ACCEPTED MANUSCRIPT

Accepted manuscripts are the articles in press that have been peer reviewed and accepted for publication by the Editorial Board of the Vojnosanitetski Pregled. They have not yet been copy edited and/or formatted in the publication house style, and the text could still be changed before final publication.

Although accepted manuscripts do not yet have all bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: article title, the author(s), publication (year), the DOI.

Please cite this article GENOME-WIDE ASSOCIATION STUDY OF MITOCHONDRIAL DNA IN CHINESE MEN IDENTIFIES SEVEN NEW SUSCEPTIBILITY LOCI FOR HIGH-ALTITUDE PULMONARY OEDEMA

Authors Caizhi Tang1, Yu Chen1, Xinyuan Liu1, Zhuang Ran1, Yongjun Luo1#, Vojnosanitetski pregled (2020); Online First June, 2020.

UDC:

DOI: https://doi.org/10.2298/VSP191027063T

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
GENOME-WIDE ASSOCIATION STUDY OF MITOCHONDRIAL DNA IN CHINESE MEN IDENTIFIES SEVEN NEW SUSCEPTIBILITY LOCI FOR HIGH-ALTITUDE PULMONARY OEDEMA

Caizhi Tang¹, Yu Chen¹, Xinyuan Liu¹, Zhuang Ran¹, Yongjun Luo¹#

¹ Department of Military Medical Geography, Army Medical Service Training Base, Army Medical University, Chongqing 400038, China

# Address for correspondence and reprints:
Prof. Yongjun Luo, Fax: +86 23 68771868; Telephone: +86 23 68771868; Mail address: Department of Military Medical Geography, Army medical training base, Army Medical University, Chongqing 400038, P.R. China; E-mail address: ajun-333333@163.com.
Abstract

**Background / Aim:** High-altitude pulmonary oedema (HAPE), which normally occurs at altitudes in excess of 3,000 m, is a potentially fatal disease due to hypoxia. The role of mitochondrial genomes in determining an individual's susceptibility to HAPE has not been determined. However, a number of genetic polymorphisms have recently been found to be overrepresented in HAPE patients. Most published genome-wide association studies (GWASs) have investigated only a small number of top-ranking single-nucleotide polymorphisms (SNPs)/genes by overview of nuclear DNA and considered each of the identified SNPs/genes independently. Little research has been conducted on mitochondrial genomes in relapsing HAPE patients by GWASs.

**Methods:** To identify biological pathways important to HAPE occurrence, we examined approximately 500,000 SNPs genome-wide from 10 unrelated cases of relapsing HAPE, and we compared the SNPs in these cases with those in the CHB population (45 controls) to find the association between genotypes and HAPE susceptibility among the mitochondrial function-related genes. We used the FUMA platform to expand those SNPs to selected candidate SNPs.

**Results:** A total of 369 candidate SNPs, 4 lead SNPs, 4 genomic risk loci and 5 mapped genes were obtained. The 7 mapped genes were ADAMTS9-AS2, NEK1, CLCN3, C4orf27(HPF1), RP11-219J21.2, ANKRD26 and YME1L1.

**Conclusions:** This study confirms the association of ADAMTS9-AS2, NEK1, CLCN3, C4orf27(HPF1), RP11-219J21.2, ANKRD26 and YME1L1 with HAPE, which may provide future targets for the treatment of this disease.

**Keywords:** polymorphisms; high altitude pulmonary oedema; genome-wide association study.

Apstrakt :

**Uvod / Cilj.** Visok plućni edem (HAPE), koji se obično javlja na visinama većim od 3.000 m, potencijalno je smrtonosna bolest usled hipoksije. Uloga mitohondrijalnih genoma u određivanju podložnosti pojedinca na HAPE nije određena. Međutim, nedavno je otkriveno da je veliki broj genetskih polimorfizama prekomerno zastupljen kod pacijenata sa HAPE. Većina objavljenih studija vezanih za genom (GVAS) istraživala je samo mali broj vrhunskih jedno-nukleotidnih polimorfizama (SNPs) / gena pregledom...
nuklearne DNK i razmotrila svaki od identifikovanih SNP / gena nezavisno. Malo istraživanja je provedeno na mitohondrijskim genima kod relapsiranih HAPE pacijenata od strane GVAS-a.

**Metode:** Da bismo identifikovali biološke puteve važne za pojavu HAPE, ispitali smo približno 500 000 SNP-a širom genoma iz 10 nepovezanih slučajeva relapsa HAPE, i uporedili smo SNPS u tim slučajevima sa onima iz CHB populacije (45 kontrola) da bismo pronašli povezanost između genotipovi i osjetljivost na HAPE među genima koji se odnose na funkciju mitohondrija. Koristili smo FUMA platformu da proširimo te SNP-ove na odabrane SNP-ove kandidata.

**Rezultati:** Ukupno je dobijeno 369 SNP-ova kandidata, 4 olova SNP-a, 4 lokusa genomskog rizika i 5 mapiranih gena. 7 mapiranih gena su bili ADAMTS9-AS2, NEK1, CLCN3, C4orf27 (HPF1), RP11-219J21.2, ANKRD26 i IME1L1.

**Zaključak:** Ova studija potvrđuje povezanost ADAMTS9-AS2, NEK1, CLCN3, C4orf27 (HPF1), RP11-219J21.2, ANKRD26 i IME1L1 sa HAPE, što može pružiti buduće ciljeve za lečenje ove bolesti.

**Ključne reči:** polimorfizmi; plućni edem na velikoj visini; studija povezanosti u genomu.
Introduction

High-altitude pulmonary oedema (HAPE) is a kind of pulmonary oedema that occurs primarily in the hypoxic environment at high altitude. HAPE occurs mostly among residents of low-lying areas who enter the plateau for the first time or when the inhabitants of the plateau enter the higher-altitude areas. The incidence rate is 0.4%~2%. Because HAPE has acute onset and rapid progress and causes considerable harm to the body, if the treatment is not timely, it can develop to coma or even death in a relatively short time, which seriously threatens life and health[1-4]. High-altitude pulmonary oedema has an obvious susceptibility tendency.

Previous studies have shown that there are significant individual differences in susceptibility to HAPE in the same high-altitude hypoxia environment[5-6]. Accumulated evidence has suggested that a large number of genetic factors are associated with genetic susceptibility to HAPE, including nitric oxide synthase 3 (NOS3), cytochrome b-245 (CYBA), angiotensin converting enzyme (ACE), surfactants A1 and A2, and hypoxia-inducible factor-1 (HIF-1)[5-8]. The genetic analysis of these studies was based on an overview of nuclear DNA. However, the role of mitochondria and their genomes is an area of genetic investigation that has been neglected.

Mitochondria are organelles that produce energy in aerobic cells and contain their own genome. Maintaining a sufficient quantity of mitochondrial DNA (mtDNA) in specific tissues is essential for cell viability. Therefore, many common human diseases, such as cancer[9, 10], cardiomyopathy[11] and liver disease[12], are associated with changing mtDNA levels. In a previous study, we sequenced the mtDNA of Ochotona curzoniae (Chinese red pika) and identified 15 novel mtDNA-encoded amino acid changes, including 3 in the subunits of cytochrome c oxidase. These amino acid substitutions may modulate mitochondrial complexes and electron transport efficiency during cold weather conditions and hypoxia adaptation[7]. In another study, we found that the sperm mtDNA copy number for those living at high altitude (5,300 m) for one month was significantly higher than for those at the lower altitude (1,400 m) or in donors who had been living at the 5,300-m altitude for 1 year[13]. However, the association between mitochondria and HAPE occurrence has not been determined.

In addition, with the emergence of genome-wide linkage disequilibrium (LD)–based marker panels and improvements in high-throughput genotyping technology, genome-wide
association studies (GWAS) have become feasible[14]. GWAS can systematically survey the whole genome for causal genetic variants for complex traits/diseases and is a powerful tool for dissecting the genetic basis for HAPE. Combining the modest association signals in the GWAS data with information on biological pathways and networks, the emerging pathway-based approaches can be designed to utilize the GWAS data to a greater extent and are likely to yield new insights into HAPE aetiology.

To identify the important aetiology mechanism of HAPE occurrence more systematically and comprehensively, we used a novel pathway-based GWAS to approximately 871166 SNPs from 10 unrelated re-occurrence HAPE, which is different from other studies based on GWAS[15]. Those studies chose patients occurring for only one time, which cannot demonstrate that these patients have HAPE susceptibility compared with the data of CHB (Chinese in Beijing, China). Although these patients did not go to high-altitude areas, the incidence rate of HAPE is too low (0.4%~2%) to affect CHB as a control group; therefore, we investigated the association between mtDNA function-related genes and HAPE susceptibility.

