



## Study of heat shock response of human umbilical vein endothelial cells (HUVECs) using cDNA microarray

M. Zhou, A. Zhang, B. Lin, J. Liu & Dr >L. X. Xu

To cite this article: M. Zhou, A. Zhang, B. Lin, J. Liu & Dr >L. X. Xu (2007) Study of heat shock response of human umbilical vein endothelial cells (HUVECs) using cDNA microarray, International Journal of Hyperthermia, 23:3, 225-258, DOI: [10.1080/02656730701295441](https://doi.org/10.1080/02656730701295441)

To link to this article: <https://doi.org/10.1080/02656730701295441>



Published online: 09 Jul 2009.



Submit your article to this journal [↗](#)



Article views: 498



View related articles [↗](#)

## Study of heat shock response of human umbilical vein endothelial cells (HUVECs) using cDNA microarray

M. ZHOU<sup>1,2</sup>, A. ZHANG<sup>1,2</sup>, B. LIN<sup>3</sup>, J. LIU<sup>2</sup>, & L. X. XU<sup>1,2</sup>

<sup>1</sup>Key Laboratory of Systems Biomedicine, <sup>2</sup>School of Life Sciences and Technology, Shanghai Jiao Tong University, Shanghai 200240, P. R. China, and <sup>3</sup>Institute for Systems Biology, Seattle, Washington, USA

(Received 16 October 2006; revised 4 December 2006; accepted 28 February 2007)

### Abstract

Genetic response of human umbilical vein cells (HUVECs) to heat shock was studied using gene expression analysis. HUVECs were subjected to heat treatment at 44°C and 55°C for 1 h, respectively. Four hours after the treatment, gene expression of the treated cells and control cells (37°C) were profiled using cDNA microarray. Data were analyzed using bioinformatics tools, and the results were verified by real-time quantitative PCR experiment. It has been shown that a large number of genes were regulated indicating global response to heat treatment at the genetic level.

**Keywords:** Endothelial cell, heat treatment, cDNA array, apoptosis, necrosis

### Introduction

Recent clinical trials indicated that hyperthermia was effective in the treatment of human malignant tumor, especially in conjugation with radiotherapy or chemotherapy [1]. Thermal effects on tumor tissue microcirculation have been studied, and injury of endothelial cells, which form the inner lining of the blood vessels, is one of the major causes to microcirculation disruption during hyperthermia [2].

Previous studies have paid a great deal of attention to the tumor cell response under hyperthermia [3–7]. Only few were on the endothelial cells, although they are essential to tumor development and progression and have been extensively studied in the area of anti-angiogenesis for drug therapy [8]. Our previous work showed that the loosened junctions between endothelial cells during hyperthermia could facilitate the nano-particle drug delivery into tumor tissue [9], implying that their physiological response may play an important role in tumor therapy.

For mammalian cells, the heat shock effects have been found to be global. They involve almost all known structural and functional systems in cells

through activation or inhibition of certain gene expressions [10, 11]: protein activities such as inhibition of translation [12], protein denaturation [13], protein degradation, changes of a variety of kinases and phosphatases [14–16] and cytoskeleton [17], cellular ion homeostasis [18, 19], etc. We also found that the actin cytoskeleton and Ca<sup>2+</sup> changed in cytoplasm and nucleolus in endothelial cells during hyperthermia [20, 21]. The global effects of hyperthermia on vascular endothelial cells need to be investigated further.

As the development of advanced technologies, complementary deoxyribonucleic acid (cDNA) microarray enables the expression analysis of tens of thousands genes simultaneously [22] and has been widely used in many areas of cell biology. Using this method, we can observe the global response of endothelial cells during hyperthermia at the genetic level. In this study, the gene expressions of the treated endothelial cells were quantitatively profiled. Gene ontology tools were used to find the significantly changed genes and their functional categories.

## Materials and methods

### Cell culture

Human umbilical vein endothelial cells (HUVECs; Cascade Biologics, Inc.) were used in this study. Cells were maintained in Medium 200 with microvascular growth supplement (Cascade Biologics, Inc.) at 37°C, 5% CO<sub>2</sub>, and 95% relative humidity. Cell viability was routinely assessed using the trypan blue exclusion method.

### Heat treatment

Ten microliters of  $2 \times 10^5$  cell/ml endothelial cells were seeded in 75-mm<sup>2</sup> screw-topped polystyrene flasks (Corning Inc., USA). After 2 days of incubation, cells reached logarithmic growth stage. The culture medium was replaced 30 min before the heat treatment. The treatment was administered by immersing flasks in a temperature-regulated water bath (DK-S22, Jinghong Co., Shanghai, China). The wall temperature of the flask in the water bath was calibrated and maintained at 44°C or 55°C (within the error limits of  $\pm 0.1^\circ\text{C}$ ) for 1 h, respectively. After the treatment, the cells were kept in the incubator for another 4 h. A total of four groups of cells were treated and two at each temperature.

### Assessment of apoptosis and necrosis ratio

The ratio of apoptosis and necrosis of heat-treated endothelial cells was assessed using Hoechst/PI (Vybrant® Apoptosis Assay Kit, Catalog Number: V13244, Invitrogen Inc.) labeling technique. Briefly, cells were harvested and washed in cold phosphate-buffered saline (PBS). The cell density was adjusted to  $1 \times 10^6$  cells/ml in PBS. One microliter of the Hoechst 33342 solution and 1 µl of the PI solution were added to each 1 ml of cell suspension. Subsequently, the cells were incubated on ice for 20–30 min. After the incubation, the stained cells were analyzed by fluorescence microscopy using UV/488 nm dual excitation and the fluorescence emission measured at  $\sim 460$  nm and  $> 575$  nm. Live cells show fluorescence at a low level, apoptotic cells show blue fluorescence at a higher level, and necrotic cells show both blue and red fluorescence. The ratios of apoptosis/necrosis were measured at 4, 12, 24, 36, 48, 60 and 72 h after the heat treatment.

### Isolation of RNA

After the heat treatment followed by 4 h incubation, cells were harvested in ice-cold phosphate-buffered saline (PBS) with trypsin (0.025%). RNA isolation was performed by following the protocol of the kit (Cat. No. 15596-026, Invitrogen Co. Ltd). RNA yield was determined spectrophotometrically, and

the quantity and quality of the RNA were estimated from the absorption at 260 nm and 280 nm. Also, gel electrophoresis on 0.9% agarose gel containing 1:10 000 ethidium bromide was performed to check the RNA. Isolated RNA was put in de-ionized water and stored at  $-70^\circ\text{C}$ . A similar procedure was followed to extract RNA from all the treated and the control cells (untreated).

### cDNA production

Two milligrams of total RNA were heated to 70°C for 5 min, then immediately frozen in liquid nitrogen and lyophilized. The lyophilized RNA was combined with a master mix containing 2 µg oligo dT, 6 µl of 5X first-strand buffer, 3 µl of 5 mM DTT (GIBCO), 3 µl of 5 nM dNTPs mixture, 1 µl RNase inhibitor, 1.5 µl SuperScript RT (GIBCO), and then incubated at 37°C. The reaction was stopped by the addition of 4 µl EDTA (0.5 M, Sigma).

### Microarray preparation, hybridization and imaging

Microarray Printing Operon Technologies Genome Oligo Set Version 3.0 contains 34 580 70mer probes representing 24 650 genes and 37 123 gene transcripts. These sense oligos were printed from 93 384 round-bottom-well oligo plates resuspended at a concentration of 25 µM in 8 µl total volume (DMSO) at a spot diameter of 120 µm and a spot center to center distance of 155 µm on Type VII slides (Amersham). The slides were UV crosslinked at the energy setting of 4500 µJ  $\times$  100 and baked at 90°C for 20 min.

The control cells (untreated) were labeled with Cy3 and the heat-treated cells (at 44°C or 55°C for 1 h) were labeled with Cy5. Stratagene's FairPlay aminoallyl kit and protocol were used. Slide hybridization and scanning using a manual hybridization chamber and a lifter slip (Erie Scientific, #25X60I-2-4789), 80 µl of the reaction consisted of 50% formamide (Fisher), 1  $\times$  hybridization buffer (Amersham, #RPK0325), and 400 picomoles of each probe (Cy3 and Cy5 labeled). The hybridization reaction mix was heated to 90°C for 1–2 min, and then was placed on ice. The hybridization reaction was added to the slide and the chamber was assembled and wrapped in foil. The chamber was placed inside a hybridization oven at 37°C for 16 h. After hybridization, the slides were subjected to a series of washes as follows: 1  $\times$  SSC, 0.1% SDS 55°C for 5 min, 0.1  $\times$  SSC, 0.1% SDS 25°C for 5 min, 0.5  $\times$  SSC 55°C for 5 min and power air-dried. The slides were scanned using a Scan Array Express HT scanner (Perkin Elmer). Data analysis-Spot finding and quantification was performed using Digital Genome (MolecularWare Inc.). Cy3 and Cy5 median intensity value minus local background

for each spot was used for further analysis using GeneSpring (Angilent). The ratios of Cy5/Cy3 were used for further analysis, and per chip normalization of the 50th percentile was used. We replicated two experiments for each treatment and control. So there are two arrays comparing 44°C treatment to control, and two arrays comparing 55°C treatment to control. As a quality control, those spots with hybridization intensities (spot median intensity minus local background) of less than 100 were deemed as background hybridization signal and removed from further analysis. For example, to identify genes that are over-expressed in 44°C heat-treated cells, the hybridization intensities should be greater than 100 in both replicated arrays. To identify genes that are over-expressed in control cells vs. heat-treated cells at 44°C the signal intensities from the control hybridization should be greater than 100 in both replicated arrays. We used ratios as measurements and analyzed two replicate arrays separately (instead of averaging the hybridization signals) and only took those showed consistently (i.e. in both arrays) up- or down-regulated genes as truly differentially expressed genes. Two folds were used as the cutoff threshold.

#### Confirmatory real-time quantitative PCR

Each RNA sample used for microarray analysis was also subjected to real-time quantitative PCR (qPCR) experiment to validate the results. Five genes were selected including two up-regulated genes TP53BP and DNAJB1, two down-regulated genes BUB1A and CCND2, and glyceraldehyde-3-phosphate dehydrogenase (GADPH), which is one of the most commonly used housekeeping genes and used as the control in comparison of gene expressions. DNAase-treated total RNA was extracted and reverse-transcribed as described above. The primers were as follows: TP53BP, 5'-CATTAGAGGACATTGACGCTG-3' (forward) and 5'-GGCAGGAGGACTGGTTTAG-3' (reverse), designed to yield a 225-bp amplicon; DNAJB1, 5'-CCCCAAACACCCGAGAA-3' (forward) and 5'-ATGGTCCACAACCTGGTAGAAAG-3' (reverse), designed to yield a 193-bp amplicon; BUB1A, 5'-ATGTGGAAGAGGGCTTAGAG-3' (forward) and 5'-CATTTTGGAAGGCATTTGTT-3' (reverse), designed to yield a 176-bp amplicon; CCND2, 5'-CAGGAGTGGAAGTGGTGG-3' (forward) and 5'-GCTCAAGCCTCATCTTACCG-3' (reverse), designed to yield a 181-bp amplicon; GADPH, 5'-TGATGACATCAAGAAGGTGGTGAAG-3' (forward) and 5'-TCCTTGGAGGCCATGTGGCCAT-3' (reverse), designed to yield a 240-bp amplicon. The PCR amplification mixture in a final volume of 25 µl consisted of 1 X Taq DNA

polymerase buffer, 0.25 mM deoxyribonucleoside triphosphate (dNTP), 0.2 µM each primer, 2.5 U Hot start Ex Taq (TaKaRa, Code No.: DRR006A) iQTM SYBR Green Supermix (BIO-RAD) and 1 µl cDNA sample. All the amplicons were confirmed by sequencing. The real-time PCR was performed using Rotor-Gene RG-3000A (Corbett Research) equipped with Rotor-Gene 6.0 for Windows. A pre-amplification denaturation for 4 min at 94°C was performed and amplification was carried out for 40 cycles. Each cycle was 94°C for 30 s, 54°C for 30 s, and 72°C for 30 s. The final extension step was performed for 10 min at 72°C. Fold differences were calculated via a mathematical model described by Pfaffl [23] using the formula:  $2^{-(\Delta\Delta Ct)}$ , where  $\Delta\Delta Ct$  is  $\Delta Ct_{(heat\ treatment)} - \Delta Ct_{(control)}$ ,  $\Delta Ct$  is  $Ct_{(test\ gene)} - Ct_{(control\ gene)}$ , and  $Ct$  is the cycle at which the threshold is crossed.

