

ORIGINAL ARTICLE

An association analysis between psychophysical characteristics and genome-wide gene expression changes in human adaptation to the extreme climate at the Antarctic Dome Argus

C Xu^{1,2}, X Ju^{2,12}, D Song^{3,12}, F Huang^{2,12}, D Tang⁴, Z Zou², C Zhang⁵, T Joshi⁵, L Jia³, W Xu⁶, K-F Xu⁶, Q Wang¹, Y Xiong¹, Z Guo¹, X Chen¹, F Huang¹, J Xu², Y Zhong², Y Zhu⁷, Y Peng⁷, L Wang⁷, X Zhang⁸, R Jiang⁹, D Li¹⁰, T Jiang^{9,11}, D Xu⁵ and C Jiang^{1,2,6}

Genome-wide gene expression measurements have enabled comprehensive studies that integrate the changes of gene expression and phenotypic information to uncover their novel associations. Here we reported the association analysis between psychophysical phenotypes and genome-wide gene expression changes in human adaptation to one of the most extreme climates on Earth, the Antarctic Dome Argus. Dome A is the highest ice feature in Antarctica, and may be the coldest, driest and windiest location on earth. It is considered unapproachable due to its hostile environment. In 2007, a Chinese team of 17 male explorers made the expedition to Dome A for scientific investigation. Overall, 133 psychophysical phenotypes were recorded, and genome-wide gene expression profiles from the blood samples of the explorers were measured before their departure and upon their arrival at Dome A. We found that mood disturbances, including tension (anxiety), depression, anger and fatigue, had a strong, positive, linear relationship with the level of a male sex hormone, testosterone, using the Pearson correlation coefficient (PCC) analysis. We also demonstrated that significantly lowest-level Gene Ontology groups in changes of gene expression in blood cells with erythrocyte removal were consistent with the adaptation of the psychophysical characteristics. Interestingly, we discovered a list of genes that were strongly related to significant phenotypes using phenotype and gene expression PCC analysis. Importantly, among the 70 genes that were identified, most were significantly related to mood disturbances, where 42 genes have been reported in the literature mining, suggesting that the other 28 genes were likely novel genes involved in the mood disturbance mechanism. Taken together, our association analysis provides a reliable method to uncover novel genes and mechanisms related to phenotypes, although further studies are needed.

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INTRODUCTION

The Antarctic Dome Argus (Dome A),^{1–4} the coldest naturally occurring place on Earth, with temperatures approaching -90°C (-130°F),^{3,5} is one of the least explored places in the world. It is located 1200 km inland ($80^{\circ}22'S$, $77^{\circ}22'E$) and is the most remote dome from the coast.⁶ Dome A has the highest ice peak in Antarctica, with an elevation of 4093 m above sea level. It is also one of the driest locations on Earth, receiving an average annual snowfall equivalent to < 2 cm of water.³ The South pole experiences 6 months of continuous light and 6 months of continuous darkness every year.^{7,8} Owing to these extreme climate conditions, Dome A is called the unapproachable pole.

No ground-based scientific investigation has ever been made at this snow-covered area prior to January 2005, when a team from the Chinese National Antarctic Research Expeditions traveled 1228 km from Zhongshan Station, the second Chinese research station in Antarctica, to Dome A.^{9,10} Automatic weather stations were deployed at this site since then as part of an Australian–Chinese collaboration. On the second expedition to Dome A, a team of scientists and journalists boarded the Xuelong (Snow Dragon) polar expedition ship that departed on 12 November 2007 from Shanghai, China, and arrived at Zhongshan Station 1 month later, on 12 December. The explorers left Zhongshan station on 22 December and reached Dome A on 12 January 2008.

¹United Laboratory of Polar Medical Sciences, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing, China; ²Department of Biochemistry and Molecular Biology, State Key Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Peking Union Medical College, Tsinghua University, Beijing, China; ³School of Computer Science, Beijing Institute of Technology, Beijing, China; ⁴Luzhou Medical School Affiliated Hospital of Traditional Chinese Medicine, Sichuan, China; ⁵Department of Computer Science, Informatics Institute and C.S. Bond Life Sciences Center, University of Missouri, Columbia, MO, USA; ⁶Center for Translational Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Beijing, China; ⁷Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Peking Union Medical College, Tsinghua University, Beijing, China; ⁸State Key Laboratory of Mycology, Institute of Microbiology, Chinese Academy of Sciences, Beijing, China; ⁹MOE Key Laboratory of Bioinformatics and Bioinformatics Division, TNLIST/Department of Automation, Tsinghua University, Beijing, China; ¹⁰Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China and ¹¹Department of Computer Science and Engineering, University of California, Riverside, CA, USA. Correspondence: C Xu, United Laboratory of Polar Medical Sciences, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing 100005, China or Professor C Jiang, Department of Biochemistry and Molecular Biology, State Key Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Peking Union Medical College, Tsinghua University, 5 Dong Dan San Tiao, Beijing 100005, China. E-mail: xuchengli@pumc.edu.cn or jiang@pumc.edu.cn

¹²These authors contributed equally to this work.

