783, rs4919686, rs3740397, rs3824755, and rs10786712 were present in a linkage disequilibrium (LD) block within *CYP17A1*. Haplotype analysis revealed that six haplotypes within that LD block differed significantly between the two groups (Table 3). Of these, the haplotypes TACCT ( $p = 0.049$ , OR [95% CI] = 1.536 [1.000–2.359]) and TACGT ( $p = 0.000$ , OR [95% CI] = 12.706 [5.078–31.795],  $p = 0.000$ ) in *CYP17A1* were associated with HAPE risk. In contrast, the haplotypes AAGGC ( $p = 0.038$ , OR [95% CI] = 0.492 [0.249–0.973]), TACCC ( $p = 0.039$ , OR [95% CI] = 0.551 [0.311–0.976]), TACGC ( $p = 0.000$ , OR [95% CI] = 0.014 [0.001–0.130]), and TAGGT ( $p = 0.025$ , OR [95% CI] = 0.720 [0.541–0.960]) in *CYP17A1* were associated with a lower risk of HAPE.

## Discussion

To date, a number of genes associated with susceptibility to HAPE have been identified, including angiotensin-converting enzyme (ACE),<sup>12–14</sup> endothelial nitric oxide synthase (eNOS),<sup>15,16</sup> angiotensin (AGT) and its receptor (AGTR1),<sup>17</sup> heat-shock protein 70 (HSP70),<sup>18</sup> HLA,<sup>19</sup> mitochondrial DNA (mtDNA),<sup>26</sup> aldosterone synthase

(*CYP11B2*),<sup>16</sup> endothelin-1 (ET-1),<sup>12</sup> pulmonary surfactant-associated protein A1 (SP-A1) and A2 (SP-A2),<sup>27</sup> and  $\beta$ 2 adrenergic receptor (ADRB2).<sup>28,29</sup> However, few studies have investigated the association between the genetic characteristics of steroid hormone metabolism genes and HAPE. In this study, we conducted a case-control association analysis to investigate the correlation between seven steroid hormone metabolism genes and HAPE in a Chinese Han population. It was found that four SNPs located in *HSD3B1*, *CYP17A1*, and *CYP11B1* were significantly associated with HAPE. Subsequent haplotype analysis revealed that six haplotypes in an LD block including five SNPs in *CYP17A1* were significantly associated with HAPE.

The minor allele C of rs6203 ( $p = 0.034$ , OR [95% CI] = 1.344 [1.022–1.767]) in *HSD3B1* was significantly associated with the risk of HAPE. *HSD3B* is a key rate-limiting enzyme in the steroid biosynthesis pathways that produce aldosterone, estradiol, testosterone, and cortisol. It has two tissue-specific isoforms (*HSD3B1* and *HSD3B2*) that have different substrate affinities.<sup>30</sup> In humans, a genetic variation in *HSD3B1* can lead to an elevation in plasma aldosterone with a resultant increase in intravascular volume and hypertension.<sup>31</sup> Research has found that rs6203 and rs1047303 in *HSD3B1* are useful genetic markers for essential hypertension, while polymorphisms of *HSD3B1* are associated with blood pressure and aldosterone levels.<sup>32</sup>



**Figure 2** Linkage disequilibrium for the five SNPs (rs10883783, rs4919686, rs3740397, rs3824755, and rs10786712) of *CYP17A1* in the (A) HAPE-p group and (B) HAPE-r group.

**Table 3** Haplotype Effects for *CYP17A1* (rs10883783-rs4919686-rs3740397-rs3824755-rs10786712)

Gene	Haplotype	HAPE-p (freq)	HAPE-r (Freq)	X <sup>2</sup>	p value	Odds Ratio (95% CI)
CYP17A1 (rs10883783-rs4919686-rs3740397-rs3824755-rs10786712)	AACCC	36.00(0.107)	56.00(0.091)	0.74	0.389681	1.214 [0.780–1.888]
	AACGC	20.00(0.059)	28.98(0.047)	0.755	0.385002	1.296 [0.721–2.329]
	<b>AAGGC</b>	<b>11.00(0.033)</b>	<b>40.00(0.065)</b>	<b>4.312</b>	<b>0.037902</b>	<b>0.492 [0.249–0.973]</b>
	<b>TACCC</b>	<b>16.38(0.048)</b>	<b>52.87(0.086)</b>	<b>4.276</b>	<b>0.038709</b>	<b>0.551 [0.311–0.976]</b>
	<b>TACCT</b>	<b>42.01(0.124)</b>	<b>52.99(0.086)</b>	<b>3.889</b>	<b>0.048666</b>	<b>1.536 [1.000–2.359]</b>
	<b>TACGC</b>	<b>0.27(0.001)</b>	<b>34.58(0.056)</b>	<b>17.76</b>	<b>0.0000255</b>	<b>0.014 [0.001–0.130]</b>
	<b>TACGT</b>	<b>33.73(0.100)</b>	<b>5.42(0.009)</b>	<b>46.813</b>	<b>8.75E-12</b>	<b>12.706 [5.078–31.795]</b>
	TAGGC	42.36(0.125)	60.58(0.098)	1.879	0.17053	1.338 [0.881–2.032]
	<b>TAGGT</b>	<b>98.26(0.291)</b>	<b>226.57(0.367)</b>	<b>5.037</b>	<b>0.024859</b>	<b>0.720 [0.541–0.960]</b>
	TCCCT	31.62(0.094)	56.15(0.091)	0.039	0.84288	1.047 [0.663–1.656]

