



HAL
open science

The nuclear receptors pregnane X receptor and constitutive androstane receptor contribute to the impact of fipronil on hepatic gene expression linked to thyroid hormone metabolism.

Béatrice Roques, Julien Leghait, Marlène Z. Lacroix, Frédéric Lasserre, Thierry Pineau, Catherine Viguié, Pascal G.P. Martin

► To cite this version:

Béatrice Roques, Julien Leghait, Marlène Z. Lacroix, Frédéric Lasserre, Thierry Pineau, et al.. The nuclear receptors pregnane X receptor and constitutive androstane receptor contribute to the impact of fipronil on hepatic gene expression linked to thyroid hormone metabolism.. *Biochemical Pharmacology*, 2013, 86 (7), pp.997-1039. 10.1016/j.bcp.2013.08.012 . hal-02650176

HAL Id: hal-02650176

<https://hal.inrae.fr/hal-02650176>

Submitted on 29 May 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



The nuclear receptors pregnane X receptor and constitutive androstane receptor contribute to the impact of fipronil on hepatic gene expression linked to thyroid hormone metabolism[☆]

Béatrice B. Roques^{a,b}, Julien Leghait^{a,b}, Marlène Z. Lacroix^{a,b}, Frédéric Lasserre^{a,c}, Thierry Pineau^{a,c}, Catherine Viguié^{a,b}, Pascal G.P. Martin^{a,c,*}

^aINRA, UMR1331, Toxalim, Research Centre in Food Toxicology, F-31027 Toulouse, France

^bUniversité de Toulouse, ENVT, INP, Toxalim, F-31076 Toulouse, France

^cUniversité de Toulouse, INP, UMR1331, Toxalim, F-31000 Toulouse, France

ARTICLE INFO

Article history:

Received 24 June 2013

Accepted 8 August 2013

Available online 17 August 2013

Keywords:

Fipronil

Thyroid hormone metabolism

Pregnane X receptor

Constitutive androstane receptor

Hepatic metabolism

Rodents

Chemical compounds studied in this article:

Fipronil (PubChem CID: 3352)

Thyroxine (PubChem CID: 5819)

Triiodothyronine (PubChem CID: 5920)

¹³C₆-levothyroxine (PubChem CID:

53442260)

ABSTRACT

Fipronil is described as a thyroid disruptor in rat. Based on the hypothesis that this results from a perturbation of hepatic thyroid hormone metabolism, our goal was to investigate the pathways involved in fipronil-induced liver gene expression regulations. First, we performed a microarray screening in the liver of rats treated with fipronil or vehicle. Fipronil treatment led to the upregulation of several genes involved in the metabolism of xenobiotics, including the cytochrome P450 Cyp2b1, Cyp2b2 and Cyp3a1, the carboxylesterases Ces2 and Ces6, the phase II enzymes Ugt1a1, Sult1b1 and Gsta2, and the membrane transporters Abcc2, Abcc3, Abcg5, Abcg8, Slco1a1 and Slco1a4. Based on a large overlap with the target genes of constitutive androstane receptor (CAR) and pregnane X receptor (PXR), we postulated that these two nuclear receptors are involved in mediating the effects of fipronil on liver gene expression in rodents. We controlled that liver gene expression changes induced by fipronil were generally reproduced in mice, and then studied the effects of fipronil in wild-type, CAR- and PXR-deficient mice. For most of the genes studied, the gene expression modulations were abolished in the liver of PXR-deficient mice and were reduced in the liver of CAR-deficient mice. However, CAR and PXR activation in mouse liver was not associated with a marked increase of thyroid hormone clearance, as observed in rat. Nevertheless, our data clearly indicate that PXR and CAR are key modulators of the hepatic gene expression profile following fipronil treatment which, in rats, may contribute to increase thyroid hormone clearance.

© 2013 The Authors. Published by Elsevier Inc. All rights reserved.