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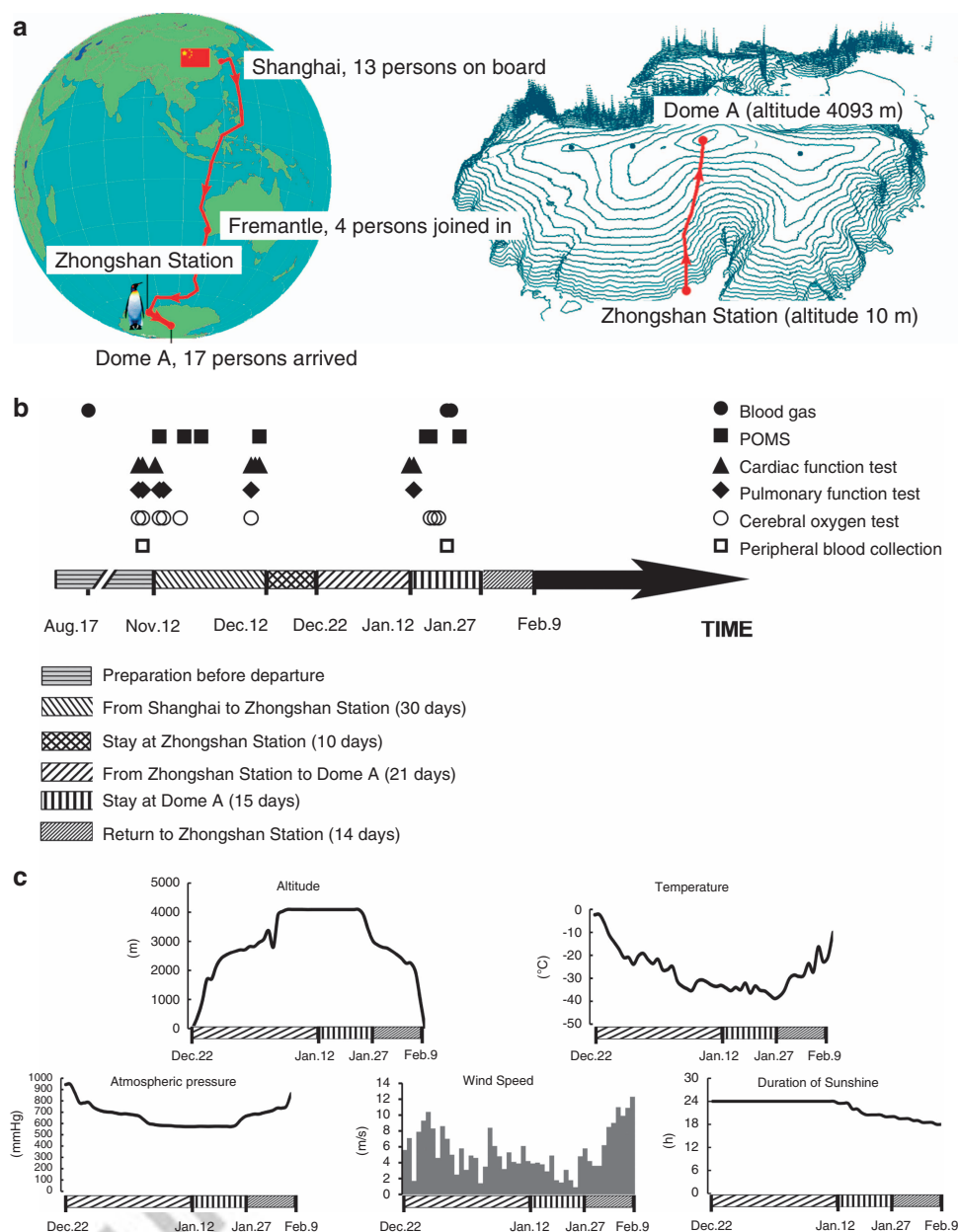


Figure 1. The maps and weather records of the Antarctic exploration. For this Antarctic exploration, 13 explorers (study participants) traveled from Shanghai to Zhongshan station in Antarctica in a Xuelong icebreaker, and four members joined the party in Fremantle, Australia. The party then proceeded to Dome A in ice tractors. The routes and elevation changes are shown in **a**. After departure and during their stay at Dome A, the participants underwent various physical and psychological tests at the indicated time points (**b**). Altitude and weather changes, including temperature, atmospheric pressure, wind and duration of sunlight, were recorded at regular intervals during the study/exploration (**c**).

On 27 January 2008, the expedition team left Dome A and then returned to Zhongshan station on 9 February 2008 (Figures 1a and b). The altitudes, temperatures, atmospheric pressures, wind speeds and times of daylight were recorded during the journey (Figure 1c).

The second expedition to Dome A provided a rare opportunity to study human adaptation to the extreme environment. A medical doctor (Supplementary Table S1, ID No. 12) closely followed the expedition team of 16 people (Supplementary Table S1, ID No. 1–No. 11, No. 13–No. 17). He collected blood samples, performed physiological tests, including assessments of heart function, lung function, cerebral oxygen levels and blood gas

levels, and administered psychological questionnaires (Profile of Mood States) to evaluate the mood of all team members. These psychophysical analyses included 133 phenotypic parameters of human adaptation prior to the 13 participants' departure from Shanghai and upon their arrival at Dome A (Figure 1b, Supplementary Table S1). In parallel, gene expression array was performed using total RNA extracted from erythrocyte-free blood cells (Figure 1, Supplementary Table S1). After normalization of these array data¹¹ (Supplementary Figure S1A), heat maps¹² revealed that the gene expression profile of one explorer (ID No. 9, who had previously been to Dome A) was distinct from that of the other participants who were making their first trip to Dome A

(Supplementary Figure S1B). Thus, the data collected from Participant No. 9 was excluded from the final analysis ($n=12$) (Supplementary Table S1).