#### Gene ontology analyses

Bioinformatics tool EASEonline [24], which provides integrated solutions for the annotation and analysis of genome-scale datasets derived from high-throughput technologies such as microarray and proteomic platforms, was used to analyze the relatively enriched gene ontology categories of experimental results. Before the analysis, the genes with no correlations to any functional categories or not detected in four groups of the treated cell were deleted. The results were saved as a.txt file, and submitted through the Internet. Fisher's exact test was performed to examine the relative enrichment of certain category ( $p < 0.1$ ).

## Results

#### Microarray results

The fluorescence data from the microarray measurements were transferred into ratios (heat treated/control). All the genes extracted from the cells heated at either 44°C or 55°C were divided into three groups: up-regulated, down-regulated, unchanged. If one gene expression increased more than 2 folds in both experiments at the same temperature, then the gene was considered to be up-regulated at that temperature. On the other hand, if one gene expression decreased to lower than 0.5 folds of the control, then the gene was considered to be down-regulated. The change between 0.5 folds to 2 folds was considered to be unchanged. Table I lists the number of genes changed in three groups (up-regulated, down-regulated, unchanged) after the heat treatment at the two temperatures (44°C and 55°C), respectively. The heat map of all up-regulated, down-regulated and unchanged is

Table I. Number of genes changed after heat treatment at the two temperatures (44°C and 55°C), respectively.

	Up-regulated	Down-regulated	Unchanged
44°C	1115	333	949
55°C	1669	287	1311

Table II. Orthogonal analyses of regulated genes at 44°C and 55°C. The number inside circle stands for the group number. The number in the table stands for the number of genes.

44°C				
55°C	Up-regulated	Down-regulated	Unchanged	
Up-regulated	A 406	B 2	C	57
Down-regulated	D 2	E 76	F	9
Unchanged	G 24	H 51	I	400

also drawn as shown in Appendix I. The heat map was created by Cluster 3.0 with hierarchical cluster. Similarity metric is Euclidean distance and Clustering method is average linkage. The four columns in the map stand for the two micro-array experiments at 44°C and 55°C (from left to right), respectively.

#### Orthogonal analysis of regulated genes

To show the gene expression difference in cells treated at the two temperatures, an orthogonal analysis was performed. In Table II, all the genes were divided into nine groups according to the change in their expression after the heat treatment at 44°C or 55°C, respectively. The criteria are given in the above.

#### Gene ontology (GO) analysis

The relatively significant genes in every category are calculated by online software EASE (NIH) as described in the Materials and methods. The relatively enriched GO categories are listed in Table III. The details of the genes in each group are given in Appendix II.

#### Quantitative real-time PCR results

In order to assess the reliability of the cDNA microarray, several genes were sequenced and the induction or repression was validated by real-time PCR. In general, the correlation between the micro-array experiments and real-time PCR analysis was very high. The results of two representative genes DNAJB1 (Genebank: BC019827) and CCND2 (Genebank: M88082) are shown in Figure 1.

Table III. Relatively enriched functional categories of each group in Table II.

Functional categories	No. of genes	Fisher's exact test
Group A		
Cell communication	55	0.0131
Signal transduction	44	0.048
Receptor signaling protein activity	6	0.085
Organismal movement	6	0.0891
Detection of external stimulus	6	0.0891
Group C		
Regulation of cell cycle	3	0.00754
Metabolism	9	0.0416
Biosynthesis	4	0.0201
Protein biosynthesis	3	0.0313
Cell cycle	3	0.0529
Nucleobase, nucleoside, nucleotide and nucleic acid metabolism	5	0.0961
Macromolecule biosynthesis	3	0.0745
Group E		
Metal ion binding	8	0.013
Cytoplasm	16	0.0263
Oxidoreductase activity	5	0.0298
Mitochondrion	5	0.0464
Calcium ion binding	4	0.0726
Lipid metabolism	4	0.096
Response to abiotic stimulus	3	0.0804
Group F		
Hydrolase activity	6	0.0737
Membrane fraction	3	0.0757
Group G		
Cytosol	7	0.000704
Large ribosomal subunit	4	0.00019
Cytosolic ribosome (sensu Eukarya)	4	0.000869
Ribosome	5	0.0033
Structural constituent of ribosome	5	0.00371
Cytoplasm	18	0.013
Structural molecule activity	7	0.0101
Cytosolic large ribosomal subunit (sensu Eukarya)	3	0.00169
Protein binding	10	0.0436
Chromatin modification	3	0.0137
Protein biosynthesis	6	0.0437
Protein metabolism	12	0.0848
Cell fraction	5	0.0663
DNA packaging	3	0.0402
Chromosome organization and biogenesis (sensu Eukarya)	3	0.0402
Establishment and/or maintenance of chromatin architecture	3	0.0402
Nuclear organization and biogenesis	3	0.0402
Ribonucleoprotein complex	5	0.0806
Calcium ion binding	4	0.0726
Regulation of transcription from Pol II promoter	3	0.059
Chaperone activity	3	0.0668

## Discussion

In this study, the gene expression profile changes in endothelial cells after heat treatment have provided a global view of the cellular response to heat. In contrast to the previous studies [3–5],



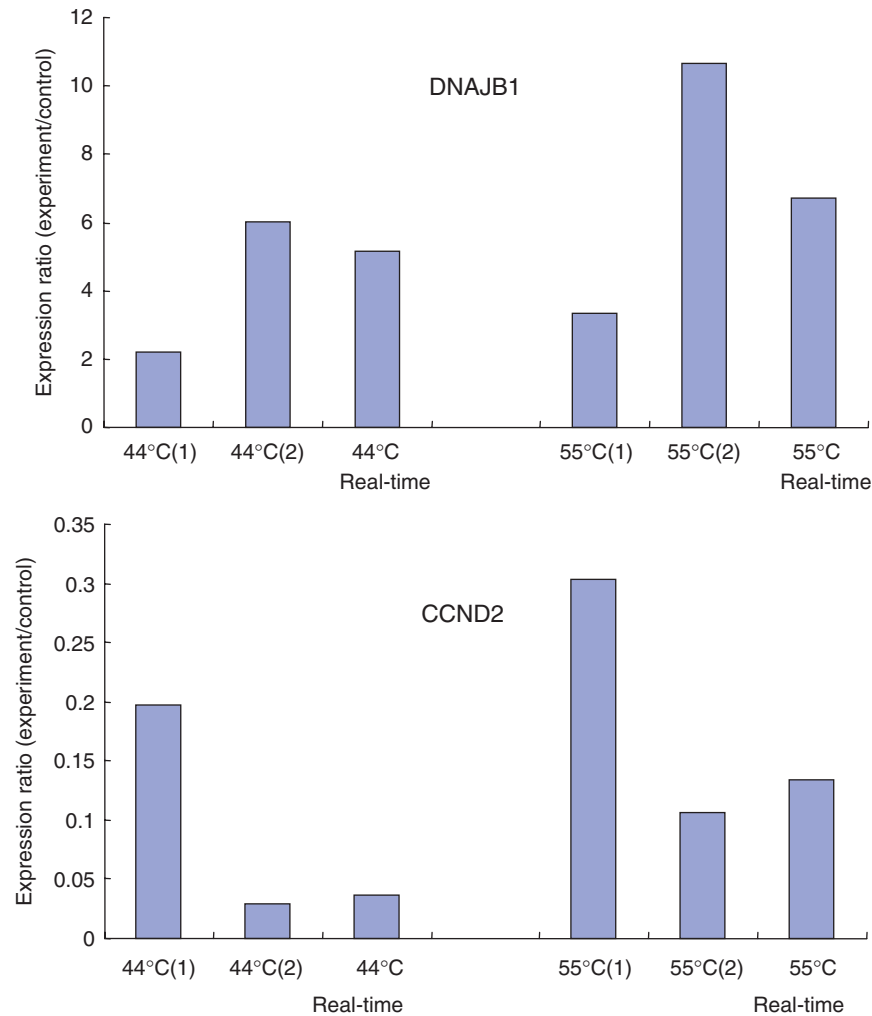


Figure 1. Comparisons between microarray results and real-time PCR of two randomly chosen genes: DNAJB1 and CCND2.

we used the largest gene array scale, about 35 000 probes on one single gene chip including 24 650 genes and 37 123 gene transcripts. The gene expression patterns of the endothelial cells under a relatively high temperature (55°C) were profiled for the first time. Thousands of genes were found changed after the treatment. There were many more up-regulated genes than the down-regulated genes. The gene ontology hierarchy method was used to group the expressed genes into different functional categories. One can find that the changed genes were related to almost every aspect of cellular physiological activities.

In Table II, groups A and B show the numbers of genes either up-regulated or down-regulated at both 44°C and 55°C. One can call these genes the general heat shock response genes, because their expressions are not dependent on the treatment temperature. Many reported heat-shock-related genes were found in these two groups. Also, there were several

functional categories that have never been reported before.

The up-regulated genes include two general gene categories of cell communication and signal transduction. There are G-protein-related genes, including MRGPRX1, GNB2, HCP5, LGR6, GPR20, C14 up-regulated through heat shock. The G-protein signaling pathway is stimulated on the cell surface and transfers the signal to the cell nucleolus. A previous study has shown that cell integrin and cytoskeleton protein were decreased after hyperthermia at 43°C [17]. But, in our results, two integrin-related genes ITGA7 (Integrin 7) and ITGA4 (Integrin, alpha 4) were all up-regulated. The decrease in the protein profile may induce the gene expression of these proteins. In the receptor signaling protein activity category, AKAP6, SHANK2, TIAM2, MAPK6, TYRO3, MAP3K7IP1 all participate in the important signaling transduction member such as PKA, MAPK.

The down-regulated general response genes mainly include the genes related to ion binding, changes in the cytoplasm (cytoplasm, oxidoreductase activity, mitochondrion, lipid metabolism) and response to abiotic stimulus. Four calcium ion binding genes—S100A11P, CAPNS1, ANXA5, EPS15—are all included in the metal ion binding category. Our previous study showed that calcium ion concentration increased in both the nucleolus and cytoplasm during hyperthermia [21]. The decrease of calcium ion binding protein may contribute to this process. Many studies have shown that heat stress can cause the increase of reactive oxygen species and accelerate metabolism rate in cells. In this study, the related genes were all down-regulated. The increase of reactive oxygen species and metabolism may negatively down-regulate the expression of the related genes. Abiotic stimulus stands for the non-living stimulus, IL8 is the gene response to biochemical stimulus, and the other two genes are not related to heat stress. May be the up-regulation detection of external stimulus can depress the other stress-related genes.

The genes in groups B and D changed reversely at the temperature of 44°C and 55°C. Results showed that the number of genes in these two groups was very small compared with the number in the general response groups mentioned above. Also there are no relatively significant genes in these groups.

Groups C, F and G, H show the numbers of genes changed differently at 44°C or 55°C. Many studies had showed that heat shock can cause cell cycle arrest [25–27]. Our previous study also showed that cell cycle was a very important factor in determining the sensitivity of cells to heat shock [20]. In the present results, most genes in group C were cell-cycle-related genes. GML participates in DNA damage response, especially signal transduction by P53 class mediator, resulting in cell cycle arrest. IGF 2 participates in many biological pathways including the cell proliferation control. MNT negatively regulates cell proliferation by binding to DNA binding proteins at its N-terminal Sin3-interaction domain. None of the cell cycle related genes was found in the cells treated at 55°C. Cells went to necrosis directly without going through any gene changes related to cell cycle.

In group G, which includes the genes that were up-regulated specifically at 55°C, these genes were mainly related to protein synthesis activities. This may suggest that, in necrotic endothelial cells, genes related to protein synthesis were up-regulated 6–8 h before the cell death. Very few studies have been done on the gene expression pattern of cells undergoing necrosis. A previous study has proven that protein denaturation occurred during and after heat treatment [13]. Protein denaturation occurs in

mammalian cells at temperatures exceeding 40–42°C [28], and more protein denaturation occurred at the temperature of 55°C. Our hypothesis is that in the beginning of the heating at 55°C, protein aggregates formed dramatically in the cytoplasm. The sudden loss of so much protein inside the cell stimulates a dramatic up-regulation of protein synthesis related genes to rescue the cells from death.

In comparison to the previously reported heat induced gene expression changes, studies, there are about 10–15% of the up-regulated or down-regulated genes in common, such as: genes HSP32 (Z82244) [4, 6], HSP70 (U65785) [4] and related chaperonin CCTD (AF026291) [4]; cell growth-, proliferation- and differentiation-related genes COIL (U06632) [4], PLAGL1 (U81992) [4], DP1 (L23959) [3] and WEE1 (X62048); membrane transport function genes NEDD4L (AB007899) [4], KPNB3 (Y08890) [4] and C3AR1 (X98248) [6]; signal transduction genes PRKACB (M34181) [6], YES1 (M15990) [6], PTPN7 (M64322) [6] and CSK (X59932) [5]. Also there are genes related to other functions such apoptosis, immune function, RNA stability and degradation, transcription, etc. Most of the overlapping genes belong to groups A, E and they are general heat responsive genes.