Materials and Methods

Patients and controls

Relapsing HAPE patients (n=10) were recruited from the Han ethnic group in China. We compared the allele frequency of HAPEs with the CHB (Chinese in Beijing, China) population (control=45) to exclude 185646 SNPs with minimum allele frequency (MAF) <0.01. The SNPs with the last successful assay were 673843. The recurrent HAPE patients consisted of 10 individuals (25.01±10.70 years old) who had at least two episodes of HAPE, as determined by the standard diagnostic criteria[16], including cough and dyspnea at rest, with pulmonary rales, cyanosis, and patchy shadows detected using chest X-ray. Relapsing HAPE patients and controls were unrelated to each other and matched gender and age. This study was approved by the ethics committee of the Third Military Medical University in China.

Isolation of DNA

The samples of HAPE patients were collected before using drugs; the venous blood (2 ml) was collected from HAPE cases and healthy controls and placed in EDTA-anticoagulation tubes, which were stored at -80 °C prior to analysis. Genomic DNA was extracted from peripheral blood according to the introduction of Omega DNA extraction
kits (Omega, USA). Genomic DNA was tested using gel electrophoresis on a 0.8% agarose gel stained with ethidium bromide.

**Genotyping**

Affymetrix Genome Wide SNP 6.0 arrays were used following the protocol supplied by the manufacturer (Affymetrix, Santa Clara, CA) at Capital Bio Corporation (Beijing, China). Briefly, 250 ng of genomic DNA was digested with Nsp and Sty enzymes, ligated with specific adaptors, and amplified by PCR using the kit primers. The amplicons were purified and quantified. The products were fragmented and labelled followed by hybridization to the array chips at 48 °C for 16–18 h. Excess unhybridized products were washed followed by scanning with a GeneChip Scanner 3000 (Affymetrix, Santa Clara, CA [19481479]). Genotypes were called using the Affymetrix BRLMM algorithm as implemented in the Genotyping Console software (Affymetrix, Santa Clara, CA). All samples had BRLMM call rates greater than the 95% cutoff. We used default parameters for the Birdseed algorithm (version 2) to determine genotypes for all samples (Affymetrix, Santa Clara, CA, USA). Genotypic data were analysed using the Affymetrix Genotyping Console 3.1 (Affymetrix) and included all autosomes but excluded the X and Y chromosomes and mitochondrial genome. First, we performed principal components analysis based on genetic distances as previously described between HAPEs (n=10) and controls (n=45). We tested 871166 SNPs, of which 177502 SNPs failed. Then, we compared the allele frequency of HAPEs with the CHB (Chinese in Beijing, China) population to exclude 185646 SNPs with minimum allele frequency (MAF) <0.01. The SNP with the last successful assay was number 673843.

**Statistical analysis**

Allele frequencies between patient and control groups were compared using the $\chi^2$ test. A stringent P value < 5×10^{-8} was considered significant for GWAS. We used Haploview 4.2 ([http://www.broadinstitute.org/haplovie](http://www.broadinstitute.org/haplovie)) to create a Manhattan plot of p values from the GWAS study. A quantile-quantile (QQ) plot of p values from GWAS was created using R project ([http://www.r-project.org](http://www.r-project.org)). We used the FUMA platform ([http://fuma.ctglab.nl/tutorial](http://fuma.ctglab.nl/tutorial)) to analyse GWAS results and selected single nucleotide polymorphisms (SNPs) of P<10^{-8}, which was the GWAS significance[17].
Results

In the GWAS, we genotyped a total of 871,166 SNPs, and 673,843 SNPs were successfully genotyped (77.35%). We ranked genotyped SNPs based on the strength of association using the allelic association test. Nominally significant results were detected for 1558 SNPs (p<5×10^-8) (Supplementary Table 1). This analysis indicates that HAPE cases are genetically similar to the combined CHB population. HapMap populations provide context for the patterns of variation observed among these populations. Genotyping data yielded an average call rate of 96.6%, and apparent inheritance errors in trio samples were detected in <0.2% of all SNPs. A Manhattan plot was generated for the SNPs in patients with recurrent HAPE in Figure I. A quantile-quantile (QQ) plot for association results is provided in Figure II for all SNPs. The group of SNPs that slightly deviated from a diagonal straight line in the QQ plot are considered to reflect SNPs with weak genetic effects, and from the plot, it seems that there is not gross inflation of false-positive results derived from genotyping errors.

We used the FUMA platform to expand those of SNP p <5×10^-8 to SNPs that included their linkage disequilibrium (r^2 ≥ 0.6). After the data were imported into FUMA, we chose the East Asian population (EAS, consistent with the GWAS population), selected the SNP minimum allele frequency (MAF≥ 0.01) and r^2 (minimum r^2 ≥ 0.6). A total of 369 candidate SNPs (Supplementary Table 2), 4 lead SNPs, 4 genomic risk loci and 5 mapped genes were obtained. The 7 mapped genes were ADAMTS9-AS2, NEK1, CLCN3, C4orf27(HPF1), RP11-219J21.2, ANKRD26 and YME1L1 (Table 1).
Figure I Manhattan plot for the whole SNPs in recurrent HAPE subjects of Chinese Han decent. Demonstrating the distribution of P values of Fisher's exact test in the whole genome under four genetic models of allele, genotype, recessive and dominant. The horizontal axis is the physical position of each SNP, and the vertical axis is the negative logarithm of the P value.
**Figure II** Quantile-quantile (QQ) plot for association results of the first-stage analysis. Red plots are the cases for all loci, and blue plots are the cases after removing the significant locus.

**Table 1** Main effects of tested SNPs on HAPE risk by FUMA.

| Symbol       | Gene            | Chromosome | Start         | End            | Strand | Type          |
|--------------|-----------------|------------|---------------|----------------|--------|---------------|
| ADAMTS9-AS2 |                 | 3          | 64670585      | 64997143       | 1      | antisense     |
| NEK1         |                 | 4          | 170314426     | 170533780      | -1     | protein coding|
| CLCN3        |                 | 4          | 170533784     | 170644824      | 1      | protein coding|
| C4orf27      |                 | 4          | 170650616     | 170679104      | -1     | protein coding|
| RP11-219J21.2|                 | 8          | 25634195      | 25634972       | 1      | lncRNA        |
| ANKRD26      |                 | 10         | 27280843      | 27389421       | -1     | protein coding|
| YME1L1       |                 | 10         | 27399383      | 27444195       | -1     | protein coding|
Discussion

We performed a GWAS to identify susceptibility genes and risk variants for HAPE in Chinese populations. Seven novel candidate genes have emerged from our staged association analyses. Specifically, NEK1, CLCN3, C4orf27, ANKRD26 and YME1L1 are protein-coding genes, and ADAMTS9-AS2 and YME1L1 are RNA genes.

ADAMTS9-AS2 (ADAMTS9 antisense RNA 2) is located at the positive strand of chromosome 3 (chr3: 64, 684, 935-65, 053, 439) with a length of 2.258 kb and is classified as an lncRNA. ADAMTS9-AS2 is an antisense transcription of ADAMTS9. ADAMTS plays important roles in connective tissue organization, coagulation, inflammation, arthritis, and angiogenesis and is regulated by the tissue inhibitor of metalloproteinase 3 gene (TIMP3)[18, 19]. In addition, studies by Kobayashi et al. in the Japanese population showed that TIMP3 was associated with HAPE susceptibility[20-22]. TIMP plays a key role in the physiological turnover of the extracellular matrix (ECM) by closely regulating the activity of matrix metalloproteinase (MMP). TIMP3 is the only TIMP closely integrated with ECM. The balance between MMP and TIMP plays an important role in maintaining the integrity of healthy tissues. The disturbance of the TIMP/MMP system is related to various pathological conditions of the lung, including pulmonary inflammation, oedema, emphysema and fibrosis, among which the loss of ECM integrity is the main feature[23]. Our results, together with those of previous studies, suggest that the balance between MMPs and TIMPs plays an important role in the pathogenesis of HAPE.

CIC-3 (chloride voltage-gated channel 3) is a protein coding gene. Among its related pathways are ion channel transport and transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds[24]. This protein plays a role in both acidification and transmitter loading of GABAergic synaptic vesicles and in smooth muscle cell activation and neointima formation[25]. This protein is required for lysophosphatidic acid (LPA)-activated Cl- current activity and fibroblast-to-myofibroblast differentiation. Yan-Ping Dai et al[26] observe that CIC-3 in rat hypertensive lung and heart is a novel upregulation. These researchers also suggest that upregulation of CIC-3 is an adaptive response of the inflamed pulmonary artery. CIC-3 may be associated with the adaptability of the pulmonary artery to the plateau environment in HAPE.

