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Individual Differences of Acupuncture Analgesia in Humans Using cDNA Microarray

Younbyoung CHAE[1], Hi-Joon PARK[2], Dae-Hyun HAHM[3], Seung-Ho YI[4], and Hyejung LEE[2]

[1]Department of Oriental Medical Science, Graduate School of East-West Medical Science, 1 Seocheon-dong, Giheung-gu, Yongin-si, Gyeunggi-do 446-701, Republic of Korea; [2]Department of Meridian and Acupuncture and [3]Institute of Oriental Medicine, College of Korean Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul, 130-701, Republic of Korea; and [4]School of Physics and Astronomy, Seoul National University, San 56-1, Shinlim-dong, Kwanak-gu, Seoul, 151-742, Republic of Korea

Abstract: A large amount of evidence suggests that acupuncture stimulation enhances the experimental pain threshold in various animal models. Acupuncture analgesia is mediated by the endogenous opioid system, and the analgesic response to acupuncture shows individual variation. This study identified and characterized the genes that differ between high responders (HR) and low responders (LR) on acupuncture stimulation, using a cDNA microarray. Fifteen participants were stimulated at the LI 4 acupuncture point, and the finger withdrawal latency (FWL) test was performed to classify the HR and LR groups. Total RNA was then extracted from blood samples from each group and used as a template to synthesize cDNA. The cDNA was applied to Code Link™ UniSet Human 20K microarray chips. The Symptom Checklist 90-Revised (SCL-90-R) was also analyzed as a measure of psychological variation. The FWL was significantly elevated in the HR group after acupuncture stimulation, whereas there was little increase in the LR group. The ratio of HR to LR subjects was 9:6. We found that 353 and 22 genes were up- and downregulated, respectively, in the HR group. However, the SCL-90-R profiles did not differ significantly between the two groups. These results suggest that the individual variation in acupuncture analgesia, verified by measuring the FWL in the HR and LR groups, resulted from genetic inheritance rather than differences in the psychological environment.

Key words: acupuncture, analgesia, individual difference, human.

For more than 2,500 years, acupuncture, an oriental therapeutic technique, has been widely used to treat a variety of functional disorders and certain types of intractable pain [1]. As a complementary alternative medicine, acupuncture has been accepted worldwide as an excellent tool for the treatment of pain. Several studies have shown that acupuncture increases the experimental pain threshold in various animal species and humans [2]. Much evidence suggests that the analgesic effect of acupuncture is mediated by endogenous opioids in the central nervous system (CNS) [3]. However, the analgesic response to acupuncture stimulation shows marked individual variation. According to the sensitivity of the analgesic response to acupuncture stimulation, the subjects in acupuncture experiments can be categorized as nonresponders or low responders (LR) and good responders or high responders (HR) [4].

The many basic studies that have examined the mechanism of individual variation in acupuncture analgesia have focused on the involvement of anti-opioid peptides (e.g., cholecystokinin octapeptide, CCK-8). The effectiveness of electroacupuncture (EA) analgesia was shown to be determined by the balance between endogenous opioid peptides and anti-opioid peptides in the CNS [5]. Several studies also reported that CCK-A receptor expression in the hypothalamus is closely related to the responsiveness of acupuncture-mediated analgesic effects in rats [6, 7]. The deletion of the NF-kB1 gene induced a loss of the analgesic effect of electroacupuncture, which implies that NF-kB1 plays an important role in the response to acupuncture [8]. Individual variation in the analgesic effect of acupuncture stimulation has also been reported in humans by showing the experimental reproducibility of electroacupuncture analgesia [9]. However, the molecular mechanism of individual differences in the antinociceptive response to acupuncture stimulation remains unclear.

A recent genomic technology, cDNA microarrays, has been successfully extended to studies of global gene expression to explain a wide range of phenomena. We hypothesized that the differences in individual sensitivity to the antinociceptive action of acupuncture treatment might be derived from intrinsic differences in the subjects' ge-

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Correspondence should be addressed to Hyejung Lee, Department of Meridian and Acupuncture, College of Korean Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul, 130-701, Republic of Korea. Tel: +82-31-201-2173, Fax: +82-31-206-9731, E-mail: handongmu@empal.com

netic backgrounds. Therefore, in this study we used cDNA microarray analysis to investigate the genes related to the responsiveness to acupuncture in humans.

