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Mitochondrial haplogroup D4 confers resistance and haplogroup B is a genetic risk factor for high-altitude pulmonary edema among Han Chinese

Y.J. Luo[1,2,3]*, W.X. Gao[1,3]*, S.Z. Li[4], X.W. Huang[4], Y. Chen[4], F.Y. Liu[1,3], Q.Y. Huang[1,3] and Y.Q. Gao[1,3]

[1]Department of Pathophysiology and High Altitude Physiology,
College of High Altitude Military Medicine, Chongqing, China
[2]Department of High Altitude Disease,
College of High Altitude Military Medicine, Chongqing, China
[3]Key Laboratory of High Altitude Medicine,
Third Military Medical University, Ministry of Education, Chongqing, China
[4]Department of Mountain Sickness,
General Hospital of Tibet Military Command, Lhasa, Tibet, China

*These authors contributed equally for this study.
Corresponding author: Y.Q. Gao
E-mail: gaoy66@yahoo.com

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ABSTRACT. High-altitude pulmonary edema (HAPE) is a life-threatening condition caused by acute exposure to high altitude. Accumulating evidence suggests that genetic factors play an important role in the etiology of HAPE. However, conclusions from association studies have been hindered by limited sample size due to the rareness of this disease. It is known that mitochondria are critical for hypoxic adaptation, and mitochondrial malfunction can be an important factor in HAPE development. Therefore, we tested the hypothesis that

mitochondrial DNA haplotypes and polymorphisms affect HAPE susceptibility. We recruited 204 HAPE patients and 174 healthy controls in Tibet (3658 m above sea level), all Han Chinese, constituting the largest sample size of all HAPE vulnerability studies. Among mtDNA haplogroups, we found that haplogroup D4 is associated with resistance to HAPE, while haplogroup B is a genetic risk factor for this condition. Haplogroup D4 (tagged by 3010A) may enhance the stability of 16S rRNA, resulting in reduced oxidative stress and protection against HAPE. Within haplogroup B, subhaplogroup B4c (tagged by 15436A and 1119C) was associated with increased risk for HAPE, while subhaplogroup B4b may protect against HAPE. We indicate that there are differences in HAPE susceptibility among mtDNA haplogroups. We conclude that mitochondria are involved in adverse reactions to acute hypoxic exposure; our finding of differences in susceptibility as a function of mitochondrial DNA haplotype may shed light on the pathogenesis of other disorders associated with hypoxia, such as chronic obstructive pulmonary disease.

Key words: HAPE; Mitochondrial DNA; mtSNP; Haplogroup; Haplotype; Hypoxia