ANKRD26 (ankyrin repeat domain 26) is a protein coding gene. Diseases associated with ANKRD26 include thrombocytopenia 2 and platelet disorder, familial, with associated
myeloid malignancy. There is a case reported that ANKRD26-related thrombocytopenia resulting in lower-limb deep vein thrombosis complicated by pulmonary embolism[27]. NEK1 (NIMA-related kinase 1) is a protein coding gene. Diseases associated with NEK1 include short-rib thoracic dysplasia 6 with or without polydactyly and amyotrophic lateral sclerosis. NEK1 is involved in DNA damage checkpoint control and proper DNA damage repair[28]. In response to injury that includes DNA damage, NEK1 phosphorylates VDAC1 to limit mitochondrial cell death[28]. YME1L1 (YME1-like 1 ATPase) is a protein coding gene. Diseases associated with YME1L1 include optic atrophy 11 and spastic paraplegia 7, autosomal recessive[29]. Gene Ontology (GO) annotations related to this gene include metalloendopeptidase activity. This protein is localized in the mitochondria and can functionally complement a YME1 disruptant yeast strain. It is proposed that this gene plays a role in mitochondrial protein metabolism and could be involved in mitochondrial pathologies[30]. ATP-dependent metalloprotease, which catalyses the degradation of folded and unfolded proteins with a suitable degron sequence in the mitochondrial intermembrane region[31], plays an important role in regulating mitochondrial morphology and function by cleaving OPA1 at position S2, giving rise to a form of OPA1 that promotes maintenance of normal mitochondrial structure and mitochondrial protein metabolism[31-33]. C4orf27 (also known as HPF1, histone PARylation factor 1) is a protein coding gene[34]. C4orf27 acts as a cofactor for serine ADP-ribosylation by conferring serine specificity on PARP1 and PARP2: this protein interacts with PARP1 and PARP1 and is able to change amino acid specificity towards serine[35]. However, ANKRD26, NEK1, YME1L1 and C4orf27 in HAPE remain unknown and require additional studies.

This study has several limitations. The small size of this study does not provide sufficient power for a conclusive analysis of association. We hope that collaboration with other investigators with access to more HAPE patients will lead to the identification of gene(s) responsible for HAPE. We do not know whether controls had travel to high-altitude regions. We believe that only 0.5-2% of the population experienced HAPE after ascending to high-altitude regions. Considering the rarity of HAPE, we think that all of these people can be used as healthy controls. In summary, we provide evidence for the contribution of ADAMTS9-AS2, NEK1, CLCN3, C4orf27 (HPF1), RP11-219J21.2, ANKRD26 and
YME1L1 to the pathogenesis of HAPE in Chinese populations. This prioritized gene deserves further evaluation to improve the understanding of HAPE genetics.

Acknowledgements
Not applicable.

Funding
We are grateful to all the people who participated in this study. This work was supported by the Second Tibetan Plateau Scientific Expedition and Research Programme (STEP) (Grant No. 2019QZKK0607), the Key Project of the Logistics Research Programme, PLA(BLJ18J005) and the National Natural Science Foundation of China (81571843).

Authors' contributions
Yongjun Luo participated in the design of the present study and performed the statistical analysis. Caizhi Tang, Yu Chen and Xinyuan Liu conducted the study and analyses and collected patient information. We also appreciate assistance in data analysis from Dr. Liyuchun in State Key Laboratory of Genetic Resources and Evolution, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, China.

Ethics approval and consent to participate
Not applicable.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.
References

1. Menon ND. High-Altitude Pulmonary Edema: A Clinical Study. N Engl J Med. 1965;273:66-73. doi: 10.1056/NEJM196507082730202. PubMed PMID: 14301200.
2. Peacock AJ. High altitude pulmonary oedema: who gets it and why? Eur Respir J. 1995;8(11):1819-21. PubMed PMID: 8620944.
3. Sartori C, Trueb L, Scherrer U. High-altitude pulmonary edema. Mechanisms and management. Cardiologia. 1997;42(6):559-67. PubMed PMID: 9234564.
4. Schoene RB. High-altitude pulmonary edema: more lessons from the master. Wilderness Environ Med. 1997;8(4):202-3. PubMed PMID: 11990162.
5. Mortimer H, Patel S, Peacock AJ. The genetic basis of high-altitude pulmonary oedema. Pharmacol Ther. 2004;101(2):183-92. Epub 2004/02/06. doi: 10.1016/j.pharmthera.2003.11.003. PubMed PMID: 14761704.
6. Ahsan A, Mohd G, Norboo T, Baig MA, Pasha MA. Heterozygotes of NOS3 polymorphisms contribute to reduced nitrogen oxides in high-altitude pulmonary edema. Chest. 2006;130(5):1511-9. Epub 2006/11/14. doi: 10.1378/chest.130.5.1511. PubMed PMID: 17099031.
7. Luo Y, Gao W, Chen Y, Liu F, Gao Y. Rare mitochondrial DNA polymorphisms are associated with high altitude pulmonary edema (HAPE) susceptibility in Han Chinese. Wilderness Environ Med. 2012;23(2):128-32. Epub 2012/06/05. doi: 10.1016/j.wem.2012.02.003. PubMed PMID: 22656658.
8. Charu R, Stobdan T, Ram RB, Khan AP, Qadar Pasha MA, Norboo T, et al. Susceptibility to high altitude pulmonary oedema: role of ACE and ET-1 polymorphisms. Thorax. 2006;61(11):1011-2. Epub 2006/10/31. doi: 10.1136/thx.2006.066019. PubMed PMID: 17071838; PubMed Central PMCID: PMCPMC2121168.
9. Wang Y, Liu VW, Xue WC, Tsang PC, Cheung AN, Ngan HY. The increase of mitochondrial DNA content in endometrial adenocarcinoma cells: a quantitative study using laser-captured microdissected tissues. Gynecologic oncology. 2005;98(1):104-10. doi: 10.1016/j.ygyno.2005.04.015. PubMed PMID: 15921730.
10. Xing J, Chen M, Wood CG, Lin J, Spitz MR, Ma J, et al. Mitochondrial DNA content: its genetic heritability and association with renal cell carcinoma. Journal of the...
11. Lewis W, Day BJ, Kohler JJ, Hosseini SH, Chan SS, Green EC, et al. Decreased mtDNA, oxidative stress, cardiomyopathy, and death from transgenic cardiac targeted human mutant polymerase gamma. Laboratory investigation; a journal of technical methods and pathology. 2007;87(4):326-35. doi: 10.1038/labinvest.3700523. PubMed PMID: 17310215; PubMed Central PMCID: PMC1831462.

12. Morten KJ, Ashley N, Wijburg F, Hadzic N, Parr J, Jayawant S, et al. Liver mtDNA content increases during development: a comparison of methods and the importance of age- and tissue-specific controls for the diagnosis of mtDNA depletion. Mitochondrion. 2007;7(6):386-95. doi: 10.1016/j.mito.2007.09.001. PubMed PMID: 17981517.

13. Luo Y, Liao W, Chen Y, Cui J, Liu F, Jiang C, et al. Altitude can alter the mtDNA copy number and nDNA integrity in sperm. Journal of assisted reproduction and genetics. 2011;28(10):951-6. Epub 2011/09/13. doi: 10.1007/s10815-011-9620-y. PubMed PMID: 21909897; PubMed Central PMCID: PMCPmc3220446.

14. Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. Nat Rev Genet. 2005;6(2):95-108. Epub 2005/02/18. doi: 10.1038/nrg1521. PubMed PMID: 15716906.

15. Yang Y-Z, Wang Y-P, Ma L, Du Y, Ge R-L. [Genome-wide association study of high-altitude pulmonary edema in Han Chinese]. Yi Chuan. 2013;35(11):1291-9. doi: 10.3724/sp.j.1005.2013.01291. PubMed PMID: 24579312.

16. Hultgren HN, Marticorena EA. High altitude pulmonary edema. Epidemiologic observations in Peru. Chest. 1978;74(4):372-6. Epub 1978/10/01. doi: 10.1378/chest.74.4.372. PubMed PMID: 699645.

17. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun. 2017;8(1):1826. doi: 10.1038/s41467-017-01261-5. PubMed PMID: 29184056; PubMed Central PMCID: PMCPMC5705698.

18. Cal S, Obaya AJ, Llamazares M, Garabaya C, Quesada V, Lopez-Otin C. Cloning, expression analysis, and structural characterization of seven novel human ADAMTSs, a family of metalloproteinases with disintegrin and thrombospondin-1 domains. Gene.
19. Apte SS. A disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motifs: the ADAMTS family. Int J Biochem Cell Biol. 2004;36(6):981-5. doi: 10.1016/j.biocel.2004.01.014. PubMed PMID: 15094112.

20. Hotta J, Hanaoka M, Droma Y, Katsuyama Y, Ota M, Kobayashi T. Polymorphisms of renin-angiotensin system genes with high-altitude pulmonary edema in Japanese subjects. Chest. 2004;126(3):825-30. doi: 10.1378/chest.126.3.825. PubMed PMID: 15364762.

21. Loffek S, Schilling O, Franzke CW. Series "matrix metalloproteinases in lung health and disease": Biological role of matrix metalloproteinases: a critical balance. Eur Respir J. 2011;38(1):191-208. Epub 2010/12/24. doi: 10.1183/09031936.00146510. PubMed PMID: 21177845.

22. Churg A, Zhou S, Wright JL. Series "matrix metalloproteinases in lung health and disease": Matrix metalloproteinases in COPD. Eur Respir J. 2012;39(1):197-209. Epub 2011/09/17. doi: 10.1183/09031936.00121611. PubMed PMID: 21920892.