MATERIALS AND METHODS

Subjects. The subjects participating in the study were recruited at a university in Korea: 15 males with a mean age of 25.4 years (SD = 2.3, range = 20–29 years). The participants were informed that they were allowed to withdraw from the study at any time. The subjects were excluded if they had psychiatric, circulatory, cardiovascular, or neurological problems; chronic pain; or recent use of tobacco, analgesics, antidepressants, or alcohol. Experiments were conducted with the understanding and written consent of each subject and approval from the Human Subjects Committee of Kyunghee University.

Measuring finger withdrawal latency (FWL). Changes in pain reactivity were assessed by measuring the finger withdrawal latency (FWL). To measure the pain threshold, a bottom-illuminated radiant heat device was used. Briefly, a condenser lens, positioned above a slide projector bulb, focused the light onto the distal digit of the participant's blackened finger on the dominant hand (Fig. 1A). Participants were instructed to remove their index finger as soon as it became painful: "Keep your finger on the platform until it becomes painful. When it becomes painful, withdraw your finger and the heat source will turn off." The pain threshold was defined as the latency from light onset to finger withdrawal, i.e., the finger withdrawal latency (FWL). The heat was terminated automatically after 22 s to avoid tissue damage. The room temperature was kept at 20 ± 2°C. After a practice trial, five baseline FWLs were assessed at 5-min intervals using this methodology and were averaged. This average latency was used to calculate the duration of all the constant heat pain tests. The degree of analgesia at each time point was expressed as the percentage of latency compared with baseline using the following formula:

$$\%\ \text{FWL} = [(\text{each latency} - \text{baseline latency})/\text{baseline latency}] \times 100.$$

The constant heat test required participants to keep their finger on the heat source until the computer turned it off.

Procedures for acupuncture stimulation. After five baseline FWL measurements, acupuncture was performed at LI 4 in the nondominant hand. The acupuncture was guided using Park sham needle devices to exclude placebo phenomena (Fig. 1B). The subjects were told they were virtually stimulated with real acupuncture or sham stimulated with sham acupuncture. However, all of them were stimulated with real acupuncture using the Park sham device. FWL was measured every 15 min for 1 h. The acupuncture needle (0.25 mm diameter, 30 mm long) was inserted at the LI 4 acupuncture point to a 10-mm depth,

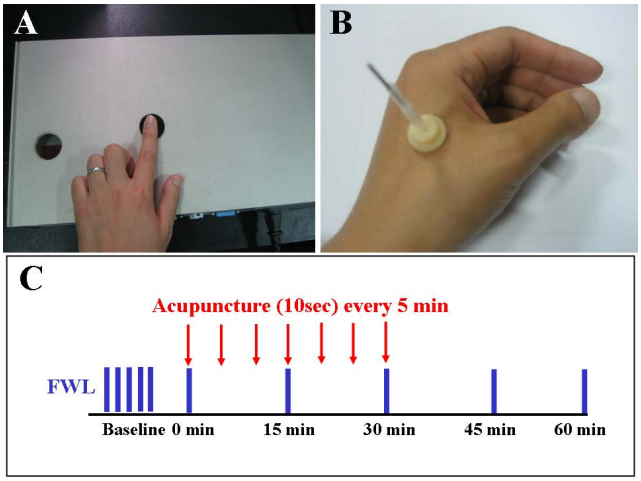

Fig. 1. A: A bottom-illuminated radiant heat device was used to measure the pain threshold. A condenser lens positioned above a slide projector bulb focused light onto the distal digit of the participant's blackened finger on the dominant hand. The pain threshold was defined as the latency from light onset to finger withdrawal, i.e., the finger withdrawal latency (FWL). **B**: Acupuncture was inserted at LI 4 in the nondominant hand. It was guided by using Park sham needle devices to exclude placebo phenomena. **C**: The experimental procedures are shown. FWL was measured every 15 min for a period of 1 h, with manual acupuncture stimulation for 10 s every 5 min, and then withdrawn 30 min later.

manipulated for 10 s every 5 min, and then withdrawn 30 min later (Fig. 1C). Based on a cluster analysis of the results of animal studies, we decided to categorize the subjects with an increase in FWL of 25% or less as low responders (LR) and those with an increase in FWL exceeding 25% as high responders (HR).