For the biological implication, some phenomena reported in previous studies can be partially explained from the genetic response point of view. Our previous study [9] showed that the hyperthermia treatment could facilitate the drug extravasation in tumor tissue, and the morphology change of endothelial cells played a major role in the process. In this study, many cytoskeleton- and integrin-related genes were found to be up-regulated and down-regulated after heat treatment, indicating the correlated genetic responses. Nikfarjam [2] found that the major reason of heat-induced tumor damage was the injury of endothelial cells. The injury of endothelial cells is mainly caused by heat-induced apoptosis or necrosis. Some apoptosis-related genes were found to be changed; i.e. specific gene Jun (BC009874) reported in our (4 folds in 44°C and 3 folds in 55°C) and other studies [3, 7]. There were many studies about the relationship between c-Jun expression and apoptosis [29] and it was showed that ceramide was involved with c-Jun expression of heat-shock-induced apoptosis [30].

In summary, the gene expression change after heat treatment has been profiled at a huge scale in this study. A large number of genes has been found either up-regulated or down-regulated, indicating that the cellular response to hyperthermia is global and pleiotric at the genetic level. Results of the preliminary analyses presented here warrant further investigation on functional protein response to hyperthermia in the near future.

## Acknowledgments

This work was supported by National Natural Science Foundation of China (NSFC50436030), Science and Technology Commission of Shanghai Municipality (05DZ22321), Ministry of Science and Technology of China (2006CB0D0100), and Special Funding from Shanghai Center for Systems Biomedicine. We also thank Mr Zhenmin Zhu for his help with data analysis and Ms Jian Wang for her help with real-time quantitative PCR experiment.

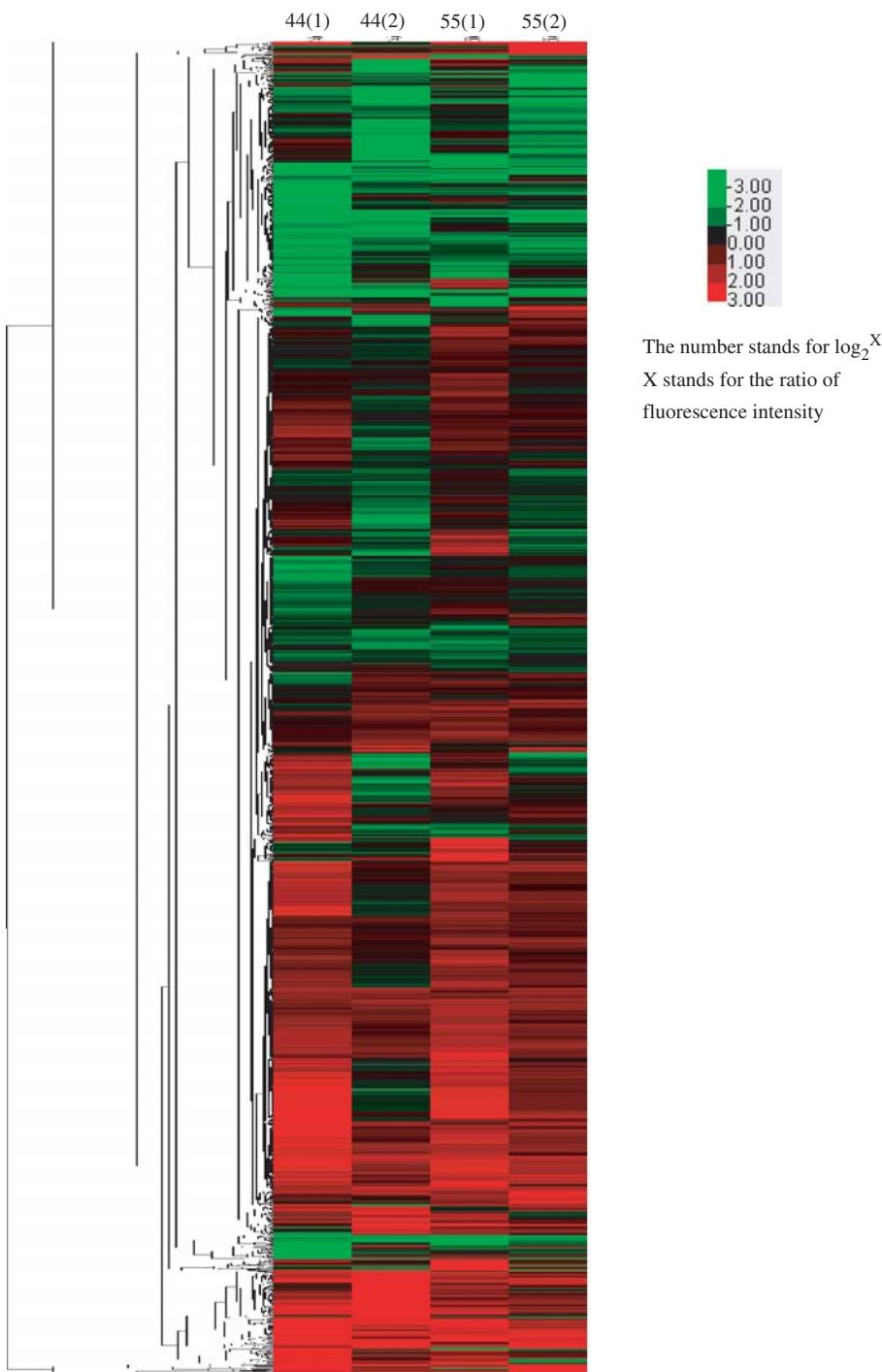
## References

- Hildebrandt B, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T, Felix R, Riess H. The cellular and molecular basis of hyperthermia. *Crit Rev Oncol Hematol* 2002;43:33–56.
- Nikfarjam M, Muralidharan V, Malcontenti-Wilson C, Christophi C. Progressive microvascular injury in liver and colorectal liver metastases following laser induced focal hyperthermia therapy. *Lasers Surg Med* 2005;37:64–73.
- Narita N, Noda I, Ohtsubo T, Fujieda S, Tokurik M, Sito T, Saito H. Analysis of heat-shock related gene expression in head-and-neck cancer using cDNA arrays. *Int J Radiat Oncol Biol Phys* 2002;53:190–196.
- Sonna LA, Gaffin SL, Pratt RE, Cullivan ML, Angel KC, Lilly CM. Effect of acute heat shock on gene expression by human peripheral blood mononuclear cells. *J Appl Physiol* 2002;92:2208–2220.
- Dinh HK, Zhao B, Schuschereba ST, Merrill G, Bowman PD. Gene expression profiling of the response to thermal injury in human cells. *Physiol Genomics* 2001;7:3–13.
- Sonna LA, Wenger CB, Flinn S, Sheldon HK, Sawka MN, Lilly CM. Exertional heat injury and gene expression changes: A DNA microarray analysis study. *J Appl Physiol* 2004;96:1943–1953.
- Hirano H, Tabuchi Y, Kondo T, Zhao QL, Ogawa R, Cui ZG, Feril LB, Kanayama S. Analysis of gene expression in apoptosis of human lymphoma U937 cells induced by heat shock and the effects of  $\alpha$ -phenyl N-tert-butyl nitron (PBN) and its derivatives. *Apoptosis* 2005;10:331–340.
- Folkman J. Angiogenesis. *Annu Rev Med* 2006;57:1–18.
- Liu P, Zhang A, Xu Y, Xu LX. Study of non-uniform nanoparticle liposome extravasation. *Int J Hyper* 2005;21:259–270.
- Lindquist S. The heat-shock response. *Annu Rev Biochem* 1986;55:1151–1191.
- Morimoto RI. Regulation of the heat shock transcriptional response: Cross talk between a family of heat shock factors, molecular chaperones, and negative regulators. *Genes Dev* 1998;12:3788–3796.
- Panniers R. Translational control during heat shock. *Biochimie* 1994;76:737–747.
- Lepock JR. Protein denaturation during heat shock. *Adv Mol Cell Biol* 1997;19:223–259.
- Obata T, Brown GE, Yaffe MB. MAP kinase pathways activated by stress: The p38 MAPK pathway. *Crit Care Med* 2000;28:67–77.
- Han SI, Ha KS, Kang KI, Kim HD, Kang HS. Heat shock-induced actin polymerization, SAPK/JNK activation, and heat-shock protein expression are mediated by genistein-sensitive tyrosine kinase in K562 cells. *Cell Biol Int* 2000;24:447–457.
- Han SI, Oh SY, Woo SH, Kim KH, Kim JH, Kim HD, Kang HS. Implication of a small GTPase Rac1 in the activation of c-Jun N-terminal kinase and heat shock factor in response to heat shock. *J Biol Chem* 2001;276:1889–1895.
- Luchentti F, Mannello F, Cnónico B, Battistelli M, Burattini S, Falcieri E, Papa S. Integrin and cytoskeleton behavior in human neuroblastoma cells during hyperthermia-related apoptosis. *Apoptosis* 2004;9:635–648.
- Gaffin SL, Koratich M, Hubbard RW. The effect of hyperthermia on intracellular sodium concentrations of isolated human cells. *Ann NY Acad Sci* 1997;81:3637–3639.
- Koratich M, Gaffin SL. Mechanisms of calcium transport in human endothelial cells subjected to hyperthermia. *J Therm Biol* 1999;24:245–249.
- Chen B, Zhou M, Xu LX. Study of vascular endothelial cell morphology during hyperthermia. *J Therm Biol* 2005;30:111–117.
- Xu LX, Chen B, Zhou M. Change of individual vascular endothelial cell calcium during hyperthermia. *J Therm Biol* 2006;31:302–306.
- Schena M, Shalon D, Heller R. Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes. *Proc Natl Acad Sci USA* 1997;93:10614–10619.
- Pfaffl MW. A new mathematical model for relative quantification in real-time RT-PCR. *Nucleic Acids Res* 2001;29:e45.
- Dennis Jr G, Sherman BT, Hosack DA, Yang J, Gao W, Lane HC, Lempicki RA. DAVID: Database for Annotation, Visualization, and Integrated Discovery. *Genome Biol* 2005;4:3. Available online: <http://apps1.niaid.nih.gov/david/>
- Kuhl NM, Rensing L. Heat shock effects on cell cycle progression. *Cell Mol Life Sci* 2000;57:450–463.
- Maldonado-Codina G, Llamazares S, Glover DM. Heat shock results in cell cycle delay and synchronisation of mitotic domains in cellularised *Drosophila melanogaster* embryos. *J Cell Sci* 1993;105:711–720.
- Kuhl NM, Rensing L. Heat shock effects on cell cycle progression. *Cell Mol Life Sci* 2000;57:450–463.
- Lepock JR. Cellular effects of hyperthermia: Relevance to the minimum dose for thermal damage. *Int J Hyperthermia* 2003;19:252–266.
- Shaulian E, Karin M. AP-1 as a regulator of cell life and death. *Nat Cell Biol* 2002;4:131–136.
- Kondo T, Matsuda T, Kitano T, Takahashi A, Tashima M, Ishikura H, Umehara H, Domae M, Uchiyama T, Okazaki T. Role of c-jun expression increased by heat shock and ceramide activated caspase-3 in HL-60 cell apoptosis. *J Biol Chem* 2000;275:7668–7676.



