Table 2. List of genes up- or down-regulated common to the FFCHs+adenomas and carcinomas

Accession No.	Gene title	Gene symbol	Non-tumor	FFCH+adenoma	Carcinoma
≥5 fold, 16 genes					
BI279202	similar to Ovostatin-2		1 ± 0.44	8.10 ± 9.86[a]	11.95 ± 6.39
BM386415	NK-3 transcription factor, locus 1 (predicted)	Nkx3-1_predicted	1 ± 0.22	5.96 ± 2.11	6.40 ± 3.65
AI070944	Hypothetical gene supported by NM_022858	Foxq1	1 ± 0.35	7.30 ± 3.55	6.34 ± 0.58
BI286077	similar to LOC284861 protein		1 ± 0.48	4.73 ± 1.23	4.59 ± 0.96
BF417890	Antigen p97 (predicted)		1 ± 0.40	5.19 ± 1.41	5.09 ± 1.09
AA945643	Chitinase 3-like 1	Chi3l1	1 ± 0.42	8.82 ± 4.04	11.31 ± 3.18
AF202115.1	Ceruloplasmin	Cp	1 ± 0.36	4.98 ± 1.70	5.68 ± 0.91
(NM_012532.1)			(1 ± 0.41	7.64 ± 4.27	9.73 ± 2.42)
(AF202115.1)			(1 ± 0.35	5.67 ± 1.93	7.53 ± 1.28)
BE105713	EST		1 ± 0.27	6.21 ± 4.08	9.03 ± 2.22
NM_019225.1	Solute carrier family 1, member 3	Slc1a3	1 ± 0.37	10.83 ± 8.32	22.08 ± 7.53
BF415436	Protocadherin 9 (predicted)		1 ± 0.23	10.60 ± 10.39	18.97 ± 5.96
NM_024157.1	Complement factor I	Cfi	1 ± 0.35	5.11 ± 1.60	6.90 ± 1.56
AI555053	Monooxigenase, DBH-like 1 (predicted)	Moxd1_predicted	1 ± 0.45	4.93 ± 0.77	6.21 ± 0.84
BF389287	EST		1 ± 0.37	6.94 ± 2.65	8.24 ± 0.11
AI072459	similar to Eph receptor A4		1 ± 0.19	6.70 ± 8.02	7.66 ± 2.21
L07316.1	Dipeptidase 1 (renal)	Dpep1	1 ± 0.27	9.15 ± 2.31	12.26 ± 1.40
NM_016994.1	Complement component 3	C3	1 ± 0.58	4.11 ± 2.28	9.33 ± 1.74
≤0.2 fold, 2 genes					
AW527736	similar to class alpha glutathione S-transferase		1 ± 0.30	0.16 ± 0.06	0.16 ± 0.02
NM_022407.2	Aldehyde dehydrogenase family 1, member A1	Aldh1A1	1 ± 0.15	0.19 ± 0.04	0.16 ± 0.01

[a]: x fold, vs non-tumor

Abbreviation: FFCH, focal folicullar cell hyperplasia.

Table 3. List of genes up- or down-regulated only in FFCHs+adenomas

Accession No.	Gene title	Gene symbol	Non-tumor	FFCH+Adenom
≥5 fold, 1 gene				
NM_012589.1	Interleulin 6	Il-6	1 ± 0.51	5.31 ± 2.98[a]
≤0.2 fold, 5 genes				
AW526088	Plasticity related gene 1		1 ± 0.16	0.24 ± 0.16
NM_021653.1	1	Dio1	1 ± 0.06	0.19 ± 0.06
M11597.1	Calcitonin/calcitonin-related polypeptide, alpha	Calca	1 ± 0.09	0.17 ± 0.09
(NM_017338.1)			(1 ± 0.12	0.17 ± 0.12
NM_053856.1	Secretogranin 3	Scg3	1 ± 0.04	0.12 ± 0.04
NM_019278.1	protein 18	Resp18	1 ± 0.06	0.15 ± 0.06