1. Introduction

The broad-spectrum phenylpyrazole insecticide fipronil (5-amino-1-(2,6-dichloro-4-(trifluoromethylphenyl)-4-(trifluoromethylsulfinyl)pyrazole-3-carbonitrile, CAS: 120068-37-3) is widely

used in granular turf products, seed treatments, topical pet care products, gel baits and liquid termiticides in many countries leading to a high rate of potential contamination of the human domestic environment. It belongs to the second generation of insecticides acting at the γ -aminobutyric acid (GABA) receptor as

[☆] This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-No Derivative Works License, which permits non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abbreviations: Abc, ATP-binding cassette; CAR, constitutive androstane receptor; Ces, carboxylesterase; Cyp, cytochrome P450; ESI⁺, electrospray ionization mode; FT3, free triiodothyronine; FT4, free thyroxine; GABA, γ -aminobutyric acid; GEO, gene expression omnibus; GO, gene ontology; Gst, glutathione S-transferase; LOQ, limit of quantification; MRM, multiple reaction monitoring; MRP, multidrug resistance-associated protein; OATP, organic anion-transporting polypeptide; PB, phenobarbital; PCN, pregnenolone-16 α -carbonitrile; Polr2a, RNA polymerase II polypeptide A; PXR, pregnane X receptor; QC, quality control; RT-qPCR, real-time quantitative polymerase chain reaction; Slco, solute carrier organic anion transporter; Sult, sulfotransferase; T3, triiodothyronine; T4, thyroxine; Tbp, TATA-box binding protein; TSH, thyroid-stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine; Ugt, 5'-diphospho (UDP)-glucuronosyltransferase.

* Corresponding author at: INRA, UMR1331, Toxalim, 180 chemin de Tournefeuille, St-Martin-du-Touch, BP 93173, 31027 Toulouse Cedex 3, France. Tel.: +33 5 61 28 55 24; fax: +33 5 61 28 52 44.

E-mail address: Pascal.Martin@toulouse.inra.fr (Pascal G.P. Martin).

a noncompetitive blocker of the GABA-gated chloride channel [1]. It was developed as a substitute for the first generation of insecticidal chloride channel blockers such as the chlorinated cyclodienes and other polychlorocycloalkanes based on its selective toxicity for insects [2], thus lowering the risk for human health.

However, fipronil does not act only on the central nervous system (CNS). Regulatory toxicological evaluations and experimental investigations have shown that fipronil can act as a thyroid disruptor as it decreases plasma thyroid hormone concentrations in rats [3–5]. Because thyroid hormones regulate important biological processes including bone growth and development, cardiac function, CNS development, thermogenesis and hepatic metabolism [6], it is critical to understand the mechanisms underlying the thyroid disrupting effects of fipronil and their potential relevance to humans. From previous studies, we know that fipronil treatment of rats is associated with a marked increase in the clearance of free and total thyroxine (T_4) resulting, at least in part, from an increase in the activity and mRNA expression of two types of phase II hepatic enzymes potentially involved in T_4 elimination, the uridine 5'-diphospho (UDP)-glucuronosyltransferases (UGT) and the sulfotransferases (SULT) [4,5]. Moreover, the main fipronil metabolic pathway, leading to fipronil sulfone formation, is mediated by hepatic cytochrome P450 (CYP) enzymes [7] which are induced in the liver by fipronil treatment [5]. Upon exposure to xenobiotics, the increased expression and activity of hepatic enzymes involved in the metabolism of both xenobiotics and endogenous compounds often results from the activation of "xenosensors" such as the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR). These two nuclear receptors have been shown to regulate the expression of overlapping sets of genes including hepatic phase I enzymes such as CYP2B and CYP3A [8] as well as phase II enzymes [9,10] and membrane transporters [11,12] involved in hepatic xenobiotic and thyroid hormone metabolism. Additionally, fipronil has been shown to be a ligand of the human PXR *in vitro* [13].

Based on this information and on a screening of the impact of fipronil on the rat liver transcriptome presented here, we hypothesized that CAR and/or PXR could mediate the impact of fipronil on hepatic thyroid hormone metabolism in rodents. Based on this hypothesis, the goals of this study were: (1) to document the changes in liver gene expression profile occurring in rats treated with doses of fipronil which induce an increase of thyroid hormone clearance, (2) to identify a set of mouse hepatic transcripts regulated by fipronil in the same manner as in rat, (3) to evaluate in CAR-deficient and PXR-deficient mouse models the contributions of these receptors to the modulation of hepatic gene expression induced by fipronil and (4) to determine if the expression of these receptors was required for fipronil metabolism and fipronil-induced increase of thyroid hormone clearance.