**Notes:** A bolded p-value indicates statistical significance. X<sup>2</sup> Chi-square. Data are presented as the odds ratio (OR) and 95% confidence interval (CI).

**Abbreviations:** HAPE-p, high-altitude pulmonary edema patients; HAPE-r, high-altitude pulmonary edema resistant (ie, the control).

The minor allele G of rs3740397 ( $p = 0.044$ , OR [95% CI] = 1.314 [1.007–1.714]) and minor allele C of rs10786712 ( $p = 0.039$ , OR [95% CI] = 0.751 [0.572–0.986]) in *CYP17A1* were significantly associated with HAPE, as were six haplotypes in *CYP17A1*. The microsomal enzyme cytochrome P450c17 $\alpha$ , a key regulatory enzyme in the steroidogenic pathway, is encoded by *CYP17A1*, which is located on chromosome 10q24.3. It has two key roles in 17 $\alpha$ -hydroxylase and 17, 20-lyase activity that determine the ability of adrenal glands and gonads to synthesize 17 $\alpha$ -hydroxylated glucocorticoids (17 $\alpha$ -hydroxylase activity) and/or sex steroids (17, 20-lyase activity).<sup>33</sup> Various disease susceptibility variants of *CYP17A1* have been widely reported. For example, genetic polymorphisms in *CYP17A1* have been linked to variations in estrogen levels and to the increased risk of polycystic ovaries,<sup>34,35</sup> breast cancer,<sup>36</sup> and other estrogen-related diseases. *CYP17A1* variants have also been reported to be associated with an increased risk of high-altitude polycythemia (HAPC) in Tibetans.<sup>37</sup>

The minor allele T of rs6402 ( $p = 0.006$ , OR [95% CI] = 0.504 [0.306–0.830]) in *CYP11B1* was significantly associated with a lower risk of HAPE. *CYP11B1* encodes 11 $\beta$ -hydroxylase, the enzyme that catalyzes the final step in the synthesis of cortisol.<sup>38</sup> Some evidence suggests that the *CYP11B1/B2* locus is important in hypertension and cardiovascular regulation.<sup>39</sup> It has been reported that there is a significant association between polymorphisms in *CYP11B2* and *CYP11B1* and a genetic predisposition towards primary hyperaldosteronism.<sup>40</sup>

Several studies have reported that some genetic loci associated with lung-related diseases overlap with loci for pulmonary fibrosis.<sup>41–43</sup> For example, two chronic obstructive pulmonary disease-associated loci (FAM13A and DSP) overlap with loci for lung function and pulmonary fibrosis,<sup>42</sup> while five pulmonary fibrosis-associated loci (DPP9, DSP, FAM13A, IVD, and MUC5B) are also significantly associated with interstitial lung abnormalities.<sup>43</sup> However, we did not find an explicit genetic association between HAPE and pulmonary fibrosis susceptibility in this study, and this has not been reported in other genetic analyses of HAPE. Of the seven selected genes, only *CYP17A1* has been reported to be associated with HAPC in Tibetans on the Qinghai-Tibetan plateau.<sup>37</sup> Thus, further research needs to be conducted to investigate the association between these genes and altitude sickness and/or other hypoxia-related diseases.

Another limitation of the study is that, due to the lack of large plateau populations, our analysis could only test a moderate number of subjects. We also did not attempt to employ population stratification in our sample, which is considered to be the most important confounder in genetic association mapping. Moreover, we did not measure the plasma levels of adrenocortical hormones for all subjects, which may correlate with some potential functional SNPs located in the steroid hormone metabolism genes.

## Conclusion

In summary, this study conducted a case-control association analysis to investigate the relationship between seven

steroid hormone metabolism genes and HAPE in a Chinese Han population. It was found that four SNPs located in *HSD3B1*, *CYP17A1*, and *CYP11B1*, and six haplotypes in *CYP17A1* were significantly associated with HAPE. Nevertheless, the relationship between these susceptibility genes and HAPE, as well as the underlying molecular mechanisms, require confirmatory research.

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## Disclosure

The authors report no conflicts of interest in this work.

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