23. Cui N, Hu M, Khalil RA. Biochemical and Biological Attributes of Matrix Metalloproteinases. Prog Mol Biol Transl Sci. 2017;147:1-73. Epub 2017/04/18. doi: 10.1016/bs.pmbts.2017.02.005. PubMed PMID: 28413025; PubMed Central PMCID: PMCPMC5430303.

24. Jentsch TJ, Pusch M. CLC Chloride Channels and Transporters: Structure, Function, Physiology, and Disease. Physiol Rev. 2018;98(3):1493-590. Epub 2018/05/31. doi: 10.1152/physrev.00047.2017. PubMed PMID: 29845874.

25. Guan YY, Wang GL, Zhou JG. The CIC-3 Cl- channel in cell volume regulation, proliferation and apoptosis in vascular smooth muscle cells. Trends Pharmacol Sci. 2006;27(6):290-6. Epub 2006/05/16. doi: 10.1016/j.tips.2006.04.008. PubMed PMID: 16697056.

26. Dai YP, Bongalon S, Hatton WJ, Hume JR, Yamboliev IA. CIC-3 chloride channel is upregulated by hypertrophy and inflammation in rat and canine pulmonary artery. Br J Pharmacol. 2005;145(1):5-14. Epub 2005/02/22. doi: 10.1038/sj.bjp.0706135. PubMed PMID: 15723096; PubMed Central PMCID: PMCPMC1576111.
27. Guison J, Blaison G, Stoica O, Hurstel R, Favier M, Favier R. Idiopathic Pulmonary Embolism in a case of Severe Family ANKRD26 Thrombocytopenia. Mediterr J Hematol Infect Dis. 2017;9(1):e2017038. Epub 2017/07/13. doi: 10.4084/MJHID.2017.038. PubMed PMID: 28698781; PubMed Central PMCID: PMCPMC5499493.

28. Chen Y, Gaczynska M, Osmulski P, Polci R, Riley DJ. Phosphorylation by Nek1 regulates opening and closing of voltage dependent anion channel 1. Biochem Biophys Res Commun. 2010;394(3):798-803. Epub 2010/03/17. doi: 10.1016/j.bbrc.2010.03.077. PubMed PMID: 20230784; PubMed Central PMCID: PMCPMC2859727.

29. El-Hattab AW, Suleiman J, Almannai M, Scaglia F. Mitochondrial dynamics: Biological roles, molecular machinery, and related diseases. Mol Genet Metab. 2018;125(4):315-21. Epub 2018/10/27. doi: 10.1016/j.ymgme.2018.10.003. PubMed PMID: 30361041.

30. Quiros PM, Langer T, Lopez-Otin C. New roles for mitochondrial proteases in health, ageing and disease. Nat Rev Mol Cell Biol. 2015;16(6):345-59. Epub 2015/05/15. doi: 10.1038/nrm3984. PubMed PMID: 25970558.

31. Rainbolt TK, Lebeau J, Puchades C, Wiseman RL. Reciprocal Degradation of YME1L and OMA1 Adapts Mitochondrial Proteolytic Activity during Stress. Cell Rep. 2016;14(9):2041-9. Epub 2016/03/01. doi: 10.1016/j.celrep.2016.02.011. PubMed PMID: 26923599; PubMed Central PMCID: PMCPMC4785047.

32. Guillery O, Malka F, Landes T, Guillou E, Blackstone C, Lombes A, et al. Metalloprotease-mediated OPA1 processing is modulated by the mitochondrial membrane potential. Biol Cell. 2008;100(5):315-25. Epub 2007/12/14. doi: 10.1042/BC20070110. PubMed PMID: 18076378.

33. Hartmann B, Wai T, Hu H, MacVicar T, Musante L, Fischer-Zirnsak B, et al. Homozygous YME1L1 mutation causes mitochondriopathy with optic atrophy and mitochondrial network fragmentation. Elife. 2016;5. Epub 2016/08/09. doi: 10.7554/eLife.16078. PubMed PMID: 27495975; PubMed Central PMCID: PMCPMC4991934.

34. Bartlett E, Bonfiglio JJ, Prokhorova E, Colby T, Zobel F, Ahel I, et al. Interplay of Histone Marks with Serine ADP-Ribosylation. Cell Rep. 2018;24(13):3488-502 e5. Epub 2018/09/27. doi: 10.1016/j.celrep.2018.08.092. PubMed PMID: 30257210; PubMed Central PMCID: PMCPMC6172693.
Supplementary Table 1 Significantly different SNPs between 10 recurrent HAPE cases and 45 Hapmap CHB subjects in the first stage