[a]: x fold, vs non-tumor

Abbreviations: FFCH, focal folicullar cell hyperplasia

Table 4. List of genes up-or down-regulated only in carcinomas

Accession No.	Gene title	Gene symb	Non-tumor	FCH+Adenom	Carcinoma
≥5 fold, 22genes					
BM391164	1810059A23		1 ± 0.18	3.70 ± 2.55[a]	5.03 ± 3.51
	Fibromodulin	Fmod	1 ± 0.33	4.04 ± 2.90	5.82 ± 1.87
AI179953	protein beta 2	Gjb2	1 ± 0.21	5.30 ± 4.53	5.06 ± 1.04
NM_012960.1	Gamma-glutamyl hydrolase	Ggh	1 ± 0.12	5.11 ± 5.18	5.96 ± 1.21
BI290053	isomerase	Idi1	1 ± 0.25	5.41 ± 2.88	5.65 ± 0.59
BF552084	EST		1 ± 0.15	4.15 ± 3.15	5.77 ± 1.03
BE106398	EST		1 ± 0.17	3.55 ± 2.10	5.48 ± 1.84
BI302694	BC022692		1 ± 0.14	4.40 ± 3.62	5.77 ± 1.02
NM_017074.1	CTL target antigen	Cth	1 ± 0.20	4.20 ± 0.76	5.54 ± 1.23
AI101583	Transient receptor potential cation channel, subfamily V, member 6	Trpv6	1 ± 0.33	3.34 ± 1.18	4.62 ± 0.81
BI285347	Complement component 4a, Complement component 4, gene 2	C4a, C4-2	1 ± 0.40	2.70 ± 1.15	5.17 ± 0.90
NM_012522.1	Cystathionine beta synthase	Cbs	1 ± 0.32	3.04 ± 1.16	5.07 ± 1.03
BI284441	Collectin sub-family member 12	Colec12	1 ± 0.14	3.65 ± 1.39	6.25 ± 1.23
AF394783.1	Sulfotransferase family 1A, phenol-preferring, member 1	Slut1A1	1 ± 0.21	2.34 ± 0.72	4.44 ± 1.05
BG668993	Integrin beta 8 (predicted)		1 ± 0.22	2.17 ± 0.72	4.37 ± 1.38
AI045116	EST		1 ± 0.16	3.89 ± 1.35	6.38 ± 0.86
NM_053923.1	Phosphatidylinositol 3-kinase, C2 domain containing, gamma	Pik3c2g	1 ± 0.19	4.29 ± 0.30	5.34 ± 0.91
AW142962	Prolactin receptor	Prlr	1 ± 0.13	3.04 ± 0.20	5.09 ± 1.18
BE107296	EST		1 ± 0.24	3.16 ± 1.00	5.89 ± 1.13
AI171987	EST		1 ± 0.23	4.02 ± 1.14	8.79 ± 0.62
AI412189	polypeptide)	Igha	1 ± 0.34	2.65 ± 0.71	6.63 ± 1.49
AI716125	Complement component 2	C2	1 ± 0.19	3.56 ± 0.46	4.62 ± 0.36
≤0.2 fold, 12 genes					
AA945955	Osteoglycin (predicted)	Ogn_predict	1 ± 0.18	0.30 ± 0.15	0.20 ± 0.05
BG377887	Glial cell line derived neurotrophic factor family receptor alpha 3	Gfra3	1 ± 0.15	0.21 ± 0.03	0.19 ± 0.04
BF413643	similar to von Willebrand factor A domain containing 1 (predicted)		1 ± 0.13	0.40 ± 0.13	0.18 ± 0.06
BE107590	Similar to KIAA0605 gene product (predicted)		1 ± 0.26	0.45 ± 0.19	0.18 ± 0.07
NM_012935.1	Crystallin, alpha B	Cryab	1 ± 0.12	0.22 ± 0.04	0.15 ± 0.03
NM_053594.1	Protein tyrosine phosphatase, receptor type, R	Ptprr	1 ± 0.12	0.30 ± 0.05	0.20 ± 0.04
NM_012829.1	Cholecystokinin	Cck	1 ± 0.14	0.26 ± 0.05	0.17 ± 0.03
AI070324	EST		1 ± 0.20	0.32 ± 0.06	0.17 ± 0.02
AI501394	Peptidylprolyl isomerase B	Ppib	1 ± 0.34	0.27 ± 0.05	0.15 ± 0.04
BF389753	EST		1 ± 0.17	0.23 ± 0.04	0.14 ± 0.03
BI279587	EST		1 ± 0.14	0.42 ± 0.06	0.20 ± 0.02
BF283398	Chemokine (C-X-C motif) ligand 12	Cxcl12	1 ± 0.17	0.43 ± 0.10	0.10 ± 0.07