Appendix I

Heat map of all up-regulated, down-regulated and unchanged genes



## Appendix II

### Group 1

#### Cell communication.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB002354	9842	adapter protein 162	biological_process	intracellular signaling cascade
AB037818	56995	tubby like protein 4	biological_process	cellular_component unknown; intracellular signaling cascade; regulation of transcription, DNA-dependent; transcription factor activity
AB044807	10207	InaD-like protein	biological_process	cellular_component unknown; intracellular signaling cascade; protein binding
AB052751	8313	axin 2 (conductin, axil)	biological_process	development; frizzled signaling pathway; intracellular; signal transducer activity; signal transduction
AB065846	259249	G protein-coupled receptor MRGX1	biological_process	G-protein coupled receptor protein signaling pathway; integral to membrane; receptor activity; rhodopsin-like receptor activity
AF034833	3679	integrin, alpha 7	biological_process	cell-matrix adhesion; cellular morphogenesis; homophilic cell adhesion; integrin complex; integrin-mediated signaling pathway; muscle development; protein binding; receptor activity
AF053356	2056	erythropoietin	biological_process	cell-cell signaling; circulation; development; erythropoietin receptor binding; extracellular space; hormone activity; response to stress; signal transduction
AF053356	2783	guanine nucleotide binding protein (G protein), beta polypeptide 2	biological_process	G-protein coupled receptor protein signaling pathway; heterotrimeric G-protein GTPase activity; heterotrimeric G-protein complex; signal transducer activity; signal transduction
AF053356	7455	zonadhesin	biological_process	apical plasma membrane; binding of sperm to zona pellucida; cell recognition; cell-cell adhesion; integral to membrane; protein binding
AF061943	51677	prostate derived STE20-like kinase PSK	biological_process	ATP binding; actin cytoskeleton organization and biogenesis; activation of MAPKK; apoptosis; cell migration; cytoplasmic vesicle; focal adhesion formation; positive regulation of JNK cascade; protein amino acid phosphorylation; protein serine/threonine kinase activity; protein-membrane targeting; regulation of cell growth; regulation of cell shape; response to stress; transferase activity
AF120324	26230	T-cell lymphoma invasion and metastasis 2	biological_process	guanyl-nucleotide exchange factor activity; intracellular signaling cascade; protein binding; receptor signaling protein activity
AF130420	9372	MAD, mothers against decapentaplegic homolog (Drosophila) interacting protein, receptor activation anchor	biological_process	SMAD protein heteromerization; SMAD protein nuclear translocation; cytoplasm; early endosome; endocytosis; protein binding; receptor activity; serine-type peptidase activity; transforming growth factor beta receptor complex assembly; zinc ion binding
AF141901	22941	SH3 and multiple ankyrin repeat domains 2	biological_process	GKAP/Homer scaffold activity; cellular_component unknown; intracellular signaling cascade; protein binding
AF172264	23043	Traf2 and NCK interacting kinase	biological_process	ATP binding; protein amino acid phosphorylation; protein kinase cascade; protein serine/threonine kinase activity; regulation of translation; response to stress; small GTPase regulatory/interacting protein activity; transferase activity
AF222689	3276	HMT1 hnRNP methyltransferase-like 2 ( <i>S. cerevisiae</i> )	biological_process	N-methyltransferase activity; S-adenosylmethionine-dependent methyltransferase activity; cell surface receptor linked signal transduction; cytoplasm; defense response; nucleus; protein amino acid methylation; transferase activity
AF227129	50834	taste receptor, type 2, member 1	biological_process	G-protein coupled receptor activity; G-protein coupled receptor protein signaling pathway; biological_process unknown; chemosensory behavior; integral to membrane; receptor activity; taste receptor activity

(continued)

## Continued.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AF236083	10886	G protein-coupled receptor 74	biological_process	G-protein coupled receptor activity; G-protein coupled receptor protein signaling pathway; cell growth and/or maintenance; detection of abiotic stimulus; integral to plasma membrane; neuropeptide receptor activity; rhodopsin-like receptor activity
AF237775	2872	MAP kinase-interacting serine/threonine kinase 2	biological_process	ATP binding; protein amino acid phosphorylation; protein kinase cascade; protein serine/threonine kinase activity; regulation of protein biosynthesis; regulation of translation; response to stress; transferase activity
AF258564	7410	vav 2 oncogene	biological_process	diacylglycerol binding; guanyl-nucleotide exchange factor activity; intracellular signaling cascade
AF276423	55914	erb2 interacting protein	biological_process	Neu/ErbB-2 receptor binding; basal plasma membrane; basal protein localization; cell adhesion; cell cycle; cell growth; cytoplasm; epidermal growth factor receptor signaling pathway; establishment and/or maintenance of epithelial cell polarity; hemidesmosome; integrin binding; integrin-mediated signaling pathway; intermediate filament cytoskeleton organization and biogenesis; nucleus; protein binding; structural constituent of cytoskeleton
AF336797	3782	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3	biological_process	calcium-activated potassium channel activity; calmodulin binding; integral to membrane; ion channel activity; ion transport; membrane fraction; neurogenesis; potassium ion transport; small conductance calcium-activated potassium channel activity; synaptic transmission; voltage-gated potassium channel complex
AF420474	5597	mitogen-activated protein kinase 6	biological_process	ATP binding; MAP kinase activity; cell cycle; protein amino acid phosphorylation; protein serine/threonine kinase activity; signal transduction; transferase activity
AJ242544	4585	mucin 4, tracheobronchial	biological_process	Neu/ErbB-2 receptor binding; biological_process unknown; cell-matrix adhesion; extracellular matrix structural constituent; integral to plasma membrane; membrane; molecular_function unknown
AJ295237	57053	cholinergic receptor, nicotinic, alpha polypeptide 10	biological_process	extracellular ligand-gated ion channel activity; integral to membrane; ion channel activity; ion transport; neurotransmitter receptor activity; nicotinic acetylcholine-activated cation-selective channel activity; receptor binding; regulation of cell proliferation; synaptic transmission; synaptic transmission, cholinergic
AK000814	8681	phospholipase A2, group IVB (cytosolic)	biological_process	arachidonic acid metabolism; calcium ion binding; calcium-dependent phospholipase A2 activity; calcium-dependent phospholipid binding; calcium-mediated signaling; cytosol; extracellular; glycerophospholipid catabolism; inflammatory response; parturition; phospholipase activity
AK027377	59352	leucine-rich repeat-containing G protein-coupled receptor 6	biological_process	G-protein coupled receptor protein signaling pathway; integral to membrane; protein-hormone receptor activity
AK092864	64759	tensin-like SH2 domain-containing 1	biological_process	intracellular signaling cascade; phosphoprotein phosphatase activity; protein amino acid dephosphorylation
AY046538	8601	regulator of G-protein signalling 20	biological_process	GTPase activator activity; membrane; protein binding; regulation of G-protein coupled receptor protein signaling pathway; signal transducer activity; signal transduction
BC000043	379	ADP-ribosylation factor 4-like	biological_process	ARF small monomeric GTPase activity; GTP binding; nucleus; protein secretion; small GTPase mediated signal transduction
BC000493	1819	developmentally regulated GTP binding protein 2	biological_process	GTP binding; cell growth and/or maintenance; signal transduction
BC002392	4354	membrane protein, palmitoylated 1, 55 kDa	biological_process	guanylate kinase activity; integral to plasma membrane; membrane; membrane fraction; protein binding; signal transduction
BC002823	10758	chromosome 6 open reading frame 4	biological_process	cellular_component unknown; intracellular signaling cascade; molecular_function unknown
BC006314	1134	cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle)	biological_process	acetylcholine receptor activity; extracellular ligand-gated ion channel activity; integral to membrane; ion channel activity; ion transport; muscle contraction; nicotinic acetylcholine-activated cation-selective channel activity; nicotinic acetylcholine-gated receptor-channel complex; signal transduction; synaptic transmission

BC007588 BC011645	90864 6236	SPRY domain-containing SOCS box protein SSB-3 Ras-related associated with diabetes	biological_process biological_process	intracellular signaling cascade GTP binding; calmodulin binding; small GTPase mediated signal transduction; small monomeric GTPase activity
BC014140	583	Bardet-Biedl syndrome 2	biological_process	biological_process unknown; cell-matrix adhesion; cellular_component unknown; integrin complex; molecular_function unknown; visual perception
BC014942	89941	ras homolog gene family, member T2	biological_process	GTP binding; calcium ion binding; small GTPase mediated signal transduction; small monomeric GTPase activity
BC015050 BC016758	11339 3059	Opa-interacting protein 5 hematopoietic cell-specific Lyn substrate 1	biological_process biological_process	cell communication; cellular_component unknown; protein binding DNA-directed RNA polymerase II, core complex; intracellular signaling cascade; regulation of transcription, DNA-dependent; transcription factor activity
BC017263	10960	lectin, mannose-binding 2	biological_process	Golgi apparatus; endoplasmic reticulum; heterophilic cell adhesion; integral to membrane; intracellular protein transport; protein transporter activity; sugar binding
BC019047	8742	tumor necrosis factor (ligand) superfamily, member 12	biological_process	angiogenesis; apoptosis; immune response; induction of apoptosis; integral to plasma membrane; signal transduction; tumor necrosis factor receptor binding
L12002	3676	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	biological_process	cell-matrix adhesion; integral to membrane; integrin complex; integrin-mediated signaling pathway; protein binding; receptor activity
U59748 U66579	50846 2843	desert hedgehog homolog (Drosophila) G protein-coupled receptor 20	biological_process biological_process	cell-cell signaling; development; peptidase activity; proteolysis and peptidolysis G-protein coupled receptor protein signaling pathway; integral to plasma membrane; rhodopsin-like receptor activity
U68032	1235	chemokine (C-C motif) receptor 6	biological_process	C-C chemokine receptor activity; G-protein coupled receptor protein signaling pathway; antimicrobial humoral response (sensu Vertebrata); cell motility; cellular defense response; chemotaxis; cytosolic calcium ion concentration elevation; humoral immune response; integral to plasma membrane; receptor activity; rhodopsin-like receptor activity; signal transduction
U94905	8525	diacylglycerol kinase, zeta 104kDa	biological_process	ATP binding; diacylglycerol binding; diacylglycerol kinase activity; intracellular signaling cascade; nucleus; protein kinase C activation; transferase activity
U96919 X15002	3631 3484	inositol polyphosphate-4-phosphatase, type I, 107kDa insulin-like growth factor binding protein 1	biological_process biological_process	signal transduction cell growth and/or maintenance; extracellular space; insulin-like growth factor binding; regulation of cell growth; signal transduction
X52773	6256	retinoid X receptor, alpha	biological_process	nucleus; receptor activity; regulation of transcription, DNA-dependent; retinoid-X receptor activity; signal transduction; steroid binding; steroid hormone receptor activity; transcription coactivator activity; transcription factor activity; vitamin metabolism
X72886	7301	TYRO3 protein tyrosine kinase	biological_process	ATP binding; cell adhesion; integral to plasma membrane; protein amino acid phosphorylation; protein binding; receptor activity; receptor signaling protein tyrosine kinase activity; signal transduction; transferase activity; transmembrane receptor protein tyrosine kinase activity
X81892	10149	G protein-coupled receptor 64	biological_process	G-protein coupled receptor activity; integral to plasma membrane; membrane; neuropeptide signaling pathway; receptor activity; spermatogenesis
Z26317	1829	desmoglein 2	biological_process	calcium ion binding; cell adhesion; cytoskeleton; homophilic cell adhesion; integral to membrane; intercellular junction; protein binding
Z26491	1312	catechol-O-methyltransferase	biological_process	catechol O-methyltransferase activity; catecholamine metabolism; integral to membrane; magnesium ion binding; microsome; neurotransmitter catabolism; soluble fraction; transferase activity
Z83845	10454	mitogen-activated protein kinase kinase kinase 7 interacting protein 1	biological_process	activation of MAPKKK; catalytic activity; enzyme activator activity; protein binding; transforming growth factor beta receptor, cytoplasmic mediator activity
Z95636	3911	laminin, alpha 5	biological_process	basal lamina; cell adhesion; protein binding; structural molecule activity

Signal transduction.				
Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB002354	9842	adapter protein 162	biological_process	intracellular signaling cascade
AB037818	56995	tubby like protein 4	biological_process	cellular_component unknown; intracellular signaling cascade; regulation of transcription, DNA-dependent; transcription factor activity
AB044807	10207	InaD-like protein	biological_process	cellular_component unknown; intracellular signaling cascade; protein binding
AB052751	8313	axin 2 (conductin, axil)	biological_process	development; frizzled signaling pathway; intracellular; signal transducer activity; signal transduction
AB065846	259249	G protein-coupled receptor MRGX1	biological_process	G-protein coupled receptor protein signaling pathway; integral to membrane; receptor activity; rhodopsin-like receptor activity
AF034833	3679	integrin, alpha 7	biological_process	cell-matrix adhesion; cellular morphogenesis; homophilic cell adhesion; integrin complex; integrin-mediated signaling pathway; muscle development; protein binding; receptor activity
AF053356	2056	erythropoietin	biological_process	cell-cell signaling; circulation; development; erythropoietin receptor binding; extracellular space; hormone activity; response to stress; signal transduction
AF053356	2783	guanine nucleotide binding protein (G protein), beta polypeptide 2	biological_process	G-protein coupled receptor protein signaling pathway; heterotrimeric G-protein GTPase activity; heterotrimeric G-protein complex; signal transducer activity; signal transduction
AF061943	51677	prostate derived STE20-like kinase PSK	biological_process	ATP binding; actin cytoskeleton organization and biogenesis; activation of MAPKK; apoptosis; cell migration; cytoplasmic vesicle; focal adhesion formation; positive regulation of JNK cascade; protein amino acid phosphorylation; protein serine/threonine kinase activity; protein-membrane targeting; regulation of cell growth; regulation of cell shape; response to stress; transferase activity
AF120324	26230	T-cell lymphoma invasion and metastasis 2	biological_process	guanyl-nucleotide exchange factor activity; intracellular signaling cascade; protein binding; receptor signaling protein activity
AF130420	9372	MAD, mothers against decapentaplegic homolog (Drosophila) interacting protein, receptor activation anchor	biological_process	SMAD protein heteromerization; SMAD protein nuclear translocation; cytoplasm; early endosome; endocytosis; protein binding; receptor activity; serine-type peptidase activity; transforming growth factor beta receptor complex assembly; zinc ion binding
AF141901	22941	SH3 and multiple ankyrin repeat domains 2	biological_process	GKAP/Homer scaffold activity; cellular_component unknown; intracellular signaling cascade; protein binding
AF172264	23043	Traf2 and NCK interacting kinase	biological_process	ATP binding; protein amino acid phosphorylation; protein kinase cascade; protein serine/threonine kinase activity; regulation of translation; response to stress; small GTPase regulatory/interacting protein activity; transferase activity
AF222689	3276	HMT1 hnRNP methyltransferase-like 2 ( <i>S. cerevisiae</i> )	biological_process	N-methyltransferase activity; S-adenosylmethionine-dependent methyltransferase activity; cell surface receptor linked signal transduction; cytoplasm; defense response; nucleus; protein amino acid methylation; transferase activity
AF227129	50834	taste receptor, type 2, member 1	biological_process	G-protein coupled receptor activity; G-protein coupled receptor protein signaling pathway; biological_process unknown; chemosensory behavior; integral to membrane; receptor activity; taste receptor activity
AF236083	10886	G protein-coupled receptor 74	biological_process	G-protein coupled receptor activity; G-protein coupled receptor protein signaling pathway; cell growth and/or maintenance; detection of abiotic stimulus; integral to plasma membrane; neuropeptide receptor activity; rhodopsin-like receptor activity