MATERIALS AND METHODS

Study participants

The study was performed on 17 healthy men (mean age 35.65 ± 9.71 years, ranging from 26 to 58 years, Supplementary Table S1), all of whom were active in a related field of research, such as glaciology, astronomy, topography, robot geology science, technical engineering and journalism. The exclusion criteria were acute or chronic diseases, such as asthma or pulmonary edema, that would have increased the risk of harm from exposure to high altitudes and low temperatures. In addition, most of the participants (16/17) resided at low altitude and had not previously stayed at high altitude for extended periods of time (for more than half a year). Of the 17 members recruited, one (Supplementary Table S1, ID No. 12) member was a medical doctor who followed the rest of the explorers to collect blood samples, to test the physiological functions and to survey the psychological conditions of the explorers. Written informed consent was obtained from all of the participants.

Study procedures

All of the 17 participants arrived at Zhongshan Station ($69^{\circ}22'S$, $76^{\circ}22'E$, altitude 10 m) on 12 December 2007 via the Xuelong (Snow Dragon) polar expedition ship after 30 days, departing from Shanghai on 12 November 2007. After 10 days of reflection and preparation, the explorers left Zhongshan station on 22 December and took 21 days to reach Dome A ($80^{\circ}22'S$, $77^{\circ}22'E$, altitude 4093 m) on 12 January 2008. They spent 15 days at Dome A for scientific research and exploration and left Dome A on 27 January 2008. They took 14 days to return to Zhongshan Station on 9 February 2008 (Figures 1a and b).

Data collection

The period of data collection for this study began prior to the departure from Shanghai (17 August 2007 to 12 November 2007) and extended during the stay at Dome A (12 January 2008 to 25 January 2008). The temperature, wind speed and barometric pressure were recorded automatically every 30 min by an on-vehicle meteorological instrument, and the duration of sunlight was also recorded every day (Figure 1c).

Arterial blood samples were analyzed using the i-STAT 1 portable blood gas handheld analyzer system (i-STAT, Princeton, NJ, USA) immediately after it was obtained. Lung function was accessed using the Jaeger MasterScope spirometer (Master Lab, Germany) according to the manufacturer's instructions and established guidelines.^{13–15} Barometric pressure was measured using the on-vehicle barometer (MingGao, China). The BioZ. ComTM digital noninvasive hemodynamic Cardiodynamics Monitor system (Cardiodynamics, San Diego, CA, USA) was used to evaluate the cardiac function. Electrocardiograms of the explorers/participants were acquired using the 12-lead portable electrocardiogram acquisition terminal (Nihon Kohdencardiofax C PEA-1100K, Tokyo, Japan) according to the directions provided by the manufacturer. After the electrocardiogram was reviewed by two cardiologists, the numerical parameters, which were automatically calculated using the Nihon Kohden's ECAPS12C interpretation program, were used for the statistical analyses. The microvascular O₂ availability in the participants' brain was measured using a continuous-wave near-infrared spectroscopy system (OxyMon Mk III, Artinis Medical Systems BV, The Netherlands) according to the manufacturer's instructions.

The sera of the explorers were collected for the cytokine/chemokine measurements and endocrine measurements. Samples were analyzed using the Bio-Plex Human Cytokine 25-Plex flow cytometry-based assay kit (Bio-Rad Laboratories, USA) with the Bio-Plex Protein Array system (Bio-Rad Laboratories). Serum concentrations of thyroid hormones were investigated using the chemoluminescence immunoassay in the clinical laboratory of Peking Union Medical College Hospital. Other endocrine factors were tested with ELISA kits (MI, USA).

A Profile of Mood States (Educational and Industrial Testing Service, San Diego, CA, USA) questionnaire¹⁶ that was translated to fit the local culture was given to each explorer in the expedition at departure and at Dome A.

Blood cells were isolated from 5 ml of peripheral blood from the explorers. After removal of the red blood cells using red blood cell lysis buffer (TaiGen, China) at room temperature, the purified blood cells lacking erythrocytes were preserved with RNAlater (Qiagen, USA) and then

transported back in a -80°C freezer. Total RNA was isolated using TRIzol reagent (Invitrogen, USA) according to the manufacturer's instructions.

The Human Gene Expression 4 $\times$ 44K v2 Microarray Kit (Agilent Technologies, Foster City, USA) was used to obtain the gene expression profiles of the blood cells isolated from the explorers at departure and during their stay at Dome A according to the manufacturer's instructions. The microarray assay was analyzed by the Shanghai Bio Corporation of China. (See Supplementary Materials and Methods for details.)