[a]: x fold, vs non-tumor

Abbreviations: FFCH, focal folicullar cell hyperplasia

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UTILIZATION OF A ONE-DIMENSIONAL SCORE FOR SURVEYING CHEMICAL-INDUCED CHANGES IN EXPRESSION LEVELS OF MULTIPLE BIOMARKER GENE SETS USING A LARGE-SCALE TOXICOGENOMICS DATABASE

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ABSTRACT — A large-scale toxicogenomcis database has now been constructed in the Toxicogenomics Project in Japan (TGP). To facilitate the analytical procedures for such large-scale microarray data, we developed a simple one-dimensional score, named TGP1 which expresses the trend of the changes in expression of biomarker genes as a whole. To evaluate the usefulness of the TGP1 score, microarray data of rat liver and rat hepatocytes deposited in the TGP database were scored for three biomarker gene sets, i.e., carcinogenesis-related, PPARα-regulated and glutathione depletion-related gene sets. The TGP1 scoring system gave reasonable results, i.e., the scores for carcinogenesis-related genes were high in omeprazole-, chlorpromazine-, hexachlorobenzene-, sulfasalazine- and Wy-14,643-treated rat livers, that for PPARα-regulated genes were high in clofibrate-, Wy-14,643-, gemfibrozil-, benzbromarone- and aspirin-treated rat livers as well as rat hepatocytes, and for glutathione deficiency-related genes were high in omeprazole-, bromobenzene-, acetaminophen- and coumarin-treated rat liver. We concluded that the TGP1 score is useful for surveying the expression changes in multiple biomarker gene sets for a large-scale toxicogenomics database, which would reduce the time of doing conventional multivariate statistical analysis. In addition, the TGP1 score can be applied to screening of compatible biomarker gene sets between rat liver and rat hepatocytes, like PPARα-regulated gene sets, which will allow us to develop an appropriate in vitro system for drug safety assessment in vivo.

KEY WORDS: Toxicogenomics, Database, Scoring system, Liver, Rat

INTRODUCTION

Toxicogenomics has been considered to be a promising methodology for understanding the molecular mechanisms of toxicity, and this has been proven by a number of studies (Kiyosawa *et al.*, 2004b; Sehata *et al.*, 2004; Ito *et al.*, 2006). Toxicogenomics research requires a high-quality microarray database that covers a sufficient number of well-studied compounds, and such databases are being developed for both public and commercial use (Boverhof and Zacharewski, 2006). The Toxicogenomics Project in Japan (TGP) has been conducted by the collaborative research of 15 pharmaceutical companies, the National Institute of Health Science and the National Institute of Biomedical Innovation, and is a five-year project started from 2002 (Takashima *et al.*, 2006; Urushidani and Nagao, 2005). The TGP database is a toxicogenomics-oriented data-

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base that consists of microarray data of rat liver, rat hepatocytes and human hepatocytes, as well as traditional toxicological data for 150 compounds. The large-scale TGP database is expected to be useful for characterizing the chemical-induced molecular dynamics and for evaluating and predicting the potential risk of chemical toxicity at early stages of drug development.

Specific gene sets whose mRNA levels are correlated with certain toxicological phenotypes, or toxicogenomics biomarkers, are useful for evaluating the toxicological significance from microarray data. For example, previous reports demonstrated that certain gene sets could be applied for evaluating a chemical-induced glutathione deficiency or risk of acetaminophen-type hepatotoxicity (Kiyosawa *et al.*, 2004a), a chemical-induced phospholipidosis not only in rodent but also in the human case (Sawada *et al.*, 2005), and evaluation of the carcinogenic potential of the chemicals (Ellinger-Ziegelbauer *et al.*, 2004). Such candidate biomarkers have been rapidly accumulated. The significance of the toxicogenoimics database will grow synergistically with accumulation of toxicogenomics biomarker information.