AF237775	2872	MAP kinase-interacting serine/threonine kinase 2	biological_process	ATP binding; protein amino acid phosphorylation; protein kinase cascade; protein serine/threonine kinase activity; regulation of protein biosynthesis; regulation of translation; response to stress; transferase activity
AF258564	7410	vav 2 oncogene	biological_process	diacylglycerol binding; guanyl-nucleotide exchange factor activity; intracellular signaling cascade
AF276423	55914	erbB2 interacting protein	biological_process	Neu/ErbB-2 receptor binding; basal plasma membrane; basal protein localization; cell adhesion; cell cycle; cell growth; cytoplasm; epidermal growth factor receptor signaling pathway; establishment and/or maintenance of epithelial cell polarity; hemidesmosome; integrin binding; integrin-mediated signaling pathway; intermediate filament cytoskeleton organization and biogenesis; nucleus; protein binding; structural constituent of cytoskeleton
AF420474	5597	mitogen-activated protein kinase 6	biological_process	ATP binding; MAP kinase activity; cell cycle; protein amino acid phosphorylation; protein serine/threonine kinase activity; signal transduction; transferase activity
AK000814	8681	phospholipase A2, group IVB (cytosolic)	biological_process	arachidonic acid metabolism; calcium ion binding; calcium-dependent phospholipase A2 activity; calcium-dependent phospholipid binding; calcium-mediated signaling; cytosol; extracellular; glycerophospholipid catabolism; inflammatory response; parturition; phospholipase activity
AK027377	59352	leucine-rich repeat-containing G protein-coupled receptor 6	biological_process	G-protein coupled receptor protein signaling pathway; integral to membrane; protein-hormone receptor activity
AK092864	64759	tensin-like SH2 domain-containing 1	biological_process	intracellular signaling cascade; phosphoprotein phosphatase activity; protein amino acid dephosphorylation
AY046538	8601	regulator of G-protein signalling 20	biological_process	GTPase activator activity; membrane; protein binding; regulation of G-protein coupled receptor protein signaling pathway; signal transducer activity; signal transduction
BC000043	379	ADP-ribosylation factor 4-like	biological_process	ARF small monomeric GTPase activity; GTP binding; nucleus; protein secretion; small GTPase mediated signal transduction
BC000493	1819	developmentally regulated GTP binding protein 2	biological_process	GTP binding; cell growth and/or maintenance; signal transduction
BC002392	4354	membrane protein, palmitoylated 1, 55 kDa	biological_process	guanylate kinase activity; integral to plasma membrane; membrane; membrane fraction; protein binding; signal transduction
BC002823	10758	chromosome 6 open reading frame 4	biological_process	cellular_component unknown; intracellular signaling cascade; molecular_function unknown
BC006314	1134	cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle)	biological_process	acetylcholine receptor activity; extracellular ligand-gated ion channel activity; integral to membrane; ion channel activity; ion transport; muscle contraction; nicotinic acetylcholine-activated cation-selective channel activity; nicotinic acetylcholine-gated receptor-channel complex; signal transduction; synaptic transmission
BC007588	90864	SPRY domain-containing SOCS box protein SSB-3	biological_process	intracellular signaling cascade
BC011645	6236	Ras-related associated with diabetes	biological_process	GTP binding; calmodulin binding; small GTPase mediated signal transduction; small monomeric GTPase activity
BC014942	89941	ras homolog gene family, member T2	biological_process	GTP binding; calcium ion binding; small GTPase mediated signal transduction; small monomeric GTPase activity
BC016758	3059	hematopoietic cell-specific Lyn substrate 1	biological_process	DNA-directed RNA polymerase II, core complex; intracellular signaling cascade; regulation of transcription, DNA-dependent; transcription factor activity
BC019047	8742	tumor necrosis factor (ligand) superfamily, member 12	biological_process	angiogenesis; apoptosis; immune response; induction of apoptosis; integral to plasma membrane; signal transduction; tumor necrosis factor receptor binding
L12002	3676	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	biological_process	cell-matrix adhesion; integral to membrane; integrin complex; integrin-mediated signaling pathway; protein binding; receptor activity

(continued)

Continued.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
U66579	2843	G protein-coupled receptor 20	biological_process	G-protein coupled receptor protein signaling pathway; integral to plasma membrane; rhodopsin-like receptor activity
U68032	1235	chemokine (C-C motif) receptor 6	biological_process	C-C chemokine receptor activity; G-protein coupled receptor protein signaling pathway; antimicrobial humoral response (sensu Vertebrata); cell motility; cellular defense response; chemotaxis; cytosolic calcium ion concentration elevation; humoral immune response; integral to plasma membrane; receptor activity; rhodopsin-like receptor activity; signal transduction
U94905	8525	diacylglycerol kinase, zeta 104 kDa	biological_process	ATP binding; diacylglycerol binding; diacylglycerol kinase activity; intracellular signaling cascade; nucleus; protein kinase C activation; transferase activity
U96919	3631	inositol polyphosphate-4-phosphatase, type I, 107 kDa	biological_process	signal transduction
X15002	3484	insulin-like growth factor binding protein 1	biological_process	cell growth and/or maintenance; extracellular space; insulin-like growth factor binding; regulation of cell growth; signal transduction
X52773	6256	retinoid X receptor, alpha	biological_process	nucleus; receptor activity; regulation of transcription, DNA-dependent; retinoid-X receptor activity; signal transduction; steroid binding; steroid hormone receptor activity; transcription coactivator activity; transcription factor activity; vitamin metabolism
X72886	7301	TYRO3 protein tyrosine kinase	biological_process	ATP binding; cell adhesion; integral to plasma membrane; protein amino acid phosphorylation; protein binding; receptor activity; receptor signaling protein tyrosine kinase activity; signal transduction; transferase activity; transmembrane receptor protein tyrosine kinase activity
X81892	10149	G protein-coupled receptor 64	biological_process	G-protein coupled receptor activity; integral to plasma membrane; membrane; neuropeptide signaling pathway; receptor activity; spermatogenesis
Z83845	10454	mitogen-activated protein kinase kinase kinase 7 interacting protein 1	biological_process	activation of MAPKKK; catalytic activity; enzyme activator activity; protein binding; transforming growth factor beta receptor, cytoplasmic mediator activity

## Receptor signaling protein activity.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB002309	9472	A kinase (PRKA) anchor protein 6	molecular_function	nuclear membrane; protein kinase A anchoring activity; protein targeting; sarcoplasmic reticulum
AF120324	26230	T-cell lymphoma invasion and metastasis 2	molecular_function	guanyl-nucleotide exchange factor activity; intracellular signaling cascade; protein binding; receptor signaling protein activity
AF141901	22941	SH3 and multiple ankyrin repeat domains 2	molecular_function	GKAP/Homer scaffold activity; cellular_component unknown; intracellular signaling cascade; protein binding
AF420474	5597	mitogen-activated protein kinase 6	molecular_function	ATP binding; MAP kinase activity; cell cycle; protein amino acid phosphorylation; protein serine/threonine kinase activity; signal transduction; transferase activity
X72886	7301	TYRO3 protein tyrosine kinase	molecular_function	ATP binding; cell adhesion; integral to plasma membrane; protein amino acid phosphorylation; protein binding; receptor activity; receptor signaling protein tyrosine kinase activity; signal transduction; transferase activity; transmembrane receptor protein tyrosine kinase activity
Z83845	10454	mitogen-activated protein kinase kinase kinase 7 interacting protein 1	molecular_function	activation of MAPKKK; catalytic activity; enzyme activator activity; protein binding; transforming growth factor beta receptor, cytoplasmic mediator activity

## Organismal movement.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AF336797	3782	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3	biological_process	calcium-activated potassium channel activity; calmodulin binding; integral to membrane; ion channel activity; ion transport; membrane fraction; neurogenesis; potassium ion transport; small conductance calcium-activated potassium channel activity; synaptic transmission; voltage-gated potassium channel complex
AJ295237	57053	cholinergic receptor, nicotinic, alpha polypeptide 10	biological_process	extracellular ligand-gated ion channel activity; integral to membrane; ion channel activity; ion transport; neurotransmitter receptor activity; nicotinic acetylcholine-activated cation-selective channel activity; receptor binding; regulation of cell proliferation; synaptic transmission; synaptic transmission, cholinergic
AK027243	582	Bardet-Biedl syndrome 1	biological_process	visual perception
BC006314	1134	cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle)	biological_process	acetylcholine receptor activity; extracellular ligand-gated ion channel activity; integral to membrane; ion channel activity; ion transport; muscle contraction; nicotinic acetylcholine-activated cation-selective channel activity; nicotinic acetylcholine-gated receptor-channel complex; signal transduction; synaptic transmission
BC014140	583	Bardet-Biedl syndrome 2	biological_process	biological_process unknown; cell-matrix adhesion; cellular_component unknown; integrin complex; molecular_function unknown; visual perception
Z26491	1312	catechol-O-methyltransferase	biological_process	catechol O-methyltransferase activity; catecholamine metabolism; integral to membrane; magnesium ion binding; microsome; neurotransmitter catabolism; soluble fraction; transferase activity

## Detection of external stimulus.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AF107403	9381	otoferlin	biological_process	biological_process unknown; cellular_component unknown; integral to membrane; molecular_function unknown; perception of sound
AF236083	10886	G protein-coupled receptor 74	biological_process	G-protein coupled receptor activity; G-protein coupled receptor protein signaling pathway; cell growth and/or maintenance; detection of abiotic stimulus; integral to plasma membrane; neuropeptide receptor activity; rhodopsin-like receptor activity
AK027243	582	Bardet-Biedl syndrome 1	biological_process	visual perception
BC012126	23562	claudin 14	biological_process	integral to membrane; perception of sound; protein complex assembly; structural molecule activity; tight junction
BC014140	583	Bardet-Biedl syndrome 2	biological_process	biological_process unknown; cell-matrix adhesion; cellular_component unknown; integrin complex; molecular_function unknown; visual perception
M31013	4627	myosin, heavy polypeptide 9, non-muscle	biological_process	ATP binding; actin binding; calmodulin binding; cellular morphogenesis; motor activity; myosin; non-muscle myosin; perception of sound

**Group 3**

## Regulation of cell cycle.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB000381	2765	GPI anchored molecule like protein	biological_process	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest; apoptosis; extrinsic to membrane; negative regulation of cell proliferation; plasma membrane; regulation of cell cycle
AK074614	3481	insulin-like growth factor 2 (somatomedin A)	biological_process	cell proliferation; development; extracellular; growth factor activity; growth pattern; hormone activity; imprinting; insulin receptor signaling pathway; insulin-like growth factor receptor binding; physiological process; regulation of cell cycle; skeletal development
Y13444	4335	MAX binding protein	biological_process	cell proliferation; development; negative regulation of cell proliferation; nucleus; regulation of cell cycle; regulation of transcription, DNA-dependent; transcription coactivator activity; transcription corepressor activity; transcription factor activity; transcription from Pol II promoter

## Metabolism.

Uniqid	Locuslink	Gene name	Classification	Locuslink Classifications
AB014564	23277	KIAA0664 protein	biological_process	protein biosynthesis; translation initiation factor activity
AK011657	20383	splicing factor, arginine/serine-rich 3 (SRp20)	biological_process	RNA binding; mRNA splice site selection; spliceosome complex
AK074614	3481	insulin-like growth factor 2 (somatomedin A)	biological_process	cell proliferation; development; extracellular; growth factor activity; growth pattern; hormone activity; imprinting; insulin receptor signaling pathway; insulin-like growth factor receptor binding; physiological process; regulation of cell cycle; skeletal development
AL390164	54815	p66 alpha	biological_process	DNA methylation; NuRD complex; negative regulation of transcription, DNA-dependent; nucleus; protein binding, bridging; transcription factor activity; transcriptional repressor activity
BC013964	252969	nei like 2 ( <i>E. coli</i> )	biological_process	DNA repair
S72422	1743	dihydrolipoamide S-succinyltransferase (E2 component of 2-oxo-glutarate complex)	biological_process	acetyl-CoA biosynthesis; acyltransferase activity; alpha-ketoglutarate dehydrogenase complex (sensu Eukarya); dihydrolipoyllysine-residue succinyltransferase activity; energy pathways; metabolism; mitochondrion; oxoglutarate dehydrogenase complex; transferase activity; tricarboxylic acid cycle
U14550	10610	sialyltransferase 7 ((alpha-N-acetylneuraminyl-2,3-beta-galactosyl-1,3)-N-acetyl galactosaminide alpha-2,6-sialyltransferase) B	biological_process	Golgi apparatus; integral to membrane; protein amino acid glycosylation; sialyltransferase activity; transferase activity, transferring glycosyl groups
X85019	2590	UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyl-transferase 2 (GalNAc-T2)	biological_process	O-linked glycosylation; polypeptide N-acetylgalactosaminyltransferase activity; transferase activity
Y13444	4335	MAX binding protein	biological_process	cell proliferation; development; negative regulation of cell proliferation; nucleus; regulation of cell cycle; regulation of transcription, DNA-dependent; transcription coactivator activity; transcription corepressor activity; transcription factor activity; transcription from Pol II promoter



Biosynthesis.