RNA extraction and gene chip analyses. Blood was collected from each individual 1 h after acupuncture stimulation. Total RNA was extracted from the blood sample using the PAXgene blood RNA kit (Qiagen, USA) according to the manufacturer's protocol. Code Link™ UniSet Human 20K cDNA microarray chip experiments were performed by Digital Genomics (Seoul, Korea), following the Code Link standard protocol. Briefly, total RNA was reverse transcribed to cDNA. Equal amounts of cDNA were then used for an *in vitro* transcription to synthesize cRNA in the presence of biotinylated nucleotides. After fragmentation, fragmented cRNA was used for hybridization in a GeneChip Fluidics Station for 16 h. Following a series of stringent washes in the Fluidics Station, the hybridized probe arrays were stained with a streptavidin-conjugated fluorescent stain before scanning. The hybridization, washing, and staining procedures were controlled using preprogrammed Microarray Suite fluidics protocols.

Questionnaire. The Symptom Checklist 90-Revised (SCL-90-R), touted as a self-report checklist consisting of 90 items, each describing a physical or psychological

symptom, has been used with a variety of medical populations, including patients with whiplash injuries. The test results from the SCL-90-R are provided on nine clinical scales (Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism), and three global indexes of psychological disturbance (Global Severity Index, GSI; Positive Symptom Total, PST; Positive Symptom Distress Index, PSDI). There is high test-retest correlation, high internal consistency of items, and convergence between the subscales of the SCL-90 and the corresponding symptom dimensions of the Minnesota Multiphasic Personality Inventory (MMPI) and Beck Depression Inventory (BDI) [10]. Quantified ratings (0.0–10.0) based on a 100-point scale were also used to analyze the anticipated acupuncture analgesia and De-Qi sensation, a distinct sensation of distension, heaviness, or numbness.

Statistical analysis. FWL is expressed as a percentage change from the control (pretreatment with acupuncture). Values are expressed as means ± SE. The two-tailed Student's *t*-test was used to compare the HR and LR groups at each time point. *P* values of less than 0.05 were considered significant.

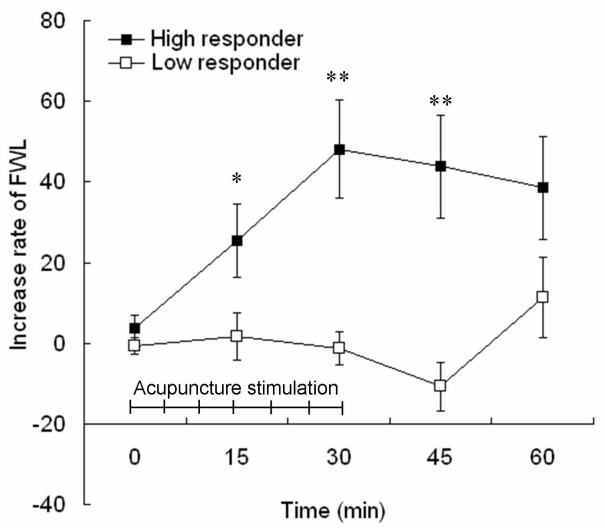

Fig. 2. Sensitivity to acute thermal nociception before and after acupuncture stimulation in humans. The high responder (HR) group had very clearly enhanced finger withdrawal latency (FWL) values, whereas the low responder (LR) group showed a partial effect of acupuncture. Data are presented as the mean ± SEM of the increase in the FWL. **P* < 0.05, ***P* < 0.01 vs. the LR.

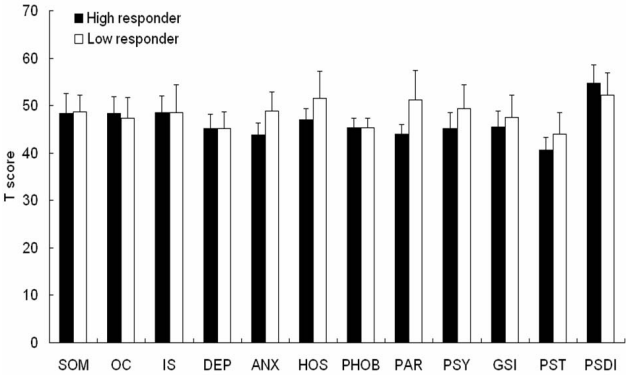

Fig. 3. Comparisons between the high responder (HR) and low responder (LR) groups on the Symptom Checklist-90-R. SOM, somatization; OC, obsessive-compulsive; IS, interpersonal sensitivity; DEP, depression; ANX, anxiety; HOS, hostility; PHOB, phobic anxiety; PAR, paranoid ideation; PSY, psychoticism; GSI, global severity index; PST, positive symptom total; PSDI, positive symptom distress index. Data are presented as the mean ± SEM of the T scores. No significant differences were observed between the two groups.