| SNP ID    | Chr | Position   | Band | Allele A | Allele B | min_P_Chi   | HWE  | MAF   |
|-----------|-----|------------|------|----------|----------|-------------|------|-------|
| rs4353667 | 2   | 162025114  | q24.2| A        | G        | 4.099E-19   | 0.940| 0.011 |
| rs509193  | 13  | 101618897  | q33.1| C        | G        | 2.021E-16   | 0.572| 0.078 |
| rs890527  | 3   | 142257543  | q23  | A        | T        | 3.287E-15   | 0.879| 0.022 |
| rs12593141| 15  | 25878695   | q13.1| C        | T        | 6.838E-15   | 0.402| 0.111 |
| rs744306  | 3   | 186272442  | q27.2| A        | G        | 1.632E-14   | 0.693| 0.056 |
| rs9470449 | 6   | 37055364   | p21.2| A        | G        | 2.140E-14   | 0.939| 0.012 |
| rs4810414 | 20  | 42306337   | q13.12| C       | G        | 5.139E-14   | 0.122| 0.133 |
| rs10016530| 4   | 184061978  | q35.1| A        | C        | 4.779E-13   | 0.940| 0.011 |
| rs8010479 | 14  | 80195033   | q31.1| C        | T        | 4.779E-13   | 0.940| 0.011 |
| rs2505465 | 10  | 26080532   | p12.1| A        | G        | 5.504E-13   | 0.693| 0.056 |
| rs12796975| 11  | 132811275  | q25  | C        | T        | 3.196E-12   | 0.755| 0.044 |
| rs7948049 | 11  | 98403015   | q22.1| A        | C        | 3.620E-12   | 0.701| 0.189 |
| rs2904699 | 8   | 17135169   | p22  | A        | G        | 3.672E-12   | 0.362| 0.100 |
| rs7929194 | 11  | 62269326   | q12.3| C        | T        | 4.884E-12   | 0.318| 0.159 |
| rs10075708| 5   | 35582672   | p13.2| A        | G        | 5.540E-12   | 0.940| 0.011 |
| rs9364178 | 6   | 168952425  | q27  | A        | G        | 1.235E-11   | 0.693| 0.056 |
| rs3785499 | 17  | 17355942   | p11.2| A        | G        | 2.244E-11   | 0.879| 0.022 |
| rs7523787 | 1   | 94103203   | p22.1| A        | G        | 2.927E-11   | 0.456| 0.100 |
| rs6471504 | 8   | 96060736   | q22.1| C        | T        | 3.137E-11   | 0.502| 0.222 |
| rs1992305 | 7   | 41347571   | p14.1| C        | G        | 3.419E-11   | 0.000| 0.022 |
| rs9668938 | 12  | 9405128    | p13.31| A       | G        | 3.419E-11   | 0.000| 0.022 |
rs8046088  16    77670982  q23.1  A    T   3.419E-11   0.000   0.500
rs1484545  3     641971   p26.3  A    G   3.819E-11   0.940   0.011
rs7199767  16    81560851  q23.3  C    G   3.950E-11   0.879   0.022
rs1536688  9     16119553  p22.3  A    G   4.179E-11   0.000   0.500
rs2132766  4     78019649  q21.1  C    T   5.684E-11   0.001   0.044
rs4707773  6     93740627  q16.1  A    C   6.125E-11   0.708   0.233
rs2253804  17    45710559  q21.3  A    G   6.770E-11   0.201   0.144
rs3780410  9     4588116   q26.3  A    G   6.838E-11   0.996   0.211
rs907425   8     57038847  q12.1  A    G   9.168E-11   0.675   0.239
rs6020381  20    48277755  q13.1  A    C   1.169E-10   0.578   0.244
rs13379947 15    59972093  q22.2  A    G   1.269E-10   0.996   0.211
rs4799715  18    29531002  q12.1  C    T   1.465E-10   0.701   0.189
rs803302   1     25328122  p36.11 A    G   1.880E-10   0.000   0.022
rs11577001 1     192870487 p31.3  C    T   1.880E-10   0.000   0.022
rs4428669  8     22951725  q21.3  A    T   1.880E-10   0.000   0.022
rs784814   14    47539712  q21.3  C    T   1.880E-10   0.000   0.022
rs16967738 17    37799793  q22.2  C    T   1.880E-10   0.000   0.022
rs7275393  21    40817980  q22.2  G    T   1.880E-10   0.000   0.022
rs11860414 16    13097760  p13.12 C    T   2.257E-10   0.000   0.023
rs6705908  2     238098704 q37.3  A    G   2.998E-10   0.227   0.151
rs17024521 1     120268277 p12    C    G   3.761E-10   0.000   0.033
rs9498354  6     149804544 q25.1  A    G   3.761E-10   0.000   0.033
rs13258727 8     16617623  p22    G    T   3.761E-10   0.000   0.033
rs497022   10    85442083  q23.1  C    T   3.761E-10   0.000   0.033
rs11051790 12    32132279  p11.21 C    G   3.761E-10   0.000   0.033
rs2941948  16    77117341  q23.1  C    G   3.761E-10   0.000   0.033
rs907661   1     117548617 p13.1  A    T   3.761E-10   0.940   0.011
rs2581409  1     112577867 p13.2  A    G   3.761E-10   0.940   0.011
rs10776807 1     109757679 p13.3  A    G   3.761E-10   0.940   0.011
rs12127734 1     102738259 p21.1  C    T   3.761E-10   0.940   0.011
rs1931256  1     95930004  p21.3  A    C   3.761E-10   0.940   0.011
| SNP         | Chr | Genomic Location | Gene Symbol | Reference Allele | Major Allele | Minor Allele | p-value | FDR  |
|-------------|-----|------------------|-------------|------------------|--------------|--------------|---------|------|
| rs6420974   | 1   | 86496645         |             | A                | C            |             | 3.76E-10 | 0.940 |
| rs6424623   | 1   | 79258910         |             | A                | T            |             | 3.76E-10 | 0.940 |
| rs12121720  | 1   | 75159525         |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs10157120  | 1   | 52983476         |             | A                | G            |             | 3.76E-10 | 0.940 |
| rs7525612   | 1   | 47664398         |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs41524944  | 1   | 44894612         |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs2816602   | 1   | 43040557         |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs2182111   | 1   | 29637387         |             | A                | T            |             | 3.76E-10 | 0.940 |
| rs2746535   | 1   | 17264939         |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs16862547  | 1   | 19316539         |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs6703014   | 1   | 151806944        |             | A                | G            |             | 3.76E-10 | 0.940 |
| rs10752607  | 1   | 152983427        |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs6702567   | 1   | 157784484        |             | A                | G            |             | 3.76E-10 | 0.940 |
| rs1288913   | 1   | 161882823        |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs4987357   | 1   | 167932764        |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs12117954  | 1   | 19316539         |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs539038    | 1   | 189048657        |             | A                | G            |             | 3.76E-10 | 0.940 |
| rs613232    | 1   | 209836516        |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs714214    | 1   | 228825228        |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs4658949   | 1   | 230014942        |             | A                | C            |             | 3.76E-10 | 0.940 |
| rs6665236   | 1   | 246060280        |             | A                | G            |             | 3.76E-10 | 0.940 |
| rs4852883   | 2   | 72708531         |             | C                | T            |             | 3.76E-10 | 0.940 |
| rs262501    | 2   | 63712161         |             | A                | G            |             | 3.76E-10 | 0.940 |
| rs6751340   | 2   | 54041121         |             | A                | G            |             | 3.76E-10 | 0.940 |
| rs17389310  | 2   | 42343095         |             | C                | G            |             | 3.76E-10 | 0.940 |
| rs13416119  | 2   | 42316434         |             | A                | G            |             | 3.76E-10 | 0.940 |
| rs17024325  | 2   | 39845266         |             | C                | G            |             | 3.76E-10 | 0.940 |
| rs4648234   | 2   | 37191174         |             | A                | G            |             | 3.76E-10 | 0.940 |
| rs12104627  | 2   | 35364483         |             | A                | T            |             | 3.76E-10 | 0.940 |
| rs11893869  | 2   | 106032330        |             | A                | G            |             | 3.76E-10 | 0.940 |
| rs260711    | 2   | 108923531        |             | C                | T            |             | 3.76E-10 | 0.940 |
rs17783857  2  140102541  q22.1  C  G  3.761E-10  0.940  0.011
rs10185178  2  171064520  q31.1  A  G  3.761E-10  0.940  0.011
rs3914402  2  174296267  q31.1  C  G  3.761E-10  0.940  0.011
rs12989588  2  194838617  q32.3  A  G  3.761E-10  0.940  0.011
rs16842071  2  201639975  q33.1  A  G  3.761E-10  0.940  0.011
rs11902586  2  213683899  q34  C  G  3.761E-10  0.940  0.011
rs11898042  2  220596890  q35  A  G  3.761E-10  0.940  0.011
rs6431283  2  233888576  q37.1  C  T  3.761E-10  0.940  0.011
rs10175460  2  231048405  q37.1  A  G  3.761E-10  0.940  0.011
rs10933609  2  241092142  q37.3  A  G  3.761E-10  0.940  0.011
rs6548631  3  79729007  p12.3  C  G  3.761E-10  0.940  0.011
rs9847658  3  70073539  p14.1  A  C  3.761E-10  0.940  0.011
rs755358  3  62509509  p14.2  C  T  3.761E-10  0.940  0.011
rs9830403  3  27938612  p24.1  C  T  3.761E-10  0.940  0.011
rs778044  3  10255233  p25.3  C  T  3.761E-10  0.940  0.011
rs352748  3  6615700  p26.1  C  G  3.761E-10  0.940  0.011
rs1144107  3  101924406  q12.2  C  T  3.761E-10  0.940  0.011
rs2056534  3  115966848  q13.31  A  G  3.761E-10  0.940  0.011
rs13326852  3  1216419170  q13.33  C  T  3.761E-10  0.940  0.011
rs6769033  3  137066778  q22.2  C  T  3.761E-10  0.940  0.011
rs344076  3  158035479  q25.31  C  T  3.761E-10  0.940  0.011
rs25566339  3  159791569  q25.32  C  T  3.761E-10  0.940  0.011
rs1684656  3  174240032  q26.31  C  T  3.761E-10  0.940  0.011
rs6788878  3  178926662  q26.32  G  T  3.761E-10  0.940  0.011
rs10002498  4  47623342  p12  C  G  3.761E-10  0.940  0.011
rs5743591  4  38479523  p14  C  G  3.761E-10  0.940  0.011
rs13105862  4  36976442  p14  C  T  3.761E-10  0.940  0.011
rs41339448  4  19206250  p15.31  A  G  3.761E-10  0.940  0.011
rs13148734  4  63013453  q13.1  A  G  3.761E-10  0.940  0.011
rs313139  4  127754207  q28.1  C  G  3.761E-10  0.940  0.011
rs1201202  4  152060202  q31.3  A  G  3.761E-10  0.940  0.011