Microarray data analysis

Microarray data analysis was performed using the GeneSpring GX software version 11.5.1 (Agilent Technologies). The normalized data were used to analyze the variance of each group and to generate a heat map for each group. From the clustering results, we found that the gene expression of subject No. 9 was significantly different from the other subjects; in addition, he had previously been to the Antarctic Dome A once, while the other studied participants/explorers had never been to Antarctic Dome A prior to this exploration. Thus, the gene expression profile of subject No. 9 was excluded from further analyses. The above normalized data were log-transformed to calculate the expression value.

A pairwise *t*-test was used to evaluate whether a probe on the microarray was differentially expressed, and the threshold was set to 0.05, resulting in 4474 probes identified as differentially expressed in our data.

The protein–protein interaction (PPI) information downloaded from STRING (<http://string-db.org/>) was used to construct a basic network. Differentially expressed genes were then mapped onto the basic PPI network, and a network filtration was performed. The genes included in this subnetwork were used for further analyses.

For the gene set analysis, we focused on the lowest-level Gene Ontology (GO) category identifications and specifically focused on the GO terms that had the most detailed functions in the Biological Process (that is, the GO terms with no other terms belonging to them; in other words, none of the other GO terms' 'is_a' attribute points to these terms).

We used the Cytoscape software (<http://www.cytoscape.org/>) for our presentation of GO terms.¹⁷ The Enrichment Map¹⁸ plug-in was integrated for the presentation of GO terms.

Statistical analysis

We screened for statistically significant differences in phenotypes using paired-sample *t*-tests. The Pearson coefficient correlation method was used for correlation analyses between phenotypes and gene expression. In our study, the multiple testing correction *P*-value of Pearson coefficient correlation was <0.05 . *P*-values were calculated using the Software R and the Benjamini & Hochberg method to control for the false discovery rate for multiple testing corrections. We used Matlab 7.0 software to generate the heat map images of the Pearson correlation coefficient (PCC) results.

RESULTS

Phenotypes with statistically significant differences between Dome A and departure

First, to identify the most dramatic changes in phenotypes at Dome A, the interrelationships among these 133 phenotypic parameters were examined (see the Supplementary Materials and Methods section for details).¹⁹ Forty-seven out of 133 phenotypes were found to be significantly altered at Dome A compared to those measured prior to departure (Figure 2, Supplementary Figure S2, Supplementary Tables S2 and S3).

Correlation analyses between 47 significant different phenotypes
Next, the PCC^{20–22} analysis was employed to evaluate the correlations between these 47 phenotypic data arrays. Consistent with the criteria of PCC,²³ we selected the related PCC coefficients for each pair of phenotypes that met the requirements of statistical significance (multiple testing corrections²⁴ and adjusted *P*-value <0.05). The calculated results were then transformed into a heat map using Matlab version 7.0 (Figure 3a, Supplementary Table S4). As noted in Figure 3a, the levels of the male sex hormone testosterone were strongly and inversely correlated with maximal changes in oxygenated hemoglobin in the right