Uniqid	Locuslink	Gene name	Classification	Locuslink Classifications
AB014564	23277	KIAA0664 protein	biological_process	protein biosynthesis; translation initiation factor activity
S72422	1743	dihydrolipoamide S-succinyltransferase (E2 component of 2-oxo-glutarate complex)	biological_process	acetyl-CoA biosynthesis; acyltransferase activity; alpha-ketoglutarate dehydrogenase complex (sensu Eukarya); dihydrolipoyllysine-residue succinyltransferase activity; energy pathways; metabolism; mitochondrion; oxoglutarate dehydrogenase complex; transferase activity; tricarboxylic acid cycle
U14550	10610	sialyltransferase 7 ((alpha-N-acetylneuraminyl-2,3-beta-galactosyl-1,3)-N-acetyl galactosaminide alpha-2,6-sialyltransferase) B	biological_process	Golgi apparatus; integral to membrane; protein amino acid glycosylation; sialyltransferase activity; transferase activity, transferring glycosyl groups
X85019	2590	UDP-N-acetyl-alpha-D-galactosamine:-polypeptide N-acetylgalactosaminyl-transferase 2 (GalNAc-T2)	biological_process	O-linked glycosylation; polypeptide N-acetylgalactosaminyltransferase activity; transferase activity

Protein biosynthesis.

Uniqid	Locuslink	Gene name	Classification	Locuslink Classifications
AB014564	23277	KIAA0664 protein	biological_process	protein biosynthesis; translation initiation factor activity
U14550	10610	sialyltransferase 7 ((alpha-N-acetylneuraminyl-2,3-beta-galactosyl-1,3)-N-acetyl galactosaminide alpha-2,6-sialyltransferase) B	biological_process	Golgi apparatus; integral to membrane; protein amino acid glycosylation; sialyltransferase activity; transferase activity, transferring glycosyl groups
X85019	2590	UDP-N-acetyl-alpha-D-galactosamine polypeptide N-acetylgalactosaminyl-transferase 2 (GalNAc-T2)	biological_process	O-linked glycosylation; polypeptide N-acetylgalactosaminyltransferase activity; transferase activity

## Cell cycle.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB000381	2765	GPI anchored molecule like protein	biological_process	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest; apoptosis; extrinsic to membrane; negative regulation of cell proliferation; plasma membrane; regulation of cell cycle
AK074614	3481	insulin-like growth factor 2 (somatomedin A)	biological_process	cell proliferation; development; extracellular; growth factor activity; growth pattern; hormone activity; imprinting; insulin receptor signaling pathway; insulin-like growth factor receptor binding; physiological process; regulation of cell cycle; skeletal development
Y13444	4335	MAX binding protein	biological_process	cell proliferation; development; negative regulation of cell proliferation; nucleus; regulation of cell cycle; regulation of transcription, DNA-dependent; transcription coactivator activity; transcription corepressor activity; transcription factor activity; transcription from Pol II promoter

## Nucleobase nucleoside, nucleotide and nucleic acid metabolism.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AK011657	20383	splicing factor, arginine/serine-rich 3 (SRp20)	biological_process	RNA binding; mRNA splice site selection; spliceosome complex
AK074614	3481	insulin-like growth factor 2 (somatomedin A)	biological_process	cell proliferation; development; extracellular; growth factor activity; growth pattern; hormone activity; imprinting; insulin receptor signaling pathway; insulin-like growth factor receptor binding; physiological process; regulation of cell cycle; skeletal development
AL390164	54815	p66 alpha	biological_process	DNA methylation; NuRD complex; negative regulation of transcription, DNA-dependent; nucleus; protein binding, bridging; transcription factor activity; transcriptional repressor activity
BC013964	252969	nei like 2 (E. coli)	biological_process	DNA repair
Y13444	4335	MAX binding protein	biological_process	cell proliferation; development; negative regulation of cell proliferation; nucleus; regulation of cell cycle; regulation of transcription, DNA-dependent; transcription coactivator activity; transcription corepressor activity; transcription factor activity; transcription from Pol II promoter

## Macromolecule biosynthesis.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB014564	23277	KIAA0664 protein	biological_process	protein biosynthesis; translation initiation factor activity
U14550	10610	sialyltransferase 7 ((alpha-N-acetylneuraminyl-2,3-beta-galactosyl-1,3)-N-acetyl galactosaminide alpha-2, 6-sialyltransferase) B	biological_process	Golgi apparatus; integral to membrane; protein amino acid glycosylation; sialyltransferase activity; transferase activity, transferring glycosyl groups
X85019	2590	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 2 (GalNAc-T2)	biological_process	O-linked glycosylation; polypeptide N-acetylgalactosaminyltransferase activity; transferase activity

## Group 5

## Metal ion binding.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB024742	9331	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 6	molecular_function	Golgi apparatus; carbohydrate metabolism; galactosyltransferase activity; integral to membrane; magnesium ion binding; manganese ion binding; transferase activity, transferring glycosyl groups
AC004668	30013	S100 calcium binding protein A11 pseudogene	molecular_function	calcium ion binding
AD001527	5438	polymerase (RNA) II (DNA directed) polypeptide I, 14.5 kDa	molecular_function	DNA-directed RNA polymerase II, core complex; DNA-directed RNA polymerase activity; RNA elongation; nucleus; regulation of transcription, DNA-dependent; transcription; transcription factor activity; transcription from Pol II promoter; transferase activity; zinc ion binding
AD001527	826	calpain, small subunit 1	molecular_function	calcium ion binding; calpain activity; positive regulation of cell proliferation
BC012822	308	annexin A5	molecular_function	blood coagulation; calcium ion binding; calcium-dependent phospholipid binding; negative regulation of coagulation; phospholipase inhibitor activity
BC017054	10797	methylene tetrahydrofolate dehydrogenase (NAD + dependent), methenyltetrahydrofolate cyclohydrolase	molecular_function	electron transporter activity; folic acid and derivative biosynthesis; hydrolase activity; magnesium ion binding; methenyltetrahydrofolate cyclohydrolase activity; methylenetetrahydrofolate dehydrogenase (NAD+) activity; mitochondrion; one-carbon compound metabolism; oxidoreductase activity
D49387	22949	leukotriene B4 12-hydroxydehydrogenase	molecular_function	alcohol dehydrogenase activity, zinc-dependent; cytoplasm; leukotriene metabolism; oxidoreductase activity; zinc ion binding
Z29064	2060	epidermal growth factor receptor pathway substrate 15	molecular_function	calcium ion binding

Cytoplasm.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB024742	9331	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 6	cellular_component	Golgi apparatus; carbohydrate metabolism; galactosyltransferase activity; integral to membrane; magnesium ion binding; manganese ion binding; transferase activity, transferring glycosyl groups
AF010472	5066	peptidylglycine alpha-amidating monooxygenase	cellular_component	peptide amidation; peptidylglycine monooxygenase activity; secretory granule
AF049895	1666	2,4-dienoyl CoA reductase 1, mitochondrial	cellular_component	2,4-dienoyl-CoA reductase (NADPH) activity; metabolism; mitochondrion; oxidoreductase activity
AF281070	1981	eukaryotic translation initiation factor 4 gamma, 1	cellular_component	RNA binding; eukaryotic translation initiation factor 4F complex; regulation of protein biosynthesis; regulation of translational initiation; translation initiation factor activity
AL050179	7168	tropomyosin 1 (alpha)	cellular_component	actin binding; biological_process unknown; cellular_component unknown; cytoskeleton; molecular_function unknown; muscle development; muscle thin filament tropomyosin; regulation of heart rate; regulation of muscle contraction; structural constituent of cytoskeleton; structural constituent of muscle
AY007112	55737	vacuolar protein sorting 35 (yeast)	cellular_component	cytosol; intracellular protein transport; protein binding; protein transporter activity; retrograde transport, endosome to Golgi
BC000747	23404	homolog of Yeast RRP4 (ribosomal RNA processing 4), 3'-5'-exoribonuclease	cellular_component	3'-5'-exoribonuclease activity; 7S RNA binding; cytoplasm; exonuclease activity; exosome (RNase complex); hydrolase activity; nucleus; rRNA processing
BC005923	4257	microsomal glutathione S-transferase 1	cellular_component	glutathione transferase activity; membrane; microsome; mitochondrion; transferase activity
BC009772	51601	lipoyltransferase 1	cellular_component	ligase activity; lipid metabolism; mitochondrion; protein modification
BC012333	6309	sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, fungal)-like	cellular_component	C-5 sterol desaturase activity; endoplasmic reticulum; integral to membrane; lathosterol oxidase activity; lipid metabolism; oxidoreductase activity; sterol biosynthesis
BC017054	10797	methylene tetrahydrofolate dehydrogenase (NAD+ dependent), methenyltetrahydrofolate cyclohydrolase	cellular_component	electron transporter activity; folic acid and derivative biosynthesis; hydrolase activity; magnesium ion binding; methenyltetrahydrofolate cyclohydrolase activity; methylenetetrahydrofolate dehydrogenase (NAD+) activity; mitochondrion; one-carbon compound metabolism; oxidoreductase activity
BC017883	26589	mitochondrial ribosomal protein L46	cellular_component	mitochondrion; structural constituent of ribosome
BC018049	5217	profilin 2	cellular_component	actin binding; actin cytoskeleton; actin cytoskeleton organization and biogenesis; cytoskeleton organization and biogenesis; phosphatidylinositol-4,5-bisphosphate binding; regulation of actin polymerization and/or depolymerization
D49387	22949	leukotriene B4 12-hydroxydehydrogenase	cellular_component	alcohol dehydrogenase activity, zinc-dependent; cytoplasm; leukotriene metabolism; oxidoreductase activity; zinc ion binding
L40383	9320	thyroid hormone receptor interactor 12	cellular_component	cellular_component unknown; cytosol; intracellular; ligase activity; protein ubiquitination; thyroid hormone receptor binding; ubiquitin-protein ligase activity
M19735	3074	hexosaminidase B (beta polypeptide)	cellular_component	beta-N-acetylhexosaminidase activity; carbohydrate metabolism; glycosphingolipid metabolism; hydrolase activity, acting on glycosyl bonds; lysosome

## Oxidoreductase activity.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AF010472	5066	peptidylglycine alpha-amidating monooxygenase	molecular_function	peptide amidation; peptidylglycine monooxygenase activity; secretory granule
AF049895	1666	2,4-dienoyl CoA reductase 1, mitochondrial	molecular_function	2,4-dienoyl-CoA reductase (NADPH) activity; metabolism; mitochondrion; oxidoreductase activity
BC012333	6309	sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, fungal)-like	molecular_function	C-5 sterol desaturase activity; endoplasmic reticulum; integral to membrane; lathosterol oxidase activity; lipid metabolism; oxidoreductase activity; sterol biosynthesis
BC017054	10797	methylene tetrahydrofolate dehydrogenase (NAD+ dependent), methenyltetrahydrofolate cyclohydrolase	molecular_function	electron transporter activity; folic acid and derivative biosynthesis; hydrolase activity; magnesium ion binding; methenyltetrahydrofolate cyclohydrolase activity; methylenetetrahydrofolate dehydrogenase (NAD+) activity; mitochondrion; one-carbon compound metabolism; oxidoreductase activity
D49387	22949	leukotriene B4 12-hydroxydehydrogenase	molecular_function	alcohol dehydrogenase activity, zinc-dependent; cytoplasm; leukotriene metabolism; oxidoreductase activity; zinc ion binding