| SNP    | Chromosome | Position  | Location | Allele 1 | Allele 2 | p-Value | OR      |
|--------|------------|-----------|----------|----------|----------|---------|---------|
| rs1594869 | 4         | 158681812 | q32.1    | A        | G        | 3.76E-10 | 0.940   |
| rs17628308 | 4        | 171106945 | q33      | A        | G        | 3.76E-10 | 0.940   |
| rs2173826 | 4         | 170922763 | q33      | A        | G        | 3.76E-10 | 0.940   |
| rs17057390 | 4         | 172849798 | q34.1    | C        | T        | 3.76E-10 | 0.940   |
| rs17074536 | 4        | 184417378 | q35.1    | C        | T        | 3.76E-10 | 0.940   |
| rs4862023 | 4         | 183246608 | q35.1    | A        | C        | 3.76E-10 | 0.940   |
| rs6879532 | 5         | 23092333  | p14.3    | A        | G        | 3.76E-10 | 0.940   |
| rs17295893 | 5        | 14125258  | p15.2    | C        | T        | 3.76E-10 | 0.940   |
| rs10472006 | 5        | 56791259  | q11.2    | C        | T        | 3.76E-10 | 0.940   |
| rs158342 | 5         | 55661090  | q11.2    | A        | C        | 3.76E-10 | 0.940   |
| rs10057147 | 5        | 53473290  | q11.2    | A        | G        | 3.76E-10 | 0.940   |
| rs255233 | 5         | 56633746  | q11.2    | C        | T        | 3.76E-10 | 0.940   |
| rs6896756 | 5         | 66947893  | q13.1    | C        | T        | 3.76E-10 | 0.940   |
| rs11959381 | 5        | 75724016  | q13.3    | C        | T        | 3.76E-10 | 0.940   |
| rs16902631 | 5       | 86679983  | q14.3    | A        | T        | 3.76E-10 | 0.940   |
| rs2963029 | 5         | 108782510 | q21.3    | C        | G        | 3.76E-10 | 0.940   |
| rs4272129 | 5         | 124365847 | q23.2    | C        | T        | 3.76E-10 | 0.940   |
| rs7707878 | 5         | 126011942 | q23.2    | A        | C        | 3.76E-10 | 0.940   |
| rs3861854 | 5         | 141280553 | q31.3    | C        | T        | 3.76E-10 | 0.940   |
| rs1432672 | 5         | 143945814 | q32      | C        | T        | 3.76E-10 | 0.940   |
| rs10037531 | 5        | 156738482 | q33.3    | A        | G        | 3.76E-10 | 0.940   |
| rs4868935 | 5         | 16491974  | q34      | A        | G        | 3.76E-10 | 0.940   |
| rs10462997 | 5        | 169942958 | q35.1    | C        | T        | 3.76E-10 | 0.940   |
| rs10067345 | 5        | 171183175 | q35.1    | A        | G        | 3.76E-10 | 0.940   |
| rs10039715 | 5        | 173603095 | q35.2    | C        | T        | 3.76E-10 | 0.940   |
| rs3129704 | 6         | 30342679  | p21.33   | C        | T        | 3.76E-10 | 0.940   |
| rs7767176 | 6         | 28033346  | p22.1    | C        | T        | 3.76E-10 | 0.940   |
| rs10484632 | 6        | 20755639  | p22.3    | A        | C        | 3.76E-10 | 0.940   |
| rs13206084 | 6        | 16653930  | p22.3    | A        | G        | 3.76E-10 | 0.940   |
| rs11969660 | 6        | 14503352  | p23      | A        | G        | 3.76E-10 | 0.940   |
| rs6919114 | 6         | 10780583  | p24.2    | A        | G        | 3.76E-10 | 0.940   |
| SNP       | Chromosome | Position     | Gene       | Alleles | p-value | p-value_adj | Minor allele frequency |
|-----------|------------|--------------|------------|---------|---------|-------------|------------------------|
| rs3804481 | 6          | 6577398      | p25.1      | A       | G       | 3.76E-10    | 0.940                  |
| rs2110903 | 6          | 107679904    | q21        | G       | T       | 3.76E-10    | 0.940                  |
| rs3757302 | 6          | 108478901    | q21        | C       | G       | 3.76E-10    | 0.940                  |
| rs6913809 | 6          | 113957665    | q22.1      | A       | C       | 3.76E-10    | 0.940                  |
| rs6569290 | 6          | 123195382    | q22.31     | A       | G       | 3.76E-10    | 0.940                  |
| rs12110924| 6          | 118674618    | q22.31     | C       | G       | 3.76E-10    | 0.940                  |
| rs12205922| 6          | 128127367    | q22.33     | A       | G       | 3.76E-10    | 0.940                  |
| rs9480356 | 6          | 156948860    | q25.3      | A       | G       | 3.76E-10    | 0.940                  |
| rs10486806| 7          | 40468520     | p14.1      | A       | G       | 3.76E-10    | 0.940                  |
| rs12536300| 7          | 33159362     | p14.3      | A       | G       | 3.76E-10    | 0.940                  |
| rs17675986| 7          | 29077382     | p15.1      | A       | T       | 3.76E-10    | 0.940                  |
| rs10251505| 7          | 7221014      | p21.3      | A       | G       | 3.76E-10    | 0.940                  |
| rs1207867 | 7          | 78239513     | q21.11     | A       | G       | 3.76E-10    | 0.940                  |
| rs7802018 | 7          | 94898249     | q21.3      | A       | G       | 3.76E-10    | 0.940                  |
| rs1558005 | 7          | 100936342    | q22.1      | A       | G       | 3.76E-10    | 0.940                  |
| rs10252737| 7          | 101486484    | q22.1      | A       | C       | 3.76E-10    | 0.940                  |
| rs13231181| 7          | 103979084    | q22.1      | C       | T       | 3.76E-10    | 0.940                  |
| rs10261618| 7          | 136853662    | q33        | A       | C       | 3.76E-10    | 0.940                  |
| rs4335058 | 7          | 132550141    | q33        | A       | C       | 3.76E-10    | 0.940                  |
| rs851734  | 7          | 146993038    | q35        | C       | G       | 3.76E-10    | 0.940                  |
| rs6967282 | 7          | 150538127    | q36.1      | A       | G       | 3.76E-10    | 0.940                  |
| rs2101138 | 8          | 26186805     | p21.2      | C       | G       | 3.76E-10    | 0.940                  |
| rs2410675 | 8          | 20915740     | p21.3      | G       | T       | 3.76E-10    | 0.940                  |
| rs369240  | 8          | 55686306     | q12.1      | C       | T       | 3.76E-10    | 0.940                  |
| rs35711827| 8          | 76793565     | q21.11     | G       | T       | 3.76E-10    | 0.940                  |
| rs1448676 | 8          | 92396335     | q21.3      | A       | C       | 3.76E-10    | 0.940                  |
| rs16870588| 8          | 104706458    | q22.3      | C       | G       | 3.76E-10    | 0.940                  |
| rs3018507 | 8          | 103347864    | q22.3      | C       | G       | 3.76E-10    | 0.940                  |
| rs7826950 | 8          | 134980387    | q24.22     | A       | C       | 3.76E-10    | 0.940                  |
| rs10088738| 8          | 139205255    | q24.23     | A       | G       | 3.76E-10    | 0.940                  |
| rs17247766| 9          | 33098605     | p13.3      | G       | T       | 3.76E-10    | 0.940                  |
| rs          | ch  | pos           | chr | pos     | pos | pos | p-value | p-value |
|-------------|-----|---------------|-----|---------|-----|-----|---------|---------|
| rs1885170   | 9   | 17554267      | p22.2| C       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs13285034  | 9   | 74559353      | q21.13| A       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs10993086  | 9   | 95990540      | q22.32| G       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs10441773  | 9   | 107233498     | q31.2| C       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs12553905  | 9   | 121402295     | q33.1| C       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs16929767  | 9   | 129113684     | q33.3| A       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs3011286   | 9   | 134883811     | q34.13| C      | T   | 3.76E-10 | 0.940  | 0.011   |
| rs2643955   | 10  | 29197524      | p11.23| G       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs11015156  | 10  | 26863974      | p12.1| G       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs11001982  | 10  | 78468130      | q22.3| A       | G   | 3.76E-10 | 0.940  | 0.011   |
| rs17465850  | 10  | 17812128      | q26.12| A       | C   | 3.76E-10 | 0.940  | 0.011   |
| rs12358414  | 10  | 3707846       | p15.2| C       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs17501883  | 10  | 44506780      | q11.21| A       | C   | 3.76E-10 | 0.940  | 0.011   |
| rs17594946  | 10  | 122702917     | q26.12| A       | C   | 3.76E-10 | 0.940  | 0.011   |
| rs12412522  | 10  | 122789916     | q26.12| C       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs2818393   | 10  | 133792619     | q26.3| A       | G   | 3.76E-10 | 0.940  | 0.011   |
| rs4755364   | 11  | 34249101      | p13  | A       | G   | 3.76E-10 | 0.940  | 0.011   |
| rs1482734   | 11  | 23211390      | p14.3| A       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs793909    | 11  | 13862425      | p15.2| C       | G   | 3.76E-10 | 0.940  | 0.011   |
| rs12807017  | 11  | 9635721       | p15.4| A       | G   | 3.76E-10 | 0.940  | 0.011   |
| rs1770441   | 11  | 60939964      | q12.2| C       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs3017605   | 11  | 6101794       | q12.2| A       | C   | 3.76E-10 | 0.940  | 0.011   |
| rs632280    | 11  | 78178911      | q14.1| G       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs7121003   | 11  | 86964252      | q14.2| A       | C   | 3.76E-10 | 0.940  | 0.011   |
| rs4512880   | 11  | 86955572      | q14.2| A       | G   | 3.76E-10 | 0.940  | 0.011   |
| rs655922    | 11  | 100153283     | q22.1| G       | T   | 3.76E-10 | 0.940  | 0.011   |
| rs522819    | 11  | 100460929     | q22.1| A       | G   | 3.76E-10 | 0.940  | 0.011   |
| rs7113906   | 11  | 101758880     | q22.2| C       | T   | 3.76E-10 | 0.940  | 0.011   |
| SNP        | Chromosome | Position   | Location | Genotype | Minor Allele Frequency | Minor Allele Frequency |
|------------|------------|------------|----------|----------|------------------------|------------------------|