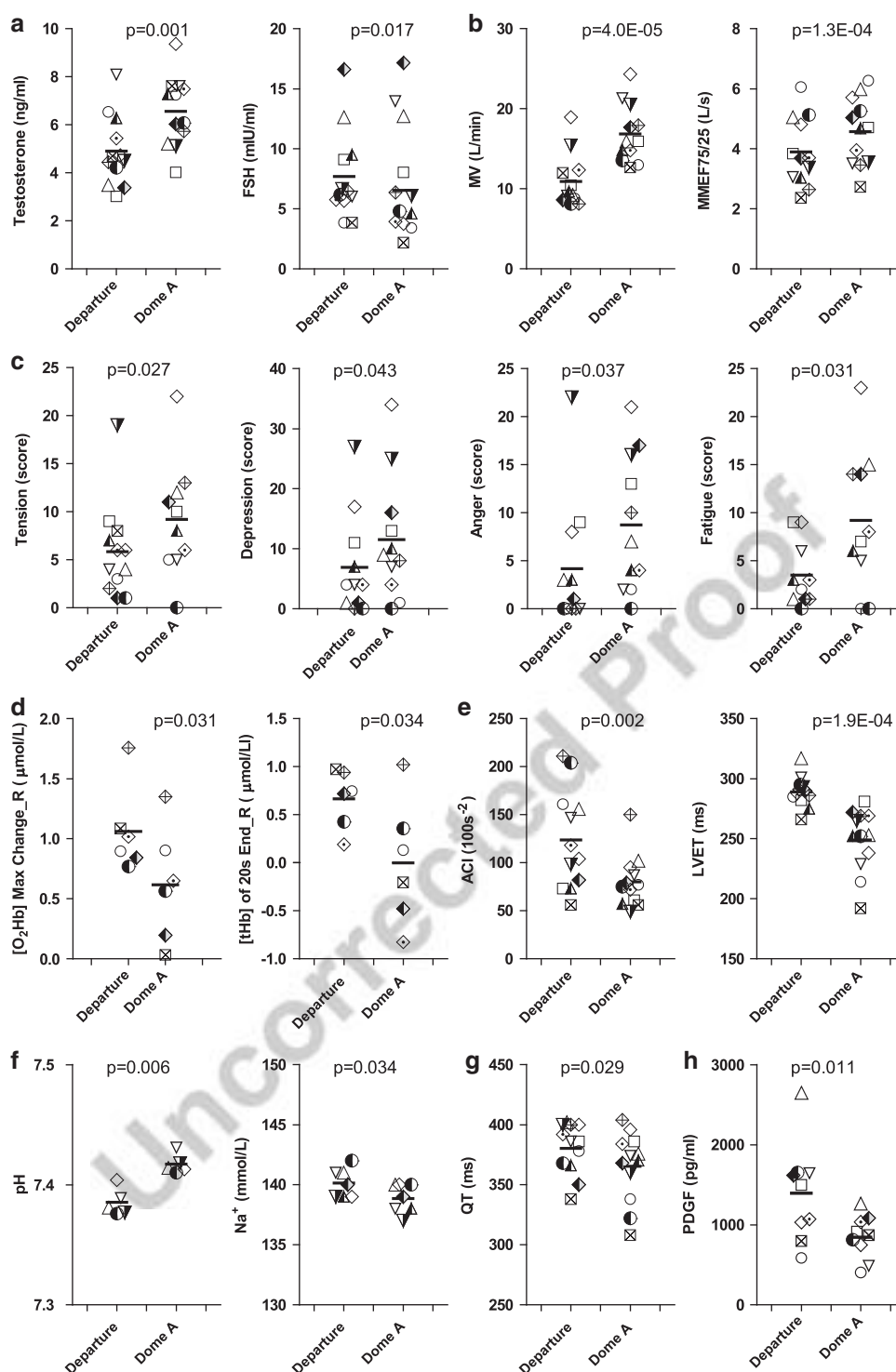


Figure 2. Significantly altered phenotypes at Dome A compared to departure. Paired *t*-test of the phenotypes between that at Dome A and that at departure. **(a)** Endocrine parameters: testosterone and follicle-stimulating hormone (FSH); **(b)** pulmonary function parameters: MV and MMEF75/25; **(c)** Profile of Mood States parameters: tension, depression, anger and fatigue; **(d)** cerebral oxygen parameters: [O₂Hb] Max Change_R and [tHb] of 20s End_R; **(e)** cardiac function parameters: ACI and LVET; **(f)** blood gas parameters: pH and Na⁺; **(g)** ECG Index parameters: QT; and **(h)** cytokine/chemokine parameters: PDGF. Each shape in the different groups represents the same person at a different position.

cerebrum. Moreover, the strongest positive correlations in the 47-phenotype heat map were between the testosterone levels and mood parameters, including tension (anxiety), depression, anger and fatigue. In contrast, the female sex hormone

follicle-stimulating hormone (FSH) had no association with any of these mood parameters (Figure 3b). This result may be limited due to the all-male sampling of this study; further studies in a broader sample population are indicated. In addition, the