When using the toxicogenomics database, one of the major obstacles is its gigantic data size. Furthermore, it becomes more complex as the toxicogenomics biomarker knowledge accumulates. Multivariate statistical techniques such as hierarchical clustering, k-means clustering, self-organizing map or principal component analysis are usually applied for analyzing the microarray data (Kaminski and Friedman, 2002; Draghici, 2003). Although such techniques provide the general characteristics of gene expression profiles rather intuitively, they are not suitable for high-throughput analysis when a series of biomarker gene sets is to be analyzed at the same time. One simple solution is to circumvent the time-consuming analytical procedure by utilizing a one-dimensional score, which reflects the level of gene expression changes for certain biomarker gene sets. The calculated scores for many samples can be presented in the multiple biomarker gene sets simultaneously, so it becomes easy to capture the toxicological endpoints that should be focused on for further detailed analysis. In the present study, we have developed a score that reflects the level of chemical-induced gene expression changes for certain biomarker gene sets in our large-scale TGP database. The score is calculated from the fold change value of each gene, calculated by dividing the mean signal of the chemical-treated group by that of the vehicle-treated group, and therefore is easy to calculate and interpret results. The usefulness of the presented score was verified in three biomarker gene sets.

MATERIALS AND METHODS

Chemicals

Thirty-eight chemicals used for the data analysis are listed in Table 1, in which the chemical name, manufacturer, highest dosage and vehicle used in the study are described. In our standard protocol, all the drugs were administered in three dose levels, i.e., high, middle (1/3 of the high dose), and low (1/10 of the high dose). In the present study, however, the data of the high dose are exclusively shown for simplicity. In certain cases (Fig. 3), the results of other dose levels are also exhibited in order to show dose-dependency.

Animal treatment

Six-week old male Sprague-Dawley rats (Charles River Japan, Inc., Kanagawa, Japan) consisted of five animals per group and were used for the in-life study. The detailed study information is the same as in the literature (Takashima *et al.*, 2006). Rats were sacrificed at 24 hr after a single dosing of chemicals. Liver was removed at necropsy, and soaked in RNAlater® (Ambion Inc., Austin, TX, USA) to prevent RNA degradation. We affirm that experimental protocols for both the animal and hepatocyte studies were reviewed and approved by the Ethics Review Committee for Animal Experimentation of the National Institute of Health Science.

Hepatocytes treatment

Hepatocytes were isolated from 6-week-old male Sprague-Dawley rats under sodium pentobarbital (120 mg/kg, ip) and anesthetized by a modified two-step collagenase perfusion method. The liver was perfused via the portal vein for 10 min with divalent cation-free, EGTA (0.5 mM)-supplemented HEPES buffered Hank's balanced salt solution followed by a 10-min perfusion with HEPES (10 mM)-buffered normal Hank's balanced salt solution containing soybean trypsin inhibitor (Sigma, T-2011, 0.05 g/L) and collagenase (WAKO 034-10533, 0.5 g/L) at the flow rate of 10 - 30 ml/min. The isolated cells were washed three times by 50 g for 1 min to obtain a parenchymal cell-enriched pellet. Hepatocytes were not used when their viability assessed by trypan blue exclusion was lower than 70%. The cells were seeded into collagen-coated six-well plates (BD BioCoat™ Collagen I Cellware,

Table 1. Chemicals.