RESULTS

Distinct individual variation in acupuncture analgesia

Of the 15 participants, nine (60%) were categorized in the HR group and six (40%) in the LR group. As shown in Fig. 1, the FWLs of the HR group were significantly elevated after acupuncture stimulation, as reported in previous studies, whereas those of the LR given acupuncture were close to basal latencies. The HR group exhibited 25.5 ± 9.0%, 48.1 ± 12.3%, 43.9 ± 12.8%, and 38.6 ± 12.8% increases of acupuncture analgesia at 15-min intervals, compared with the baseline during and after acupuncture stimulation. The LR group displayed 9.0 ± 5.9%, –1.1 ± 4.1%, –10.8 ± 6.0%, and 11.5 ± 10.0% increases of acupuncture analgesia at 15-min intervals, compared with baseline during and after acupuncture stimulation (Fig. 2).

Identification of differentially expressed genes)

To identify the gene expression profiles in the HR and LR groups, a cDNA microarray chip containing 19,881 genes was used. A twofold change in signal intensity was applied as the cutoff for considering the differential expression of a gene as significant. Over twofold fluctuation in the gene expression levels is considered not only to be sufficient to induce significant biochemical and physiological changes in living cells, but also to be acceptable in transcriptome analysis [11]. This criterion has been used as the standard in other studies. Using this criterion, we selected 375 of the 19,881 genesas showing significant individual variation. In the HR group, 353 and 22 genes were up- and downregulated, respectively. Based on the potential functions of the genes, we classified them into seven groups, as shown in Table 1; this is published as supporting information on the Gene Ontology Web site (http://www.geneontology.org).

Table 1. Genes increased in high responder to acupuncture analgesia compared to low responder.

Gene Bank ID	Fold	Gene	Molecular function
Apoptosis			
AF192559	3.7	Mitochondrial carrier homologue 1 (*C. elegans*)	protein binding
AB033078	2.7	Sphingosine-1-phosphate lyase 1	carboxylyase activity
Cell cycle			
AB002323	3.4	Dynein, cytoplasmic, heavy polypeptide 1	ATPase activity, coupled
AL523888	2.3	Suppressor of Ty 3 homologue (*S. cerevisiae*)	transcription initiation factor activity
Cell death			
AF192559	3.7	Mitochondrial carrier homolog 1 (*C. elegans*)	protein binding
AB033078	2.7	Sphingosine-1-phosphate lyase 1	carboxylyase activity
Immune response			
NM_005532	3.4	Interferon, alpha-inducible protein 27	molecular function unknown
AA354668	3.2	CD1E antigen, e polypeptide	—
AB037836	2.8	Phosphatidylinositol 3,4,5-trisphosphate-dependent RAC exchanger 1	phospholipid binding
D86983	2.7	Melanoma-associated gene	peroxidase activity
AB052906	2.5	UL16 binding protein 2	MHC class I receptor activity
BC019236	2.0	Major histocompatibility complex, class I, A	MHC class I receptor activity
Response to stress			
NM_005532	3.4	Interferon, alpha-inducible protein 27	molecular function unknown
U85768	2.9	Chemokine (C-C motif) ligand 24	chemokine activity
AB037836	2.8	Phosphatidylinositol 3,4,5-trisphosphate-dependent RAC exchanger 1	phospholipid binding
U90878	2.6	PDZ and LIM domain 1 (elfin)	zinc ion binding
NM_006724	2.1	Mitogen-activated protein kinase kinase kinase 4	magnesium ion binding
Signal transduction			
NM_005972	7.6	Pancreatic polypeptide receptor 1	neuropeptide Y receptor activity
X57110	5.4	Cas-Br-M (murine) ecotropic retroviral transforming sequence	ubiquitin-protein ligase activity
BC031087	4.4	Gamma-aminobutyric acid (GABA) A receptor, gamma 1	extracellular ligand-gated ion channel activity
Y00815	4.3	Protein tyrosine phosphatase, receptor type, F	receptor activity
AF192559	3.7	Mitochondrial carrier homologue 1 (*C. elegans*)	protein binding
U79286	3.3	HMT1 hnRNP methyltransferase-like 1 (*S. cerevisiae*)	signal transducer activity
Y16610	2.9	Spastic paraplegia 7, paraplegin (pure and complicated autosomal recessive)	metalloendopeptidase activity
U85768	2.9	Chemokine (C-C motif) ligand 24	chemokine activity
AB037836	2.8	Phosphatidylinositol 3,4,5-trisphosphate-dependent RAC exchanger 1	phospholipid binding
AF147391	2.8	Phospholipase C, gamma 1	receptor signaling protein activity
AF288571	2.6	Lymphoid enhancer-binding factor 1	transcription factor activity
BC021565	2.5	Sorting nexin 8	—
AK026902	2.3	Guanine nucleotide binding protein (G protein), alpha 13	receptor signaling protein activity
AF159447	2.3	Suppressor of fused homologue (*Drosophila*)	signal transducer activity

Table 1. Continued.