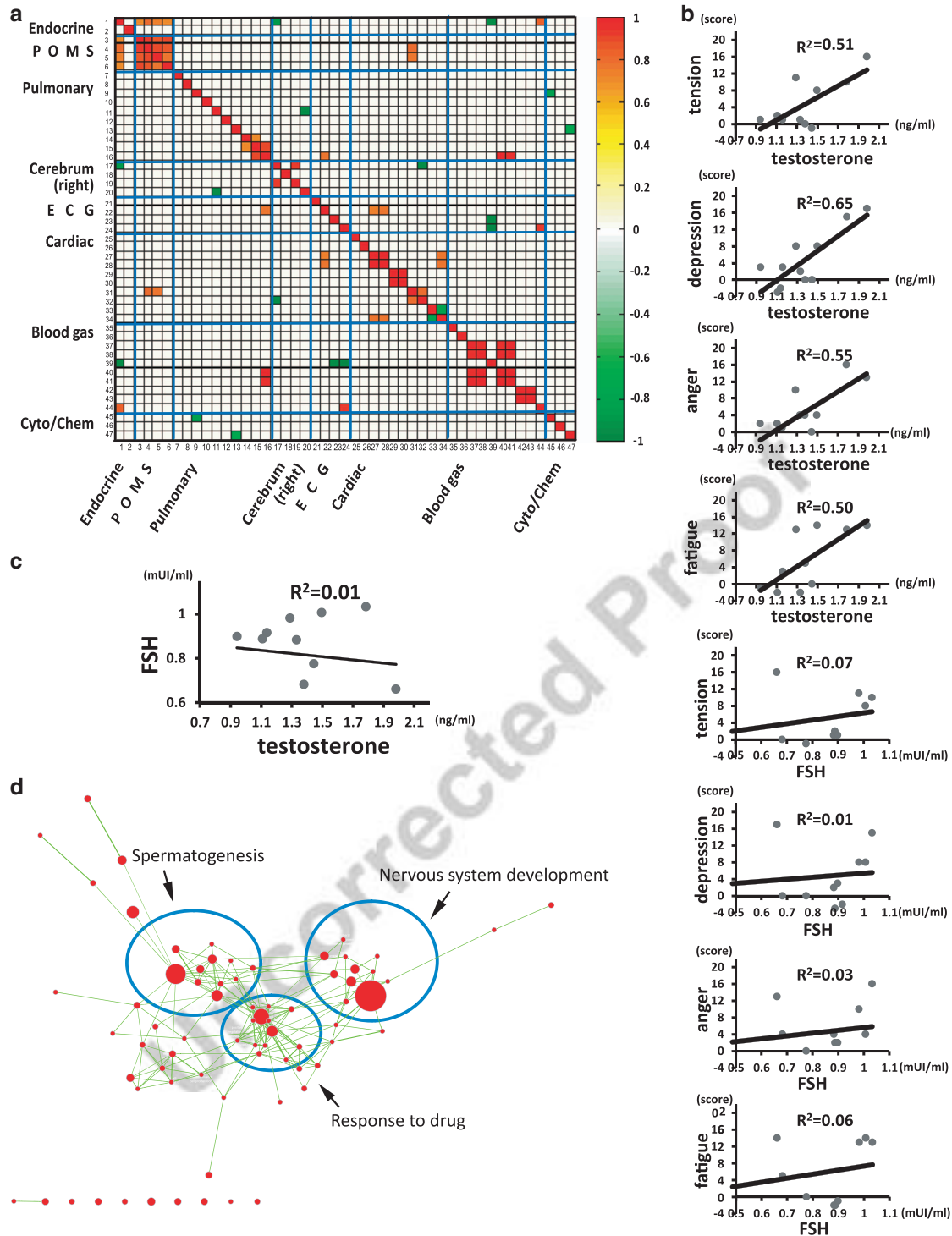


Figure 3. PCC analysis of phenotypes and enrichment of functional gene sets using Gene Ontology (GO) terms. **(a)** A total of 47 significantly different phenotypes were processed for Pearson correlation coefficient (PCC) analysis. These phenotypes included tests of physical functions and psychological investigations. The heat map of the PCC results (adjusted $P < 0.05$) was generated using Matlab 7.0 software. The warm colors represent significant positive correlations, and the cold colors represent significant negative correlations. White indicates no significant association. The numbered rows in the heat map are consistent with the numbered phenotypes in Supplementary Table 4. **(b)** Correlation analysis of testosterone and follicle-stimulating hormone (FSH) changes with mood parameters. Upper four figures: correlation analyses of testosterone with tension, depression, anger and fatigue, $R=0.72, 0.81, 0.74$ and 0.70 , respectively; adjusted $P < 0.05$. Lower four figures: correlation analyses of FSH with tension, depression, anger and fatigue, $R=0.26, 0.12, 0.18$ and 0.24 , respectively; adjusted $P > 0.05$. **(c)** Correlation analysis of testosterone and FSH ($R=-0.12$, adjust $P > 0.05$). **(d)** 10 895 protein-protein interactions with 1121 genes for the enrichment of functional gene sets using GO terms were presented using Cytoscape software. Each node is a gene set (the lowest level of GO terms is BP). Each group (node) is a gene set, represented in the lowest level of the Biological Process analyses. The size of each node was established to be proportional to the number of differentially expressed and interacting genes for this term. The edges between two nodes represent a gene overlap between two sets.

testosterone levels were significantly elevated at Dome A, whereas the FSH levels were robustly decreased (Figure 2), suggesting that testosterone level alterations may have contributed to the severe mood disturbances of these explorers. However, the testosterone levels were not correlated with the FSH levels (Figure 3c).

Differentially expressed gene identification and related PPI network

Second, a gene expression array was utilized to examine links between phenotypic alterations and gene expression changes in the study participants at Dome A. Out of the 41 000 probe sets assessed, 4474 probe sets (2083 upregulated and 2391 down-regulated) showed differential expression with statistical significance and were further selected for subsequent analyses. Overall, 1121 genes were identified to be significantly and differentially expressed, and interacted in 10 895 out of 808 119²⁵ human PPIs.²⁶

Gene functional enrichment analysis of 1121 PPI network genes

For the gene enrichment analysis, we focused on the lowest-level GO²⁷ category identification. The results of the GO terms with the functional enrichment test were illustrated using the Cytoscape software combined with its Enrichment Map plugin^{17,28} (Figure 3d). In general, most of the genes were clustered into three groups: spermatogenesis, nervous system development and responses to drugs (Figure 3d). These biological processes were distinctly associated with the conditions in Dome A that were consistent with the subsequent phenotypic changes, that is, elevated testosterone levels, oxygen loss in the right brain and severe mood disturbances.

Correlation analyses between 47 phenotypes and 1121 PPI network genes

To further identify the genes that were responsible for these phenotypic changes, we examined the correlations of 47 significantly altered phenotypes with 1121 robustly differentially expressed genes. The inclusion criteria were similar to those used in the phenotypic correlation analysis previously described (Figure 4, Supplementary Tables S5–S52). Importantly, 92 genes were strongly correlated with testosterone elevation (Supplementary Tables S5 and S6), whereas only 11 genes were moderately associated with FSH (Supplementary Tables S5 and S7). Among the 1121 differentially expressed genes, a total of 942 genes were identified to be associated with the 47 significantly changed phenotypes at Dome A (Supplementary Tables S5–S52). Interestingly, the vast majority of genes (343) were substantially related to mood parameters (Supplementary Tables S5). These results suggested that gene expression changes are correlated with some of the altered phenotypic changes that occur during exposure to an extreme environment.