ID	Chemicals (abbreviation)	Manufacturer	*in vivo*		*in vitro*	
			Dosage (mg/kg)	Vehicle	Concentration (μM)	Vehicle
001	Acetaminophen (APAP)	Sigma-Aldrich	1000	MC	10000	Medium
002	Isoniazid (INAH)	Sigma-Aldrich	200	MC	10000	Medium
003	Carbon tetrachloride	Sigma-Aldrich	300	OIL	10000	DMSO
004	Phenobarbital	Sigma-Aldrich	100	MC	10000	Medium
005	Valproate sodium (VPA)	Wako Pure Chemical Industries, Ltd.	450	MC	5000	Medium
006	Clofibrate	Wako Pure Chemical Industries, Ltd.	300	OIL	300	DMSO
007	Methotrexate	Wako Pure Chemical Industries, Ltd.	100	MC	3000	Medium
008	Rifampicin	Wako Pure Chemical Industries, Ltd.	200	MC	70	DMSO
009	Alpha-naphthy lisothiocyanate (ANIT)	Kanto Chemical Co., Inc.	15	OIL	200	DMSO
010	Allyl alcohol	Tokyo Chemical Industry Co., Ltd	30	OIL	70	Medium
011	Phenylbutazone	Sigma-Aldrich	200	MC	400	DMSO
012	Omeprazole (OPZ)	Wako Pure Chemical Industries, Ltd.	1000	MC	600	DMSO
013	Ethionine (ET)	Tokyo Chemical Industry Co., Ltd	250	MC	10000	Medium
014	Aspirin (ASA)	Wako Pure Chemical Industries, Ltd.	450	MC	3000	DMSO
015	Indomethacin	Sigma-Aldrich	5	MC	200	DMSO
016	Chlorpromazine (CPZ)	Wako Pure Chemical Industries, Ltd.	45	MC	20	DMSO
017	Thioacetamide	Sigma-Aldrich	45	MC	10000	Medium
018	Carbamazepine	Sigma-Aldrich	300	MC	300	DMSO
019	Diclofenac sodium (DFNa)	CAYMAN / Tokyo Chemical Industry Co., Ltd.	10	MC	400	DMSO
020	Nitrofurantoin	ICN	100	MC	125	DMSO
021	Benzbromarone (BBr)	Sigma-Aldrich	200	MC	100	DMSO
022	Hexachlorobenzene (HCB)	Tokyo Chemical Industry Co., Ltd	300	OIL	30	DMSO
023	Diazepam	Wako Pure Chemical Industries, Ltd.	250	MC	250	DMSO
024	Cyclophosphamide	Sigma-Aldrich	15	MC	2000	Medium
025	Methapyrilene hydrochloride	Sigma-Aldrich	100	MC	600	Medium
026	Phenytoin	Tokyo Chemical Industry Co., Ltd	600	MC	300	DMSO
027	Coumarin (CMA)	Tokyo Chemical Industry Co., Ltd	150	OIL	300	DMSO
028	Allopurinol	Sigma-Aldrich	150	MC	140	DMSO
029	Propylthiouracil	Tokyo Chemical Industry Co., Ltd	100	MC	4000	Medium
030	Wy-14,643 (WY)	Tokyo Chemical Industry Co., Ltd	100	OIL	150	DMSO
031	Gemfibrozil (GFZ)	Sigma-Aldrich	300	OIL	100	DMSO
032	Bromobenzene (BBz)	Tokyo Chemical Industry Co., Ltd	300	OIL	200	DMSO
033	Amiodarone hydrochloride	Sigma-Aldrich	200	MC	7	DMSO
034	Sulfasalazine (SS)	Sigma-Aldrich	1000	MC	150	DMSO
035	Cimetidine	Tokyo Chemical Industry Co., Ltd	1000	MC	300	DMSO
042	Glibenclamide	Sigma-Aldrich	1000	OIL	20	DMSO
045	Perhexiline maleate	Sigma-Aldrich	150	MC	15	DMSO
046	Azathioprine	ICN	30	MC	75	DMSO

BD Bioscience) at a density of 1×10^6 cells/well in 2 ml HMC Bulletkit medium (CAMBREX) supplemented with 10% fetal bovine serum. Following an attachment period of 3 hr, the medium was replaced and kept overnight before drug exposure at 37°C in an atmosphere of 5% CO_2. The test compounds were added to the medium directly or as a 1000× stock solution in dimethylsulfoxide (DMSO). After 2, 8 and 24 hr-exposure, cells were dissolved with RLT buffer (Qiagen) and collected for expression profiling. GeneChip analysis was performed in a duplicated manner for each time and concentration point.

Microarray analysis

The detailed information is described in the previous literature (Takashima *et al.*, 2006). Briefly, 3 liver samples out of 5 samples collected in the animal were used for analysis. Total RNA was isolated using RNeasy Mini Kit with Bio Robot 3000 (Qiagen, Inc., Valencia, CA, USA), and 5 μg of the total RNA was used for cDNA synthesis using T7-(dT)24 oligonucleotide primer (Affymetrix, Inc., Santa Clara, CA, USA) and SuperScript Choice System (Invitrogen, Carlsbad, CA, USA). Biotin-labeled cRNA was synthesized using BioArray High Yield RNA Transcription Labeling Kit (Enzo Diagnostics, Farmingdale, NY, USA). The hybridization cocktail was prepared with 10 μg of fragmented cRNA, and hybridized to RAE 230A GeneChip array (Affymetrix, Inc.) at 45°C for 18 hr. The hybridized GeneChip array was washed and stained by streptavidin-phycoerythrin using Fluidics Station 400 (Affymetrix, Inc.) and scanned by GeneArray Scanner (Affymetrix, Inc.). The scanned image files were analyzed using Microarray Suite ver. 5.0. All the microarray data were scaled by global normalization where the mean signal intensity of each data was adjusted to 500. A heat map representing gene expression levels was created using Spotfire software (Spotfire, Inc., Somerville, MA).