Gene Bank ID	Fold	Gene	Molecular function
AK024465	2.3	Guanine nucleotide binding protein (G protein), gamma 7	signal transducer activity
AK002201	2.2	Myosin IXB	calmodulin binding
AF305616	2.2	Transmembrane, prostate androgen-induced RNA	molecular function unknown
AL832396	2.2	Cas-Br-M (murine) ecotropic retroviral transforming sequence	ubiquitin-protein ligase activity
NM_006724	2.1	Mitogen-activated protein kinase kinase kinase 4	magnesium ion binding
NM_019043	2.1	Amyloid beta (A4) precursor protein-binding, family B, member 1 interacting protein	—
BM724842	2.0	FYN oncogene related to SRC, FGR, YES	ATP binding
AK025877	2.0	V-abl Abelson murine leukemia viral oncogene homolog 2 (arg, Abelson-related gene)	protein-tyrosine kinase activity
AF038440	2.0	Phospholipase D2	hydrolase activity
AF217985	2.0	RAB4B, member RAS oncogene family	GTP binding
Transcription			
NM_006618	7.1	Jumonji, AT rich interactive domain 1B (RBP2-like)	DNA binding
AF288571	2.6	Lymphoid enhancer-binding factor 1	transcription factor activity
AL117568	2.4	Huntingtin interacting protein 2	ubiquitin-protein ligase activity
AL523888	2.3	Suppressor of Ty 3 homologue (*S. cerevisiae*)	transcription initiation factor activity
NM_001273	2.2	Chromodomain helicase DNA binding protein 4	ubiquitin-protein ligase activity
AK023525	2.2	Hypothetical protein FLJ35867	zinc ion binding
AI718785	2.1	Meis1, myeloid ecotropic viral integration site 1 homologue (mouse)	RNA polymerase II transcription factor activity
AK000346	2.1	Nuclear transcription factor Y, gamma	DNA binding
NM_002702	2.1	POU domain, class 6, transcription factor 1	transcription factor activity
AB033092	2.0	Metastasis-associated 1 family, member 3	transcription factor activity

Comparisons of the symptom checklist 90-R (T scores)

Multiple analyses of variance were performed for each group to check for differences in the subscale scores between the HR and LR groups. No significant differences were found between the two groups. The visual analysis of the two profiles produced similar shapes. The SCL-90-R profiles for the two groups are plotted in Fig. 3. The Anxiety, Hostility, and Psychoticism subscale scores were slightly higher in the LR group.

Comparison of the anticipation of acupuncture analgesia and De-Qi sensation

To examine the differences in the anticipation of an analgesic effect of acupuncture and De-Qi sensation between the HR and LR groups, a 100-point visual analogue scale (VAS) was calculated for each group. The degrees of anticipation of acupuncture analgesia for the HR and LR groups were 64.1 ± 6.2 and 70.6 ± 7.0, respectively. The De-Qi sensation of the two groups showed similar patterns at each time point (Table 3). No significant differences were observed between the two groups.

DISCUSSION

Our experiments demonstrated that acupuncture stimulation produced an increased FWL in humans. Of the 15 participants, nine (60%) were categorized as the HR group and six (40%) as the LR group. These results agree with previous reports describing marked individual variation of the analgesic effects in rats responding to acupuncture stimulation [6, 7]. The gene expression profiles were analyzed using blood samples from the participants, who had been classified in the HR and LR groups depending on their sensitivity to acupuncture analgesia. We identified the genes that were differentially expressed in the two groups, providing a global view of genetic heterogeneity in humans. These differential changes may contribute to elucidating the mechanism of the individual variation of the analgesic effect of acupuncture.

A variety of factors may underlie the individual differences in nociceptive susceptibility, including sex differences, psychological distress, and cultural influences, as well as nociceptive integration in the CNS [12]. As the responsiveness to noxious stimuli is more pronounced in fe-

Table 2. Genes decreased in high responder to acupuncture analgesia compared to low responder.