## Oxidoreductase activity.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AF010472	5066	peptidylglycine alpha-amidating monooxygenase	molecular_function	peptide amidation; peptidylglycine monooxygenase activity; secretory granule
AF049895	1666	2,4-dienoyl CoA reductase 1, mitochondrial	molecular_function	2,4-dienoyl-CoA reductase (NADPH) activity; metabolism; mitochondrion; oxidoreductase activity
BC012333	6309	sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, fungal)-like	molecular_function	C-5 sterol desaturase activity; endoplasmic reticulum; integral to membrane; lathosterol oxidase activity; lipid metabolism; oxidoreductase activity; sterol biosynthesis
BC017054	10797	methylene tetrahydrofolate dehydrogenase (NAD+ dependent), methenyltetrahydrofolate cyclohydrolase	molecular_function	electron transporter activity; folic acid and derivative biosynthesis; hydrolase activity; magnesium ion binding; methenyltetrahydrofolate cyclohydrolase activity; methylenetetrahydrofolate dehydrogenase (NAD+) activity; mitochondrion; one-carbon compound metabolism; oxidoreductase activity
D49387	22949	leukotriene B4 12-hydroxydehydrogenase	molecular_function	alcohol dehydrogenase activity, zinc-dependent; cytoplasm; leukotriene metabolism; oxidoreductase activity; zinc ion binding



## Mitochondrion.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AF049895	1666	2,4-dienoyl CoA reductase 1, mitochondrial	cellular_component	2,4-dienoyl-CoA reductase (NADPH) activity; metabolism; mitochondrion; oxidoreductase activity
BC005923	4257	microsomal glutathione S-transferase 1	cellular_component	glutathione transferase activity; membrane; microsome; mitochondrion; transferase activity
BC009772	51601	lipoyltransferase 1	cellular_component	ligase activity; lipid metabolism; mitochondrion; protein modification
BC017054	10797	methylene tetrahydrofolate dehydrogenase (NAD+ dependent), methenyltetrahydrofolate cyclohydrolase	cellular_component	electron transporter activity; folic acid and derivative biosynthesis; hydrolase activity; magnesium ion binding; methenyltetrahydrofolate cyclohydrolase activity; methylenetetrahydrofolate dehydrogenase (NAD+) activity; mitochondrion; one-carbon compound metabolism; oxidoreductase activity
BC017883	26589	mitochondrial ribosomal protein L46	cellular_component	mitochondrion; structural constituent of ribosome

## Calcium ion binding.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AC004668	30013	S100 calcium binding protein A11 pseudogene	molecular_function	calcium ion binding
AD001527	826	calpain, small subunit 1	molecular_function	calcium ion binding; calpain activity; positive regulation of cell proliferation
BC012822	308	annexin A5	molecular_function	blood coagulation; calcium ion binding; calcium-dependent phospholipid binding; negative regulation of coagulation; phospholipase inhibitor activity
Z29064	2060	epidermal growth factor receptor pathway substrate 15	molecular_function	calcium ion binding

## Lipid metabolism.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
BC009772	51601	lipoyltransferase 1	biological_process	ligase activity; lipid metabolism; mitochondrion; protein modification
BC012333	6309	sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, fungal)-like	biological_process	C-5 sterol desaturase activity; endoplasmic reticulum; integral to membrane; lathosterol oxidase activity; lipid metabolism; oxidoreductase activity; sterol biosynthesis
D49387	22949	leukotriene B4 12-hydroxydehydrogenase	biological_process	alcohol dehydrogenase activity, zinc-dependent; cytoplasm; leukotriene metabolism; oxidoreductase activity; zinc ion binding
M19735	3074	hexosaminidase B (beta polypeptide)	biological_process	beta-N-acetylhexosaminidase activity; carbohydrate metabolism; glycosphingolipid metabolism; hydrolase activity, acting on glycosyl bonds; lysosome

## Response to abiotic stimulus.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AF107403	9381	otoferlin	biological_process	biological_process unknown; cellular_component unknown; integral to membrane; molecular_function unknown; perception of sound
AF385628	3576	interleukin 8	biological_process	G-protein coupled receptor protein signaling pathway; angiogenesis; calcium-mediated signaling; cell cycle arrest; cell motility; cell-cell signaling; chemokine activity; chemotaxis; extracellular space; immune response; induction of positive chemotaxis; interleukin-8 receptor binding; intracellular signaling cascade; negative regulation of cell proliferation; neutrophil activation; neutrophil chemotaxis; regulation of cell adhesion; regulation of retroviral genome replication; soluble fraction
BC021093	84641	hypothetical protein FLJ14753	biological_process	integral to membrane; tetracycline transport; tetracycline:hydrogen antiporter activity

## Group 6

## Hydrolase activity.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AL117503	7398	ubiquitin specific protease 1	molecular_function	cysteine-type endopeptidase activity; hydrolase activity; ubiquitin thiolesterase activity; ubiquitin-dependent protein catabolism; ubiquitin-specific protease activity
BC000346	8446	dual specificity phosphatase 11 (RNA/RNP complex 1-interacting)	molecular_function	RNA binding; RNA processing; hydrolase activity; nucleus; protein amino acid dephosphorylation; protein-tyrosine-phosphatase activity
BC015505	11325	DEAD (Asp-Glu-Ala-Asp) box polypeptide 42	molecular_function	ATP binding; ATP-dependent helicase activity; hydrolase activity; nucleic acid binding
BC022445	5685	proteasome (prosome, macropain) subunit, alpha type, 4	molecular_function	endopeptidase activity; proteasome core complex (sensu Eukarya); ubiquitin-dependent protein catabolism
BC022865	539	ATP synthase, H + transporting, mitochondrial F1 complex, O subunit (oligomycin sensitivity conferring protein)	molecular_function	ATP biosynthesis; hydrogen ion transporter activity; hydrolase activity; membrane fraction; mitochondrion; proton transport; proton-transporting ATP synthase complex (sensu Eukarya); transporter activity
J03004	2771	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 2	molecular_function	G-protein coupled receptor protein signaling pathway; GTP binding; heterotrimeric G-protein GTPase activity; negative regulation of adenylate cyclase activity; response to nutrients; signal transducer activity; signal transduction

## Cell fraction.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AF059274	10675	chondroitin sulfate proteoglycan 5 (neuroglycan C)	cellular_component	Golgi apparatus; Golgi vesicle membrane; growth factor activity; integral to plasma membrane; intracellular transport; membrane fraction; neurogenesis; protein binding
BC022865	539	ATP synthase, H + transporting, mitochondrial F1 complex, O subunit (oligomycin sensitivity conferring protein)	cellular_component	ATP biosynthesis; hydrogen ion transporter activity; hydrolase activity; membrane fraction; mitochondrion; proton transport; proton-transporting ATP synthase complex (sensu Eukarya); transporter activity
Y07909	2012	epithelial membrane protein 1	cellular_component	cell death; cell growth; cell proliferation; development; epidermal differentiation; integral to membrane; membrane fraction

Group 6

Cytosol.				
Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB055804	5204	prefoldin 5	cellular_component	chaperone activity; nucleus; prefoldin complex; protein folding; regulation of transcription, DNA-dependent; transcription corepressor activity
AC004263	6175	ribosomal protein, large, P0	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
AL050366	8473	O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase)	cellular_component	O-linked glycosylation; acetylglucosaminyltransferase activity; cytosol; nucleus; protein binding; response to nutrients; signal transduction; transferase activity, transferring glycosyl groups
D10755	29673	proteasome (prosome, macropain) subunit, alpha type 6	cellular_component	RNA binding; cytosol; endopeptidase activity; hydrolase activity; peptidase activity; proteasome core complex (sensu Eukarya); ubiquitin-dependent protein catabolism
X06423	65136	ribosomal protein S8	cellular_component	RNA binding; cytosolic ribosome (sensu Eukarya); cytosolic small ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribonucleoprotein complex; ribosome; ribosome biogenesis; structural constituent of ribosome
X80699	19941	ribosomal protein L26	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome

Large ribosomal subunit.				
Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AC004263	6175	ribosomal protein, large, P0	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
AF083248	51121	ribosomal protein L26-like 1	cellular_component	intracellular; large ribosomal subunit; protein biosynthesis; structural constituent of ribosome
X80699	19941	ribosomal protein L26	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome

## Cytosolic ribosome (sensu Eukarya).

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AC004263	6175	ribosomal protein, large, P0	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
X06423	65136	ribosomal protein S8	cellular_component	RNA binding; cytosolic ribosome (sensu Eukarya); cytosolic small ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribonucleoprotein complex; ribosome; ribosome biogenesis; structural constituent of ribosome
X80699	19941	ribosomal protein L26	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome

## Ribosome.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AC004263	6175	ribosomal protein, large, P0	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
AF083248	51121	ribosomal protein L26-like 1	cellular_component	intracellular; large ribosomal subunit; protein biosynthesis; structural constituent of ribosome
X06423	65136	ribosomal protein S8	cellular_component	RNA binding; cytosolic ribosome (sensu Eukarya); cytosolic small ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribonucleoprotein complex; ribosome; ribosome biogenesis; structural constituent of ribosome
X80699	19941	ribosomal protein L26	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome

## Structural constituent of ribosome.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AC004263	6175	ribosomal protein, large, P0	molecular_function	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
AF083248	51121	ribosomal protein L26-like 1	molecular_function	intracellular; large ribosomal subunit; protein biosynthesis; structural constituent of ribosome
X06423	65136	ribosomal protein S8	molecular_function	RNA binding; cytosolic ribosome (sensu Eukarya); cytosolic small ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribonucleoprotein complex; ribosome; ribosome biogenesis; structural constituent of ribosome
X80699	19941	ribosomal protein L26	molecular_function	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	molecular_function	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome

Cytoplasm.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB055804	5204	prefoldin 5	cellular_component	chaperone activity; nucleus; prefoldin complex; protein folding; regulation of transcription, DNA-dependent; transcription corepressor activity
AC004263	6175	ribosomal protein, large, P0	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
AF083248	51121	ribosomal protein L26-like 1	cellular_component	intracellular; large ribosomal subunit; protein biosynthesis; structural constituent of ribosome
AL050366	8473	O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine: polypeptide-N-acetylglucosaminyl transferase)	cellular_component	O-linked glycosylation; acetylglucosaminyltransferase activity; cytosol; nucleus; protein binding; response to nutrients; signal transduction; transferase activity, transferring glycosyl groups
AL110183	522	ATP synthase, H <sup>+</sup> transporting, mitochondrial F0 complex, subunit F6	cellular_component	energy pathways; hydrogen ion transporter activity; membrane fraction; mitochondrial inner membrane; mitochondrion; proton transport; transporter activity
BC005936	55967	13 kDa differentiation-associated protein	cellular_component	NADH dehydrogenase (ubiquinone) activity; NADH dehydrogenase activity; mitochondrion; oxidoreductase activity; respiratory gaseous exchange
BC009677	93974	ATPase inhibitory factor 1	cellular_component	energy pathways; enzyme inhibitor activity; mitochondrion
BC012035	7095	translocation protein 1	cellular_component	cotranslational membrane targeting; endoplasmic reticulum; integral to membrane; protein transport; protein transporter activity; receptor activity
BC013873	1069	centrin, EF-hand protein, 2	cellular_component	calcium ion binding; centrosome; cytokinesis; mitosis
BC015766	87	actinin, alpha 1	cellular_component	actin binding; actin cytoskeleton; calcium ion binding; structural constituent of cytoskeleton
BC017448	9158	fibroblast growth factor (acidic) intracellular binding protein	cellular_component	fibroblast growth factor binding; fibroblast growth factor receptor signaling pathway; membrane fraction; mitochondrion; nucleus; protein binding
D10755	29673	proteasome (prosome, macropain) subunit, alpha type 6	cellular_component	RNA binding; cytosol; endopeptidase activity; hydrolase activity; peptidase activity; proteasome core complex (sensu Eukarya); ubiquitin-dependent protein catabolism
D87666	3320	heat shock 90 kDa protein 1, alpha	cellular_component	ATP binding; biological_process unknown; cellular_component unknown; chaperone activity; cytoplasm; heat shock protein activity; molecular_function unknown; protein folding
M25246	7431	vimentin	cellular_component	cytoplasm; intermediate filament; protein binding; structural constituent of cytoskeleton
X06423	65136	ribosomal protein S8	cellular_component	RNA binding; cytosolic ribosome (sensu Eukarya); cytosolic small ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribonucleoprotein complex; ribosome; ribosome biogenesis; structural constituent of ribosome
X80699	19941	ribosomal protein L26	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome
Y00672	7175	translocated promoter region (to activated MET oncogene)	cellular_component	cytoplasm; nuclear pore; nucleus; protein-nucleus import; transport