Biomarker gene sets

Three lists of probe sets of RG U34A arrays are selected from the literature whose signals were reported to be increased by certain chemical treatments: i) carcinogenicity-related gene probe sets (Ellinger-Ziegelbauer *et al.*, 2004), ii) PPARα-regulated gene probe sets (Richert *et al.*, 2003), and iii) glutathione deficiency-correlated gene probe sets (Kiyosawa *et al.*, 2004a). The information for the selected probe sets is summarized in Table 2, and lists of the probe sets for each biomarker gene set are presented from Table 3 to Table 5. Since the selected probe sets were those of RG U34A array, the corresponding probe sets of RAE 230A array were determined by selecting "good match probe sets", where the probe sets whose corresponding probe sequences do not overlap between those of RG U34A and RAE 230A array were removed. The "good match probe set" information is provided in the NetAffx Website (Liu *et al.*, 2003).

Calculation of TGP1 score

The TGP1 score was calculated as shown in Fig. 1. Signal log ratio was calculated by dividing the mean signal value of the chemical-treated group by that of corresponding control. First, the sum of the signal log ratios for the used probe sets was calculated, and then divided by the number of probe sets used (Index 1). Next, the sum of squared signal log ratios for the used probe sets was calculated, and then divided by the number of probe sets used (Index 2). Finally, the TGP1 score was calculated by multiplying Index 1 with Index 2.

Individual gene expression analysis

The fold change in carcinogenesis- and glutathione deficiency-related genes is calculated by dividing signal data of the chemical-treated group by mean signal data (n=3 for rat liver and n=2 for rat hepatocytes) of corresponding control. The signal log ratio

Table 2. Summary of biomarker gene sets used in the present study.

	Number of probe sets		
Biomarker	RG U34A	RAE 230A	Reference
Carcinogenicity-related	55	26	Ellinger-Ziegelbauer *et al.*, 2004
PPARα-regulated	30	17	Richert *et al.*, 2003
Glutathione deficiency-related	69	45	Kiyosawa *et al.*, 2004

Three biomarker gene sets whose expression levels were reported to be increased by carcinogens, PPARα activators or glutathione depletors, were selected from the literature, and used for calculation of the TGP1 score. These genes were originally identified using a RG U34A GeneChip array, and the corresponding "good match" probe sets of the RAE 230A GeneChip array were re-selected according to the information provided by the NetAffx website.

Table 3. Carcinogenesis-related gene probe sets.