Gene Bank ID	Fold	Gene	Molecular function
Response to stress			
M24069	3.0	Cold shock domain protein A	transcription factor activity
Transcription			
AF287272	2.3	Kruppel-like factor 5 (intestinal)	zinc ion binding transcription factor activity

Table 3. Anticipation of acupuncture analgesia and De-Qi sensation.

Group	Anticipation of acupuncture analgesia	De-Qi sensation (VAS, 0–100)						
		0 min	5 min	10 min	15 min	20 min	25 min	30 min
HR (*N* = 9)	64.1 ± 6.2	50.5 ± 10.9	51.8 ± 10.2	53.7 ± 9.8	58.8 ± 9.3	62.1 ± 9.1	62.4 ± 9.1	62.3 ± 10.1
LR (*N* = 6)	70.6 ± 7.0	48.6 ± 7.2	53.0 ± 5.1	59.0 ± 6.5	59.5 ± 8.8	65.1 ± 8.8	67.5 ± 8.1	62.7 ± 7.8

The degree of anticipation of acupuncture analgesia and the De-Qi sensation in the two groups showed similar patterns. Data are presented as the mean ± SEM. on the visual analogue scale. No significant differences were observed between the two groups. HR: high responder group; LR: low responder group; VAS: visual analogue scale.

males than in males, women were not included in this study to minimize sex-based variation. Many studies have found that psychological distress, such as depression or anxiety, is correlated with increased sensitivity to laboratory pain [13, 14]. The SCL-90-R was also analyzed as a measure of psychological variation [10]. Because the profiles of the two groups were not significantly different in overall shape or elevation, the individual differences in acupuncture analgesia observed in our data were not attributable to psychological distress.

The effect of acupuncture could be the result of a variety of factors, such as a placebo effect, nonspecific physiological responses to stimulating the skin, specific responses to stimulation of the particular acupuncture points chosen for treatment, and the patient's expectations. An appropriate placebo technique for use in a clinical trial of acupuncture should (i) be free from any important physiological activity (physiological inactivity) and (ii) have a psychological impact similar to that of real acupuncture treatment (credibility and acceptance) [15]. The Park sham device is very credible in this respect and was used for all of the subjects [16]. The device gives the visual illusion that it penetrates the skin, but no penetration occurs because its shaft telescopes into the handle when downward pressure is applied. All of the subjects were stimulated with real acupuncture; however, they did not discriminate real acupuncture from sham acupuncture (data not shown). We strongly believe that the Park sham device successfully excluded placebo phenomena in our experiments.

De-Qi, a sensation of numbness and fullness that develops at the site of stimulation, is considered an important variable in studies of the efficacy and mechanism of action of acupuncture treatment [17, 18]. Most of the participants perceived a similar De-Qi sensation (Table 3). Therefore we assumed that the difference in acupuncture analgesia between the two groups in this experiment was not derived from a difference in the De-Qi sensation. Moreover, the anticipation of acupuncture analgesia did not differ significantly between the two groups (Table 3).

Throughout the current study, the 375 responsive genes to acupuncture analgesia in the blood of human were retrieved and classified into either the up- or downregulated group using the arbitrary twofold cutoff criterion. The main group of upregulated genes was 24 signaling-related biomolecules, such as PPYR1, CBLB, GABRG1, and PTPRF. We also identified several upregulated genes associated with stress, for example, IFI27 and CCL24. And the transcriptional regulators, such as JARID1B and LEF1, could be recommended as a novel key element mediating the acupuncture analgesia. Furthermore, immune response-related genes, including IFI27 and CD1E, would also be regarded as a good candidate gene in acupuncture analgesia. Many genes related to immune functions, signal transduction, and transcription were upregulated in the HR group, indicating a similar activation of pathways related to defense systems (Table 1). Otherwise, stress-inducible proteins like Cold shock domain protein A (CSDA) and transcription factors like Kruppel-like factor 5 (KLF5) were downregulated (Table 2). These might be used as new targets for understanding individual differences of acupuncture analgesia, though further studies comprising genetic and structural aspects of each target in a highly sophisticated manner are required.

CONCLUSION

Our data provide a global view of the genetic differences in the response to acupuncture analgesia in humans. Further extensive investigations are required to determine the functional contribution of each potential target gene to individual differences in acupuncture analgesia. With con-

firmation of their contributory roles in acupuncture analgesia, some of these genes or their encoded proteins may be targets for developing new acupuncture therapy.

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