Highly related genes functional enrichments of phenotypes

Next, to identify the functions of genes that are highly related to phenotypes, we specifically used 'detailed' GO terms that have the most detailed functions (at the lowest level) in the Biological Process to automatically group GO terms. Spermatogenesis and platelet-derived growth factor receptor signaling were the largest GO terms in testosterone and FSH enrichment, respectively (Supplementary Figures S3A and S3B, Supplementary Tables S6 and S7). Interestingly, the two largest GO terms in the tension enrichment map were nervous system development and spermatogenesis (Supplementary Figure S3C, Supplementary Table S8), which are two pathways that have been previously enriched (Figure 3d). Responses to drugs and spermatogenesis were enriched in the depression map (Supplementary Figure S3D, Supplementary Table S9), whereas no Biological Process GO term

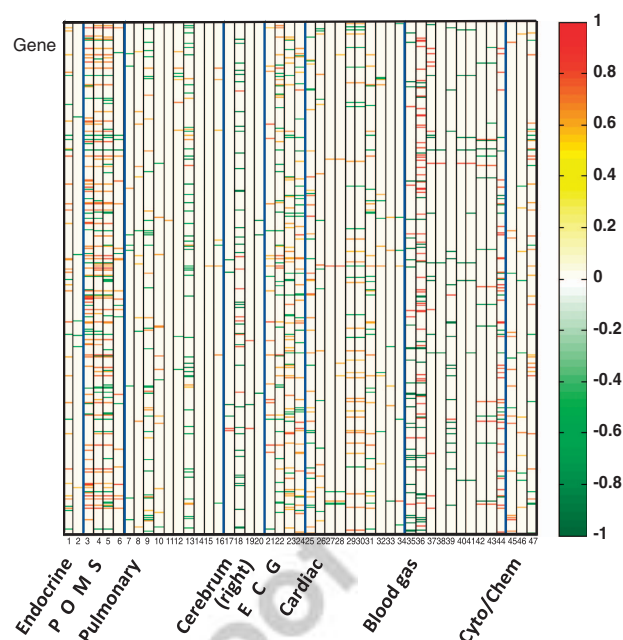


Figure 4. Pearson correlation coefficient (PCC) analyses of 47 phenotypes with 1121 significantly differentially expressed genes (adjusted $P < 0.05$). The heat map of the PCC results (adjusted $P < 0.05$) was generated using Matlab 7.0 software. The warm colors represent significant positive correlations, and the cold colors represent significant negative correlations. White indicates no significant association.

was enriched in the map for anger (Supplementary Figure S3E, Supplementary Table S10). The maximal GO term in the fatigue enrichment map was forebrain development (Supplementary Figure S3F, Supplementary Table S11). These GO enrichment results were consistent with the phenotype correlation data (Figures 3a and d).

Literature mining in relevant fields for genes strongly related to mood

In addition, we performed PubMed literature searches on genes that were strongly ($|R| > 0.8$) correlated with the four mood parameters (Figures 5a–c, Supplementary Table S53). We found that tension (39 genes), depression (24 genes) and anger (43 genes) shared 11 genes (Figure 5a), six of which have been reported in the relevant fields (Figure 5b, Supplementary Table S11). In stark contrast, only one out of three genes in fatigue (which does not overlap with the other three mood parameters) had been previously demonstrated (Figure 5c). Overall, 42 out of 70 genes had previous links to the four mood parameters ($|R| > 0.8$) (Figures 5b and c, Supplementary Table S53), which further corroborated the reliability and robustness of our statistical analysis. Moreover, the other 28 genes were not previously known to be associated with changes in mood state (Figures 5b and c).

DISCUSSION

It has been previously reported that mood disturbances could be induced under cold stress and at high-altitude environments, for example, in Antarctica.^{29,30} The male sex hormone testosterone has been demonstrated to relieve social distress, anxiety and depression in both patients and healthy individuals.^{31–38} Testosterone therapy on males with hormone deficiency or aging has been shown to be beneficial in treating these disease-associated mood disturbances.^{39,40} However, we demonstrated that