Affymetrix probe set ID		
RG U34A	RAE 230A	Gene name
X62952_at	1367574_at	Vimentin
L13039_s_at	1367584_at	Annexin A2
M58404_at	1367655_at	Thymosin, beta 10
X13044_at	1367679_at	CD74 antigen
rc_AI169327_at	1367712_at	Tissue inhibitor of metalloproteinase 1
D10729_s_at	1367786_at	Proteosome subunit, beta type 8
M32062_at	1367850_at	Fc receptor, IgG, low affinity III
M34253_at	1368073_at	Interferon regulatory factor 1
AF045464_s_at	1368121_at	Aldo-keto reductase family 7, member A3
M76704_s_at	1368311_at	*O*-6-Methylguanine-DNA methyltransferase
U62940_at	1368552_at	GrpE-like 1
U10894_s_at	1368558_s_at	Allograft inflammatory factor 1
AB010635_s_at	1368905_at	Carboxylesterase 2
U73174_g_at	1369061_at	Glutathione reductase
M31038_at	1369110_x_at	RT1 class Ib, locus Aw2
L12138_at	1369499_at	Thymidylate synthase
D42148_at	1369735_at	Growth arrest specific 6
U02322_s_at	1369783_a_at	Neuregulin 1
rc_AA900505_at	1369958_at	RhoB gene
X60351cds_s_at	1370026_at	Crystallin, alpha B
AJ011969mRNA_at	1370153_at	Growth differentiation factor 15
D10757_at	1370186_at	Proteosome subunit, beta type 9
E00717UTR#1_s_at	1370269_at	CYP1A1
U66470_at	1370361_at	Cell growth regulator with EF hand domain 1
M81855_at	1370583_s_at	ATP-binding cassette, sub-family B (MDR/TAP), member 1
J05181_at	1370688_at	Glutamate-cysteine ligase, catalytic subunit
AF084186_s_at	1370838_s_at	Alpha-spectrin 2
M15562_at	1370883_at	RT1 class II, locus Da
Z12298cds_s_at	1370956_at	Decorin
X56596_at	1371033_at	RT1 class II, locus Bb
S72506_s_at	1371089_at	Glutathione S-transferase Yc2 subunit
M63991_at	1371143_at	Serine (or cysteine) peptidase inhibitor, clade A, member 7
X75207_s_at	1371150_at	Cyclin D1
X51707cds_s_at	1371377_at	Ribosomal protein S19
rc_AI639488_at	1384427_at	Transformed mouse 3T3 cell double minute 2 (predicted)
AF083269_at	1386925_at	Actin-related protein 2/3 complex, subunit 1B
M60921_at	1386994_at	B-cell translocation gene 2, anti-proliferative
L03201_at	1387005_at	Cathepsin S
rc_AA875455_at	1387021_at	Wild-type p53-induced gene 1
AF001898_at	1387022_at	Aldehyde dehydrogenase family 1, member A1
U24174_at	1387391_at	Cyclin-dependent kinase inhibitor 1A
J02679_s_at	1387599_a_at	NAD(P)H dehydrogenase, quinone 1
M26125_at	1387669_a_at	Epoxide hydrolase 1
U17035_s_at	1387969_at	Chemokine (C-X-C motif) ligand 10
X57523_at	1388149_at	Transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)
rc_AA893246_at	1388325_at	ATPase, H+ transporting, V1 subunit D
rc_AA944397_at	1388850_at	Heat shock protein 1, alpha

Table 3. Continued.

U49729_at	none	–
X70871_at	none	–
S56936_s_at	none	–
D38062exon_s_at	none	–
M17412_at	none	–
X59375mRNA_at	none	–
rc_AA894027_at	none	–
rc_AA945082_at	(1371089_at)	–

Probe sets whose signals are reported as increased by treatment of carcinogens in RG U34A GeneChip analysis were selected from the previous literature, and the corresponding probe sets of RAE 230A GeneChip were determined by referring to "good match probe sets" information provided by Affymetrix. Seven probe sets of RG U34A GeneChip did not show any corresponding probe sets in RAE 230A GeneChip, and were presented as "none" in the table. S72506_s_at and rc_AA945082_at are redundant probe sets of RG U34A GeneChip for 1371089_at probe set in RAE 230A GeneChip.

Table 4. PPARα-regulated gene probe sets.

Affymetrix probe set ID		
RG U34A	RAE 230A	Gene name
J02752_at	1367680_at	Acyl-Coenzyme A oxidase 1
AF072411_g_at	1367689_a_at	CD36 antigen
D43623_g_at	1367742_at	Carnitine palmitoyltransferase 1b
K03249_at	1368283_at	Enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase
M57718mRNA_s_at	1368934_at	CYP4A10
V01235_at	1369111_at	Fatty acid binding protein 1, liver
X65296cds_s_at	1370363_at	Carboxylesterase 3
AF044574_g_at	1370818_at	2-4-Dienoyl-Coenzyme A reductase 2
rc_AA893239_at	1371012_at	2-Hydroxyphytanoyl-Coenzyme A lyase
L00320cds_f_at	1371076_at	CYP2B2
U08976_at	1386885_at	Enoyl coenzyme A hydratase 1
rc_AA946368_at	1386901_at	Similar to CD36 antigen
M21208mRNA_s_at	1387123_at	CYP17A1
J02749_g_at	1387783_a_at	Acetyl-Coenzyme A acyltransferase 1
Y09333_g_at	1388210_at	Acyl-CoA thioesterase 1
AB010428_s_at	1398250_at	Acyl-CoA thioesterase 1
AB005743_g_at	none	–
rc_AA924267_s_at	none	–
X07259cds_s_at	none	–
rc_AA925752_at	none	–
K01721mRNA_s_at	none	–
M14972_i_at	none	–
X72792cds_s_at	none	–
rc_AA799489_g_at	none	–
AF072411_at	(1367689_a_at)	–
L46791_at	(1370363_at)	–
J00728cds_f_at	(1371076_at)	–
M11251cds_f_at	(1371076_at)	–
J02749_at	(1387783_a_at)	–
Y09333_at	(1388210_at)	–