## Structural molecule activity.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AC004263	6175	ribosomal protein, large, P0	molecular_function	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
AF083248	51121	ribosomal protein L26-like 1	molecular_function	intracellular; large ribosomal subunit; protein biosynthesis; structural constituent of ribosome
BC015766	87	actinin, alpha 1	molecular_function	actin binding; actin cytoskeleton; calcium ion binding; structural constituent of cytoskeleton
M25246	7431	vimentin	molecular_function	cytoplasm; intermediate filament; protein binding; structural constituent of cytoskeleton
X06423	65136	ribosomal protein S8	molecular_function	RNA binding; cytosolic ribosome (sensu Eukarya); cytosolic small ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribonucleoprotein complex; ribosome; ribosome biogenesis; structural constituent of ribosome
X80699	19941	ribosomal protein L26	molecular_function	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	molecular_function	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome

## Cytosolic large ribosomal subunit (sensu Eukarya).

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AC004263	6175	ribosomal protein, large, P0	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
X80699	19941	ribosomal protein L26	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome

## Protein binding.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB055804	5204	prefoldin 5	molecular_function	chaperone activity; nucleus; prefoldin complex; protein folding; regulation of transcription, DNA-dependent; transcription corepressor activity
AK093927	5534	protein phosphatase 3 (formerly 2B), regulatory subunit B, 19kDa, alpha isoform (calcineurin B, type I)	molecular_function	biological_process unknown; calcineurin complex; calcium ion binding; calcium-dependent protein serine/threonine phosphatase activity; calmodulin inhibitor activity
AL050366	8473	O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase)	molecular_function	O-linked glycosylation; acetylglucosaminyltransferase activity; cytosol; nucleus; protein binding; response to nutrients; signal transduction; transferase activity, transferring glycosyl groups
BC001062	65987	potassium channel tetramerisation domain containing 14	molecular_function	membrane; potassium ion transport; protein binding; voltage-gated potassium channel activity; voltage-gated potassium channel complex
BC015766	87	actinin, alpha 1	molecular_function	actin binding; actin cytoskeleton; calcium ion binding; structural constituent of cytoskeleton
BC017201	3490	insulin-like growth factor binding protein 7	molecular_function	extracellular; insulin-like growth factor binding; negative regulation of cell proliferation; regulation of cell growth
BC017245	11047	adhesion regulating molecule 1	molecular_function	cell adhesion; integral to plasma membrane; membrane fraction; protein binding
BC017448	9158	fibroblast growth factor (acidic) intracellular binding protein	molecular_function	fibroblast growth factor binding; fibroblast growth factor receptor signaling pathway; membrane fraction; mitochondrion; nucleus; protein binding
L11369	5097	protocadherin 1 (cadherin-like 1)	molecular_function	calcium ion binding; cell adhesion; cell-cell signaling; homophilic cell adhesion; integral to plasma membrane; intercellular junction; membrane; neurogenesis; protein binding
M25246	7431	vimentin	molecular_function	cytoplasm; intermediate filament; protein binding; structural constituent of cytoskeleton

## Chromatin modification.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
BC024391	20922	suppressor of Ty 4 homolog ( <i>S. cerevisiae</i> )	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
BC024391	20923	suppressor of Ty 4 homolog 2 ( <i>S. cerevisiae</i> )	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
X86691	1108	chromodomain helicase DNA binding protein 4	biological_process	ATP binding; ATP-dependent DNA helicase activity; chromatin; chromatin assembly/disassembly; chromatin binding; chromatin modification; chromosome organization and biogenesis (sensu Eukarya); nucleus; regulation of transcription from Pol II promoter; zinc ion binding

Protein biosynthesis.				
Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AC004263	6175	ribosomal protein, large, P0	biological_process	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
AF083248	51121	ribosomal protein L26-like 1	biological_process	intracellular; large ribosomal subunit; protein biosynthesis; structural constituent of ribosome
AL050366	8473	O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase)	biological_process	O-linked glycosylation; acetylglucosaminyltransferase activity; cytosol; nucleus; protein binding; response to nutrients; signal transduction; transferase activity, transferring glycosyl groups
X06423	65136	ribosomal protein S8	biological_process	RNA binding; cytosolic ribosome (sensu Eukarya); cytosolic small ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribonucleoprotein complex; ribosome; ribosome biogenesis; structural constituent of ribosome
X80699	19941	ribosomal protein L26	biological_process	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	biological_process	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome

Protein metabolism.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB055804	5204	prefoldin 5	biological_process	chaperone activity; nucleus; prefoldin complex; protein folding; regulation of transcription, DNA-dependent; transcription corepressor activity
AC004263	6175	ribosomal protein, large, P0	biological_process	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
AF083248	51121	ribosomal protein L26-like 1	biological_process	intracellular; large ribosomal subunit; protein biosynthesis; structural constituent of ribosome
AF083420	8428	serine/threonine kinase 24 (STE20 homolog, yeast)	biological_process	ATP binding; protein amino acid phosphorylation; protein serine/threonine kinase activity; protein-tyrosine kinase activity; signal transduction; transferase activity
AL050366	8473	O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase)	biological_process	O-linked glycosylation; acetylglucosaminyltransferase activity; cytosol; nucleus; protein binding; response to nutrients; signal transduction; transferase activity, transferring glycosyl groups
BC012035	7095	translocation protein 1	biological_process	cotranslational membrane targeting; endoplasmic reticulum; integral to membrane; protein transport; protein transporter activity; receptor activity
D10755	29673	proteasome (prosome, macropain) subunit, alpha type 6	biological_process	RNA binding; cytosol; endopeptidase activity; hydrolase activity; peptidase activity; proteasome core complex (sensu Eukarya); ubiquitin-dependent protein catabolism
D87666	3320	heat shock 90 kDa protein 1, alpha	biological_process	ATP binding; biological_process unknown; cellular_component unknown; chaperone activity; cytoplasm; heat shock protein activity; molecular_function unknown; protein folding
X06423	65136	ribosomal protein S8	biological_process	RNA binding; cytosolic ribosome (sensu Eukarya); cytosolic small ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribonucleoprotein complex; ribosome; ribosome biogenesis; structural constituent of ribosome
X80699	19941	ribosomal protein L26	biological_process	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	biological_process	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome
Y00672	7175	translocated promoter region (to activated MET oncogene)	biological_process	cytoplasm; nuclear pore; nucleus; protein-nucleus import; transport

## Cell fraction.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AL110183	522	ATP synthase, H <sup>+</sup> transporting, mitochondrial F0 complex, subunit F6	cellular_component	energy pathways; hydrogen ion transporter activity; membrane fraction; mitochondrial inner membrane; mitochondrion; proton transport; transporter activity
AY055759	1604	decay accelerating factor for complement (CD55, Cromer blood group system)	cellular_component	complement activation, classical pathway; integral to plasma membrane; membrane; soluble fraction
BC017245	11047	adhesion regulating molecule 1	cellular_component	cell adhesion; integral to plasma membrane; membrane fraction; protein binding
BC017448	9158	fibroblast growth factor (acidic) intracellular binding protein	cellular_component	fibroblast growth factor binding; fibroblast growth factor receptor signaling pathway; membrane fraction; mitochondrion; nucleus; protein binding
X92689	2591	UDP-N-acetyl-alpha-D-galactosamine polypeptide N-acetylgalactosaminyltransferase 3 (GalNAc-T3)	cellular_component	carbohydrate metabolism; integral to membrane; membrane fraction; polypeptide N-acetylgalactosaminyltransferase activity; transferase activity

## DNA packaging.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
BC024391	20922	suppressor of Ty 4 homolog ( <i>S. cerevisiae</i> )	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
BC024391	20923	suppressor of Ty 4 homolog 2 ( <i>S. cerevisiae</i> )	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
X86691	1108	chromodomain helicase DNA binding protein 4	biological_process	ATP binding; ATP-dependent DNA helicase activity; chromatin; chromatin assembly/disassembly; chromatin binding; chromatin modification; chromosome organization and biogenesis (sensu Eukarya); nucleus; regulation of transcription from Pol II promoter; zinc ion binding

## Chromosome organization and biogenesis (sensu Eukarya).

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
BC024391	20922	suppressor of Ty 4 homolog ( <i>S. cerevisiae</i> )	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
BC024391	20923	suppressor of Ty 4 homolog 2 ( <i>S. cerevisiae</i> )	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
X86691	1108	chromodomain helicase DNA binding protein 4	biological_process	ATP binding; ATP-dependent DNA helicase activity; chromatin; chromatin assembly/disassembly; chromatin binding; chromatin modification; chromosome organization and biogenesis (sensu Eukarya); nucleus; regulation of transcription from Pol II promoter; zinc ion binding

## Establishment and/or maintenance of chromatin architecture.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
BC024391	20922	suppressor of Ty 4 homolog ( <i>S. cerevisiae</i> )	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
BC024391	20923	suppressor of Ty 4 homolog 2 ( <i>S. cerevisiae</i> )	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
X86691	1108	chromodomain helicase DNA binding protein 4	biological_process	ATP binding; ATP-dependent DNA helicase activity; chromatin; chromatin assembly/disassembly; chromatin binding; chromatin modification; chromosome organization and biogenesis (sensu Eukarya); nucleus; regulation of transcription from Pol II promoter; zinc ion binding

## Nuclear organization and biogenesis.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
BC024391	20922	suppressor of Ty 4 homolog ( <i>S. cerevisiae</i> )	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
BC024391	20923	suppressor of Ty 4 homolog 2 ( <i>S. cerevisiae</i> )	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
X86691	1108	chromodomain helicase DNA binding protein 4	biological_process	ATP binding; ATP-dependent DNA helicase activity; chromatin; chromatin assembly/disassembly; chromatin binding; chromatin modification; chromosome organization and biogenesis (sensu Eukarya); nucleus; regulation of transcription from Pol II promoter; zinc ion binding

## Ribonucleoprotein complex.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AC004263	6175	ribosomal protein, large, P0	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome; translational elongation
AF083248	51121	ribosomal protein L26-like 1	cellular_component	intracellular; large ribosomal subunit; protein biosynthesis; structural constituent of ribosome
X06423	65136	ribosomal protein S8	cellular_component	RNA binding; cytosolic ribosome (sensu Eukarya); cytosolic small ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribonucleoprotein complex; ribosome; ribosome biogenesis; structural constituent of ribosome
X80699	19941	ribosomal protein L26	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); cytosolic ribosome (sensu Eukarya); intracellular; protein biosynthesis; ribosome; ribosome biogenesis; structural constituent of ribosome
X82202	81767	ribosomal protein L19	cellular_component	RNA binding; cytosolic large ribosomal subunit (sensu Eukarya); intracellular; protein biosynthesis; ribosome; structural constituent of ribosome



## Calcium ion binding.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AK093927	5534	protein phosphatase 3 (formerly 2B), regulatory subunit B, 19 kDa, alpha isoform (calcineurin B, type I)	molecular_function	biological_process unknown; calcineurin complex; calcium ion binding; calcium-dependent protein serine/threonine phosphatase activity; calmodulin inhibitor activity
BC013873	1069	centrin, EF-hand protein, 2	molecular_function	calcium ion binding; centrosome; cytokinesis; mitosis
BC015766	87	actinin, alpha 1	molecular_function	actin binding; actin cytoskeleton; calcium ion binding; structural constituent of cytoskeleton
L11369	5097	protocadherin 1 (cadherin-like 1)	molecular_function	calcium ion binding; cell adhesion; cell-cell signaling; homophilic cell adhesion; integral to plasma membrane; intercellular junction; membrane; neurogenesis; protein binding

## Regulation of transcription from Pol II promoter.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
BC024391	20922	suppressor of Ty 4 homolog (S. cerevisiae)	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
BC024391	20923	suppressor of Ty 4 homolog 2 (S. cerevisiae)	biological_process	chromatin remodeling; nucleus; regulation of transcription from Pol II promoter; regulation of transcription, DNA-dependent; transcription; transcription factor activity
X86691	1108	chromodomain helicase DNA binding protein 4	biological_process	ATP binding; ATP-dependent DNA helicase activity; chromatin; chromatin assembly/disassembly; chromatin binding; chromatin modification; chromosome organization and biogenesis (sensu Eukarya); nucleus; regulation of transcription from Pol II promoter; zinc ion binding

## Chaperone activity.

Uniqid	Locuslink	Gene name	Classification	Locuslink classifications
AB055804	5204	prefoldin 5	molecular_function	chaperone activity; nucleus; prefoldin complex; protein folding; regulation of transcription, DNA-dependent; transcription corepressor activity
D87666	3320	heat shock 90 kDa protein 1, alpha	molecular_function	ATP binding; biological_process unknown; cellular_component unknown; chaperone activity; cytoplasm; heat shock protein activity; molecular_function unknown; protein folding
U10149	3306	heat shock 70 kDa protein 2	molecular_function	ATP binding; heat shock protein activity; male meiosis; spermatid development