2. Materials and methods

2.1. Animals and treatments

Female Wistar rats (Charles River, L'Abresle, France) and wild-type C57BL/6J male mice (Janvier, Le Genest St Isle, France) were acclimatized for at least 2 weeks to housing conditions (22 ± 2 °C, 12 h light/dark cycle, free access to water and food: A04 diet, Safe, Augy, France). Female rats were chosen for gene expression studies because the effect of fipronil on thyroid hormone clearance has been best described in this gender [4,5]. On the other hand, we used male mice for pharmacokinetic and gene expression studies because (i) most published studies on CAR/PXR activation by xenobiotics have been performed in male mice and (ii) we wanted to avoid the potentially confounding effect of the estrous cycle in the mouse

pharmacokinetic study. This latter point is more critical for the mouse than for the rat pharmacokinetic study because only a single blood sample can be obtained from each mouse for the estimation of the labeled T_4 clearance. *In vivo* studies were conducted under E.U. guidelines for the use and care of laboratory animals. CAR^{-/-} [14] and PXR^{-/-} [11] male mice on a C57BL/6J genetic background are a generous gift from Pr David Moore (Baylor College of Medicine, Houston, TX, USA) and Pr Steven Kliewer (University of Texas Southwestern Medical School, Dallas, TX, USA) respectively. Colony founders were kindly provided by Pr Urs A Meyer (Biozentrum, University of Basel, Basel, Switzerland). Fipronil (95.6% purity, 3B Medical Systems, Libertyville, IL, USA) was administered orally as a suspension through feeding needles, daily for 14 days. Control animals received the vehicle alone (methylcellulose 0.5% (w/v) and Tween 80 0.01% (w/v) for rats and Arabic gum 3% (w/v) for mice). All administrations were performed under a volume of 2 mL/kg of body weight for rats and 2.5–3 mL/kg of body weight for mice. To evaluate T_4 clearance, adult male mice from the different genotypes were administered an intraperitoneal (ip) bolus (10.2 µg/kg) of levothyroxine labeled with a stable isotope ($^{13}C_6$ -LT₄, Isosciences, King of Prussia, PA, USA) dissolved in 10 mM PBS pH = 7.4 containing 0.1% (w/v) bovine serum albumin. The following four different animal experiments were performed:

1. Two- to three-month-old female Wistar rats (202.4 ± 6.0 g body weight) treated with fipronil (3 mg/kg per day) or not were used for microarray ($n = 7$ –8 per group) and qPCR liver gene expression studies ($n = 10$ –14 per group including the animals used for the microarray study).
2. Nine-week-old male C57BL/6J mice (23.3 ± 0.9 g body weight) treated with fipronil (5 mg/kg per day) or not ($n = 8$ per group) were used for qPCR gene expression studies.
3. Fifteen to 22-week-old male C57BL/6J wild-type (30.7 ± 2.1 g body weight), CAR^{-/-} (32.4 ± 4.2 g body weight) and PXR^{-/-} mice (29.4 ± 3.4 g body weight) treated with fipronil (3 mg/kg per day) or not were used to estimate $^{13}C_6$ -LT₄ clearance ($n = 5$ mice/genotype/treatment for 0.25 and 4 h and $n = 10$ mice/genotype/treatment for 2, 8, 12 and 24 h) and for qPCR gene expression studies ($n = 5$ mice/genotype/treatment).
4. Nine-week-old male C57BL/6J wild-type (25.7 ± 1.2 g body weight), CAR^{-/-} (26.3 ± 2.1 g body weight) and PXR^{-/-} mice (26.3 ± 2.1 g body weight) treated with fipronil (10 mg/kg per day) or not were used for qPCR gene expression studies.

Plasma parameters such as fipronil and fipronil sulfone, thyroid hormones or TSH were also obtained from these different studies as described throughout the manuscript.

2.2. Blood and tissue samples

Blood samples were collected in heparinized tubes by aortic puncture following euthanasia (rats) or intracardiac puncture under isoflurane anesthesia (mice). Plasma was prepared by centrifugation ($4000 \times g$, 15 min, +4 °C) and stored at -20 °C until use. Following euthanasia, the liver was promptly removed, weighted, rinsed in ice-cold saline solution, dissected (~100 mg fragments), snap-frozen in liquid nitrogen and kept at -80 °C until use.