| rs1375423  | 11         | 104601723  | q22.3    | A        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs1902238  | 11         | 106468971  | q22.3    | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs7122110  | 11         | 120527150  | q23.3    | A        | G                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs11216478 | 11         | 117016434  | q23.3    | A        | G                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs41507249 | 11         | 122112574  | q24.1    | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs583194   | 11         | 125456998  | q24.2    | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs10894844 | 11         | 133952614  | q25      | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs17472165 | 12         | 26494853   | p11.23   | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs3863355  | 12         | 25850114   | p12.1    | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs4350408  | 12         | 22043980   | p12.1    | G        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs11045116 | 12         | 19186252   | p12.3    | A        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs12307636 | 12         | 9512800    | p13.31   | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs1805731  | 12         | 8986493    | p13.31   | A        | G                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs7312896  | 12         | 662066     | p13.33   | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs9325199  | 12         | 70273227   | q21.1    | A        | C                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs310836   | 12         | 76001666   | q21.2    | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs4143188  | 12         | 81326916   | q21.31   | A        | C                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs10877572 | 12         | 92977940   | q22      | A        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs9669774  | 12         | 113260669  | q24.21   | C        | G                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs17441172 | 12         | 117352644  | q24.23   | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs7298854  | 12         | 125553390  | q24.32   | A        | C                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs10847172 | 12         | 125560866  | q24.32   | A        | G                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs9314935  | 13         | 28583729   | q12.3    | A        | G                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs9548515  | 13         | 38338848   | q13.3    | A        | C                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs2503454  | 13         | 46987969   | q14.2    | A        | G                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs12429341 | 13         | 47347285   | q14.2    | A        | G                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs17060868 | 13         | 61588183   | q21.31   | A        | C                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs9516058  | 13         | 91762201   | q31.3    | A        | G                      | 3.76E-10               | 0.940                  | 0.011                  |
| rs9514865  | 13         | 107995471  | q33.3    | C        | T                      | 3.76E-10               | 0.940                  | 0.011                  |
| SNP    | Chromosome | Position | Gene | Minor Allele | Major Allele | p-value | Effect Size |
|--------|------------|----------|------|--------------|--------------|---------|-------------|
| rs6650482 | 13         | 111970835 | q34  | A            | G            | 3.76E-10 | 0.940       |
| rs7160516 | 14         | 43848866  | q21.3| A            | G            | 3.76E-10 | 0.940       |
| rs10484082 | 14        | 51162516  | q22.1| C            | T            | 3.76E-10 | 0.940       |
| rs17107847 | 14        | 78091511  | q24.3| G            | T            | 3.76E-10 | 0.940       |
| rs6574673 | 14         | 81183387  | q31.1| G            | T            | 3.76E-10 | 0.940       |
| rs6574612 | 14         | 80473827  | q31.1| C            | T            | 3.76E-10 | 0.940       |
| rs4905612 | 14         | 97248348  | q32.2| A            | G            | 3.76E-10 | 0.940       |
| rs7160516 | 14         | 43848866  | q21.3| A            | G            | 3.76E-10 | 0.940       |
| rs8041819 | 15         | 50401611  | q21.2| A            | G            | 3.76E-10 | 0.940       |
| rs11858794 | 15       | 57498627  | q22.2| A            | G            | 3.76E-10 | 0.940       |
| rs9944345 | 15         | 49976666  | q12.1| A            | G            | 3.76E-10 | 0.940       |
| rs2058673 | 15         | 45580279  | p12.1| A            | C            | 3.76E-10 | 0.940       |
| rs16957304 | 16        | 65892470  | q22.3| A            | C            | 3.76E-10 | 0.940       |
| rs935976  | 16         | 85593861  | p12.1| A            | C            | 3.76E-10 | 0.940       |
| rs6540041 | 16         | 85961876  | q24.2| A            | T            | 3.76E-10 | 0.940       |
| rs12150174 | 17       | 62856936  | q24.2| A            | C            | 3.76E-10 | 0.940       |
| rs7503902 | 17         | 59833749  | q23.3| A            | G            | 3.76E-10 | 0.940       |
| rs1790534 | 17         | 30665290  | q12.1| A            | G            | 3.76E-10 | 0.940       |
| SNP          | Chromosome | Position       | Gene        | Effect | Minor Allele | Minor Allele Value | P Value | Bonferroni Corrected P Value |
|--------------|------------|----------------|-------------|--------|--------------|--------------------|---------|------------------------------|
| rs11873775   | 18         | 24417919       | C           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs654975     | 18         | 58418480       | G           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs1704816    | 18         | 62280193       | C           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs12962239   | 18         | 73493166       | A           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs12981996   | 19         | 20342025       | A           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs16996008   | 19         | 19226400       | A           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs6511939    | 19         | 14545425       | A           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs11672838   | 19         | 14948335       | C           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs7003       | 19         | 14486790       | C           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs12983312   | 19         | 10190245       | C           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs407743     | 19         | 6593417        | C           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs1558133    | 19         | 1253965        | C           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs8112607    | 19         | 3816246        | C           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs1661906    | 19         | 58201490       | A           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs6510101    | 19         | 62999086       | G           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs6042568    | 20         | 1418343        | C           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs13041282   | 20         | 29836903       | A           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs2868093    | 20         | 42397212       | G           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs6073310    | 20         | 42139597       | C           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs928072     | 20         | 48368185       | A           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs6020818    | 20         | 48926335       | C           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs1980424    | 21         | 15164448       | A           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs13048221   | 21         | 14381307       | A           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs551680     | 21         | 39876578       | A           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs2535708    | 22         | 16564169       | A           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs7293008    | 22         | 2772666        | C           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs3730114    | 22         | 24421306       | C           | T      | 3.76E-10     | 0.940              | 0.011   |
| rs17834914   | 22         | 45605985       | A           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs8137937    | 22         | 45846062       | C           | G      | 3.76E-10     | 0.940              | 0.011   |
| rs243505     | 7          | 148066272      | A           | G      | 4.008E-10    | 0.360              | 0.267   |
| rs7119096    | 11         | 127453448      | C           | T      | 4.429E-10    | 0.649              | 0.122   |
| rs    | SNP   | CHROM | POS | CHRPOS | AF1 | AF2 | OR   | P   | EASE  |
|-------|-------|-------|-----|--------|-----|-----|------|-----|-------|
| rs7872136 | 9     | 85091738 | q21.32 | A | G | 4.597E-10 | 0.939 | 0.011 |
| rs4584989  | 2     | 108686189 | q13   | C | T | 4.597E-10 | 0.939 | 0.011 |
| rs4378452  | 12    | 109988416 | q24.11 | A | G | 4.597E-10 | 0.939 | 0.011 |
| rs8130198  | 21    | 42503393 | q22.3 | C | T | 4.597E-10 | 0.939 | 0.011 |
| rs7909124  | 10    | 97709510  | q23.33 | C | G | 5.641E-10 | 0.939 | 0.012 |
| rs17261573 | 2     | 80528623  | p12   | C | G | 5.868E-10 | 0.996 | 0.211 |