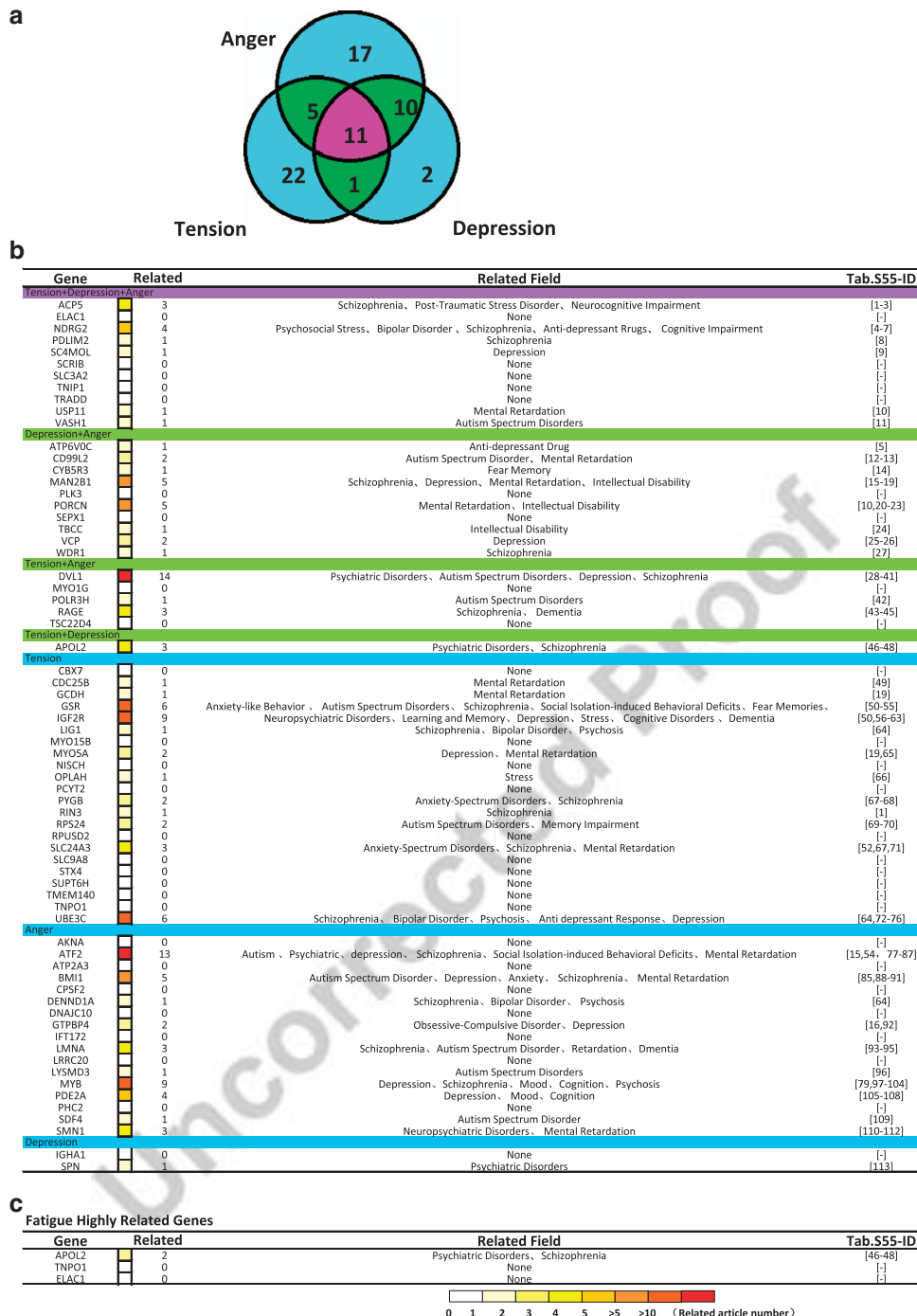


Figure 5. Published articles on phenotypes that are highly related to the mood disturbance genes identified in this study. **(a)** Genes highly correlated with tension, depression and anger ($|R| \geq 0.8$ and adjusted $P < 0.05$). Purple: genes related to all three mood parameters; green: genes strongly related to two of the three mood parameters; blue: genes strongly related to a single mood parameter. **(b)** Genes that are strongly related to tension, depression and anger in articles published in relevant fields. **(c)** Genes that are strongly related to fatigue in articles published in relevant fields. Warm colors represent the related article number; the deeper the color, the greater the number of related articles.

testosterone levels have strong and positive linear correlations with tension (anxiety), depression and fatigue during human adaptation to Dome A, and that the change of testosterone might help healthy men respond to an extreme environment.

Furthermore, changes in the gene expression patterns of blood cells revealed three biological processes: spermatogenesis, nervous system development and responses to drugs, as the major lowest-level GO terms in people at Dome A, which was consistent

with their phenotype changes. These data supported the potential of gene expression profiling of human blood cells in predicting psychophysical changes in an extreme environment.

In summary, this is the first study analyzing genome-wide gene expression profile changes in human blood cells deprived of red cells and the psychophysical characteristic alterations in adapting to extreme climates, such as the Antarctic Dome A. This might be the first report indicating that gene expression changes in human

blood cells in the absence of red cells may result in psychophysical changes. Novel genes in mood disturbances have also been identified using our powerful analytic methods. In addition, these findings require further validation using larger study cohorts with psychophysical characteristics like in this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

CX and CJ conceived the project; CX and DT collected the original physical and psychological data and blood samples from the 24th Chinese Antarctic inland expeditioners; CX, CJ, XJ, Fengming H, QW, YX, ZG, XC and Fumin H organized and analyzed the original data; XJ, ZZ, Fumin H, ZG and MS performed the ELISA experiments and blood cell RNA preparations; CJ, Fengming H and XJ analyzed the phenotype correlations; DS, CZ, T Joshi, JX and XZ performed the original gene microarray data analysis; CJ and Fengming H analyzed the phenotype–gene expression changes correlations and literature searches; LJ, YP, Y Zhong, Y Zhu and LW provided technical support; DX, T Jiang, RJ, DL, KX and WX provided helpful ideas and fruitful discussions; CJ, Fengming H, XJ and DS wrote the manuscript; and all of the authors commented on and revised the manuscript.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (<http://www.nature.com/mp>)