Probe sets whose signals are reported to be increased by treatment of PPARα activators in the RG U34A GeneChip analysis were selected from the literature, and the corresponding probe sets of RAE 230A GeneChip were determined by referring to "good match probe sets" information provided by Affymetrix. Eight probe sets of RG U34A GeneChip did not show any corresponding probe sets in RAE 230A GeneChip, and were presented as "none" in the table. Six probe sets of RG U34A GeneChip had redundant probe sets for the same genes, and the corresponding probe sets are presented in brackets in the table.

Table 5. Glutathione deficiency-related gene probe sets.

Affymetrix probe set ID		
RG U34A	RAE 230A	Gene name
rc_AI231807_at	1367559_at	Ferritin light chain
M29358_g_at	1367573_at	Ribosomal protein S6
J02752_at	1367680_at	Acyl-Coenzyme A oxidase 1
X78848cds_f_at	1367774_at	Glutathione *S*-transferase A5
M64733mRNA_s_at	1367784_a_at	Clusterin
AF026554_at	1367815_at	Solute carrier family 5, member 6
rc_AA892821_at	1367843_at	Aldo-keto reductase family 7, member A2
Y17295cds_s_at	1367969_at	Peroxiredoxin 6
U04733_s_at	1367988_at	CYP2C23
M57428_s_at	1368116_a_at	Ribosomal protein S6 kinase, polypeptide 1
AF045464_s_at	1368121_at	Aldo-keto reductase family 7, member A3
K00136mRNA_at	1368180_s_at	LOC494499 protein
AF025670_g_at	1368305_at	Caspase 6
D86745cds_s_at	1368376_at	Nuclear receptor subfamily 0, group B, member 2
U06274_s_at	1368397_at	UDP glycosyltransferase 2 family, polypeptide B4
AF087943_s_at	1368490_at	CD14 antigen
U73174_at	1369061_at	Glutathione reductase
AF068202_at	1369069_at	A kinase (PRKA) anchor protein 1
D13122_f_at	1369588_a_at	ATPase inhibitor
L11007_at	1369950_at	Cyclin-dependent kinase 4
rc_AI233261_i_at	1370030_at	Glutamate cysteine ligase, modifier subunit
rc_AI171506_at	1370067_at	Malic enzyme 1
D16478_at	1370164_at	Hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit
U33500_g_at	1370566_at	retinol dehydrogenase 2
J05132_s_at	1370613_s_at	UDP glycosyltransferase 1 family, polypeptide A1
J05181_at	1370688_at	Glutamate-cysteine ligase, catalytic subunit
M13506_at	1370698_at	Liver UDP-glucuronosyltransferase, phenobarbital-inducible form
AJ001517cds_at	1370772_a_at	Hemochromatosis
S72506_s_at	1371089_at	Glutathione *S*-transferase Yc2 subunit
M20629_s_at	1371100_at	Esterase 2
M11794cds#2_f_at	1371237_a_at	Metallothionein
S70011_g_at	1372715_at	Sideroflexin 1 (predicted)
S55305_s_at	1386866_at	Tyrosine 3-monooxgenase/tryptophan 5-monooxgenase activation protein, gamma polypeptide
L07736_at	1386946_at	Carnitine palmitoyltransferase 1, liver
X04229cds_s_at	1386985_at	Glutathione *S*-transferase, mu 1
M33329_f_at	1387006_at	Rat senescence marker protein 2A gene, exons 1 and 2
E03424cds_s_at	1387221_at	GTP cyclohydrolase 1
M30282_at	1387323_at	Kallikrein B, plasma 1
M95762_at	1387372_at	Solute carrier family 6, member 13
J02679_s_at	1387599_a_at	NAD(P)H dehydrogenase, quinone 1
M26125_at	1387669_a_at	Epoxide hydrolase 1
X55286_g_at	1387848_at	3-Hydroxy-3-methylglutaryl-Coenzyme A reductase
rc_AI072634_at	1388155_at	Keratin complex 1, acidic, gene 18
D17309_at	1398310_at	Aldo-keto reductase family 1, member D1