| rs6762195  | 3     | 126740626 | q21.2  | C | T | 7.214E-10 | 0.726 | 0.278 |
| rs11199331 | 10    | 122174433 | q26.12 | A | T | 8.142E-10 | 0.290 | 0.244 |
| rs6854931  | 4     | 6828065   | p16.1 | A | G | 1.034E-09 | 0.940 | 0.011 |
| rs6720335  | 2     | 233540064 | q37.1  | A | G | 1.128E-09 | 0.000 | 0.044 |
| rs41453247 | 14    | 54982693  | q22.3  | A | G | 1.128E-09 | 0.000 | 0.500 |
| rs581459   | 1     | 36147697  | p34.3 | C | T | 1.129E-09 | 0.848 | 0.222 |
| rs250238   | 5     | 50302287  | q11.1 | A | C | 1.129E-09 | 0.502 | 0.222 |
| rs16992471 | 19    | 4591295   | p13.3 | A | C | 1.129E-09 | 0.502 | 0.222 |
| rs241301   | 1     | 227029050 | q42.13 | C | T | 1.276E-09 | 0.103 | 0.289 |
| rs2078330  | 16    | 73137556  | q22.3  | C | T | 1.276E-09 | 0.859 | 0.289 |
| rs8100750  | 19    | 55775407  | q13.33 | C | T | 1.462E-09 | 0.667 | 0.178 |
| rs7221423  | 17    | 78551921  | q25.3  | C | T | 1.561E-09 | 0.130 | 0.078 |
| rs8118315  | 20    | 4109500   | p13   | C | T | 1.573E-09 | 0.000 | 0.489 |
| rs17483466 | 2     | 111513929 | q13   | A | G | 1.880E-09 | 0.940 | 0.011 |
| rs9878562  | 3     | 53864028  | p21.1 | C | T | 1.880E-09 | 0.000 | 0.033 |
| rs31745    | 5     | 10400408  | q31.3 | A | G | 1.880E-09 | 0.000 | 0.033 |
| rs1778994  | 9     | 125595350 | q33.2 | A | C | 1.880E-09 | 0.940 | 0.011 |
| rs10501627 | 11    | 86029148  | q14.2 | A | C | 1.880E-09 | 0.000 | 0.033 |
| rs568739   | 11    | 127565639 | q24.3 | A | G | 1.880E-09 | 0.940 | 0.011 |
| rs7142084  | 14    | 91892784  | q32.12 | C | T | 1.880E-09 | 0.000 | 0.033 |
| rs11854845 | 15    | 69688499  | q23   | A | G | 1.880E-09 | 0.940 | 0.011 |
| rs11806573 | 1     | 62591934  | p31.3 | A | C | 1.880E-09 | 0.940 | 0.011 |
| rs473223   | 1     | 54896976  | p32.3 | A | G | 1.880E-09 | 0.940 | 0.011 |
| rs12066062 | 1     | 149925647 | q21.3 | C | T | 1.880E-09 | 0.940 | 0.011 |
| rs11583867 | 1     | 183984337 | q25.3 | A | G | 1.880E-09 | 0.940 | 0.011 |
| SNP         | Chr | Pos  | Ref  | Alt  | p-value |
|-------------|-----|------|------|------|---------|
| rs2867890   | 1   | 203736379 | q32.1 | A   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs12731771  | 1   | 202027279 | q32.1 | C   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs11118935  | 1   | 206171611 | q32.2 | A   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs12074002  | 1   | 209897308 | q32.3 | C   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs2965012   | 1   | 216853172 | q41   | G   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs6696165   | 1   | 242834795 | q44   | C   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs11125521  | 1   | 54205862  | p16.2 | A   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs1403450   | 2   | 45696779  | p21   | C   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs908679    | 2   | 22283114  | p24.1 | A   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs1983376   | 2   | 17289515  | p24.2 | A   | C   | 1.880E-09 | 0.940 | 0.011 |
| rs1188931   | 2   | 106141807 | q12.2 | C   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs13021341  | 2   | 144247607 | q22.2 | C   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs1113988   | 2   | 168059681 | q24.3 | A   | C   | 1.880E-09 | 0.940 | 0.011 |
| rs3914752   | 2   | 170833364 | q31.1 | A   | C   | 1.880E-09 | 0.940 | 0.011 |
| rs10179515  | 2   | 212255007 | q34   | C   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs1082901   | 3   | 77834657  | p12.3 | A   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs1502616   | 3   | 59505361  | p14.2 | C   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs9845785   | 3   | 31504110  | p23   | C   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs17015506  | 3   | 24956816  | p24.2 | A   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs17036852  | 3   | 12518475  | p25.1 | A   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs9864656   | 3   | 137126228 | q22.2 | C   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs7639012   | 3   | 155697801 | q25.2 | G   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs16832690  | 3   | 183003503 | q26.33| A   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs17513709  | 4   | 40496876  | p14   | G   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs6831500   | 4   | 17810438  | p15.32| C   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs17592868  | 4   | 68897521  | q13.2 | C   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs3792662   | 4   | 95689234  | q22.3 | C   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs10517681  | 4   | 159059047 | q32.1 | A   | C   | 1.880E-09 | 0.940 | 0.011 |
| rs11723043  | 4   | 189744112 | q35.2 | C   | T   | 1.880E-09 | 0.940 | 0.011 |
| rs16901423  | 5   | 31715101  | p13.3 | A   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs13362111  | 5   | 33328915  | p13.3 | C   | G   | 1.880E-09 | 0.940 | 0.011 |
| rs           | Chromosome | Position     | Allele 1 | Allele 2 | p-Value | OR  | 95% CI Lower | 95% CI Upper |
|--------------|------------|--------------|----------|----------|---------|-----|--------------|--------------|
| rs7734697    | 5          | 7469304      | A        | T        | 1.880E-09 | 0.940 | 0.011       |
| rs2897554    | 5          | 8311997      | C        | T        | 1.880E-09 | 0.940 | 0.011       |
| rs41459348   | 5          | 94239098     | C        | T        | 1.880E-09 | 0.940 | 0.011       |
| rs10477915   | 5          | 107955270    | C        | T        | 1.880E-09 | 0.940 | 0.011       |
| rs10042652   | 5          | 141636901    | G        | T        | 1.880E-09 | 0.940 | 0.011       |
| rs10072565   | 5          | 166242667    | A        | G        | 1.880E-09 | 0.940 | 0.011       |
| rs9313568    | 5          | 17134886     | A        | C        | 1.880E-09 | 0.940 | 0.011       |
| rs6867969    | 5          | 172157416    | C        | T        | 1.880E-09 | 0.940 | 0.011       |
| rs13156607   | 5          | 168832565    | C        | T        | 1.880E-09 | 0.940 | 0.011       |
| rs9475536    | 6          | 56008167     | p12.1    | C        | 1.880E-09 | 0.940 | 0.011       |
| rs513248     | 6          | 53546485     | p12.1    | A        | 1.880E-09 | 0.940 | 0.011       |
| rs7766333    | 6          | 25070202     | p22.2    | A        | 1.880E-09 | 0.940 | 0.011       |
| rs6900027    | 6          | 10760336     | p24.2    | A        | 1.880E-09 | 0.940 | 0.011       |
| rs10455706   | 6          | 71345716     | q13      | C        | 1.880E-09 | 0.940 | 0.011       |
| rs10944336   | 6          | 88718737     | q15      | C        | 1.880E-09 | 0.940 | 0.011       |
| rs9489754    | 6          | 98342750     | q16.1    | A        | 1.880E-09 | 0.940 | 0.011       |
| rs4377817    | 6          | 115194976    | q22.1    | C        | 1.880E-09 | 0.940 | 0.011       |
| rs17250161   | 6          | 153849770    | q25.2    | C        | 1.880E-09 | 0.940 | 0.011       |
| rs1737317    | 6          | 163709828    | q26      | A        | 1.880E-09 | 0.940 | 0.011       |
| rs856588     | 7          | 46703840     | p12.3    | C        | 1.880E-09 | 0.940 | 0.011       |
| rs11979904   | 7          | 38684422     | p14.1    | A        | 1.880E-09 | 0.940 | 0.011       |
| rs10257031   | 7          | 35907991     | p14.2    | A        | 1.880E-09 | 0.940 | 0.011       |
| rs2098273    | 7          | 36484536     | p14.2    | C        | 1.880E-09 | 0.940 | 0.011       |
| rs17457143   | 7          | 20559116     | p15.3    | C        | 1.880E-09 | 0.940 | 0.011       |
| rs3807573    | 7          | 5636086      | p22.1    | C        | 1.880E-09 | 0.940 | 0.011       |
| rs6463483    | 7          | 5497369      | p22.1    | C        | 1.880E-09 | 0.940 | 0.011       |
| rs6460734    | 7          | 71597254     | q11.22   | C        | 1.880E-09 | 0.940 | 0.011       |
| rs4730058    | 7          | 104347376    | q22.1    | C        | 1.880E-09 | 0.940 | 0.011       |
| rs706561     | 7          | 136925970    | q33      | C        | 1.880E-09 | 0.940 | 0.011       |
| rs17667159   | 7          | 156988826    | q36.3    | A        | 1.880E-09 | 0.940 | 0.011       |
| rs17595134   | 8          | 40076812     | p11.21   | C        | 1.880E-09 | 0.940 | 0.011       |
| rs7822050 | 8 | 72730829 | q13.3 | C | T | 1.880E-09 | 0.940 | 0.011 |
| rs16938568 | 8 | 74209396 | q21.11 | C | T | 1.880E-09 | 0.940 | 0.011 |
| rs16874193 | 8 | 107268534 | q23.1 | A | C | 1.880E-09 | 0.940 | 0.011 |
| rs2799753 | 9 | 38475256 | p13.1 | A | T | 1.880E-09 | 0.940 | 0.011 |
| rs7021837 | 9 | 13844176 | p23 | A | G | 1.880E-09 | 0.940 | 0.011 |
| rs10959547 | 9 | 11110180 | p23 | C | G | 1.880E-09 | 0.940 | 0.011 |
| rs35613585 | 9 | 74634393 | q21.13 | C | G | 1.880E-09 | 0.940 | 0.011 |
| rs1330288 | 9 | 74626903 | q21.13 | A | G | 1.880E-09 | 0.940 | 0.011 |
| rs12686427 | 9 | 88530367 | q21.33 | C | T | 1.880E-09 | 0.940 | 0.011 |
| rs4314720 | 9 | 112411728 | q31.3 | C | T | 1.880E-09 | 0.940 | 0.011 |
| rs41407147 | 9 | 121795392 | q33.1 | G | T | 1.880E-09 | 0.940 | 0.011 |
| rs12554146 | 9 | 13317958 | q34.13 | A | T | 1.880E-09 | 0.940 | 0.011 |
| rs2797468 | 10 | 29197311 | p11.23 | A | C | 1.880E-09 | 0.940 | 0.011 |
| rs16926660 | 10 | 26523271 | p12.1 | C | T | 1.880E-09 | 0.940 | 0.011 |
| rs11256585 | 10 | 10468085 | p14 | C | T | 1.880E-09 | 0.940 | 0.011 |
| rs1005907 | 10 | 4863106 | p15.1 | A | G | 1.880E-09 | 0.940 | 0.011 |
| rs4881163 | 10 | 3395755 | p15.2 | C | G | 1.880E-09 | 0.940 | 0.011 |
| rs12242220 | 10 | 49698112 | q11.22 | C | T | 1.880E-09 | 0.940 | 0.011 |
| rs17500631 | 10 | 52297578 | q11.23 | G | T | 1.880E-09 | 0.940 | 0.011 |

Received on October 27, 2019.
Accepted June 23, 2020.
Online First June, 2020.