2.3. Gene expression studies by RT-qPCR and microarrays

Total RNA was extracted using TRIzol reagent (Life Technologies, Saint Aubin, France). For real-time quantitative polymerase chain reaction (qPCR), 2 µg of total RNA were reverse transcribed with the High Capacity cDNA reverse transcription kit (Life Technologies, Saint Aubin, France). Amplifications with specific primers (Table 1) and SYBR Green fluorescence monitoring (Power SYBR Green PCR

Table 1
Primers used in real-time qPCR experiments.

Gene	DNA sequences	Forward primer (5'-3')	Reverse primer (5'-3')
Rat primers			
<i>Tbp</i>	NM001004198	ccaccaccagctctgagagc	agccaagattcacggtggat
<i>Polr2a</i>	XM002727723	cggcgctctgagtcgc	aacttggggactaatggatcc
<i>Car</i>	NM022941	gagtataaacacgcatactcatatgaaa	ctggcctcagctgcaa
<i>Pxr</i>	NM052980	aggacacgcaccctttg	ccgtccgtgctgctgaat
<i>Cyp2b1</i>	NM001134844	gcactgaaaaagagtgaagctttc	ggaacaattcttggggca
<i>Cyp2b2</i>	NM01198676	ctccgctatggttctctgct	agggatggtggcctgtga
<i>Cyp3a1</i>	NM013105	ttctgcaaaaacttctctccag	ctttagaataatgggtttgtgtgtg
<i>Ces2</i>	NM001044258	gaaacaaattcacgctcggc	gcccagtatctggcctgtg
<i>Ces6</i>	NM144743	ctctgataaactgaggtggtctacaag	catccagataggtggctactgtctt
<i>Ugt1a1</i>	NM012683	cttcagaaaaagccatccca	ccaaagagaaaaaccacgatgc
<i>Sult1b1</i>	NM022513	gaacaaaaatgttctcggagcaag	tgtggagttttctcaagagttcaa
<i>Gsta2</i>	NM017013	ggtaaatatgtccccagaccaa	ccgggtcacgctgttacct
<i>Abcc2</i>	NM012833	cccattatcctgcttga	tcacgccgaattgcaagc
<i>vAbcc3</i>	NM080581	gggagctgggctccaagt	ggaaccagccagcaaa
<i>Abcg5</i>	NM053754	tctcctgtacatcgagagtgcc	cgctccagcagctgtgtt
<i>Abcg8</i>	NM130414	accaactgtggactgctgct	ccggagctcattggaatctg
<i>Slco1a1</i>	NM017111	agattagacttctcactctgtgtcatt	taataacctgattaagttgtcagctc
<i>Slco1a4</i>	NM131906	aaacttctctatgcaaaaatcattaga	tgcagaggaataaatacaaaactaac
<i>Cyp4a1</i>	NM175837	ccactatgacattctgaaacctatgta	tgccagctgttccatttgg
<i>Cd36</i>	NM031561	ggaggctattctcatcgc	tgaagcaatggcttctcttca
<i>Hmgcs2</i>	NM173094	caacgctgccaactggatg	ggcgcttaccacttgggtaga
<i>Thrsp</i>	NM012703	tccatcacatcttaccacc	gggtctcatgcttctctc
Mouse primers			
<i>Tbp</i>	NM013684	acttctgtcaagaatgctgaa	gcagttgtccgtggctctct
<i>Polr2a</i>	NM009089	aagagagtgctgagttcggagctcct	tccgtgttcttgggtatttga
<i>Car</i>	NM009803	gctgcaaggcttctctcaga	cttccagcaaacggcagaca
<i>Pxr</i>	NM010936	agagatcatccctctctgccac	gatctggtctcaataggcaggt
<i>Cyp2b10</i>	NM009999	ttttctgcttctcaacagagaa	atggagctgaaagaaaggaacaac
<i>Cyp3a11</i>	NM007818	tcacacacacagttgttagcgagaa	gtttacagctccatctggtagag
<i>Ces2c</i>	NM145603	cgggctgctgcttctctat	ctgtatgtgtgttctgaggggt
<i>Ces2a</i>	NM001190330	tcctgtgtgacactctcatgtg	ccaaccaggaagtctagccaa
<i>Ugt1a1</i>	NM201645	tcagagaactttatgtagaggtggt	catgtccccagaggcg
<i>Sult1b1</i>	NM019878	ggtgacattgtaataaccactaccct	gggtgataacatctcttcaatttcaac
<i>Gsta2</i>	NM008182	cacactcctctggagctggat	ccccggcattgaagtgtgta
<i>Abcc2</i>	NM013806	cctgaatctcacgcgcta	cagatggagctcagacatgctg
<i>Abcc3</i>	NM029600	tcttctgataaccactcaatgga	gcgggagcttgaacttca
<i>Abcg5</i>	NM031884	tcgccacgctcatttca	gccaaaagagcagcagagaaaata
<i>Abcg8</i>	NM026180	atccattggccacctgtg	gcgtctgtcagctgctg
<i>Slco1a1</i>	NM013797	ggtgcaacacaagaagcagatt	atltggtaggtatgcacatgtaat
<i>Slco1a4</i>	NM030687	tatggaaaatccactgctgagatagtc	aatcaaacaccaatataatccg
<i>Cyp4a10</i>	NM010011	attagtgagagtgaggacagcaacag	tgctgcaaatcgggttgg
<i>Cd36</i>	NM007643	gttaaaacaaagaggtccttacacatacag	cagtgaaaggctcaaatgagc
<i>Hmgcs2</i>	NM008256	tgcaagaaactcgctcaca	aaatagactccagggcaagga
<i>Thrsp</i>	NM009381	aacggagggagcgaagaag	gttgatgcacctcgggctc
<i>Cyp2c29</i>	NM007815	gctcaaaagcctactgtca	catgagtgtaaatcgtctca
<i>Cyp4a14</i>	NM007822	tcagtctatttctggtgctgttc	gagctccttctctcagatggt
<i>Sult1c2</i>	NM026935	aatgggtgatgtagaagtgccg	ggagatgggtctcttaatactctg
<i>Sult1d1</i>	NM016771	gatgacattttgatccacataatcc	cccatgtgtgatcaaatccagta
<i>Sult1e1</i>	NM023135	atttcaacttctccacgggaac	ccaaaactctcaataactcagcatag
<i>Ugt1a2</i>	NM201645	tccttctcttatattccaacctac	gaaaacaacgatccatgctc
<i>Ugt1a6</i>	NM145079	gctactagagcagctgctctaaac	aagtgtctgagcagcaggaagaa
<i>Ugt1a9</i>	NM201644	aagaacatgctatttctctactt	ttctgcatagctcctgggtctga
<i>Ugt2b1</i>	NM152811	gttttctctgggatcaatggttaaa	tttctaccatcaaatccacagaac
<i>Ugt2b5</i>	NM009467	ccattgcaaacctgctaacc	actaacattgaccacagagaaaaga
<i>Abcb1a</i>	NM011076	catgacagatagcttgaagtgtag	ggcaaacatggctctttatcg
<i>Slco1b2</i>	NM020495	gacaaggcactcgcgatgga	gccttgcatatgtagctaatga
<i>Dio1</i>	NM007860	cttggctccacagccga	acgttgtctttaaagccagc
<i>Dio3</i>	NM172119	tttagatttctgtgcatccgc	ttcggctcaggggtggt

Master Mix from Life Technologies, Saint Aubin, France) were performed on a Vii7 instrument (Life Technologies, Saint Aubin, France). qPCR data were normalized by the geometric mean of TATA-box binding protein (*Tbp*) and RNA polymerase II polypeptide A (*Polr2a*) mRNA levels and analyzed using the $2^{-\Delta\Delta Ct}$ method.

Microarray data were obtained from 1 μ g of hepatic total RNA labeled with Cy3 using One-Color Quick Amp Labeling kit (Agilent, Massy, France) and hybridized to Agilent Whole Rat Genome microarrays (4x44K) following the manufacturer's instructions. All experimental details are available in the Gene Expression Omnibus (GEO) database under accession GSE39378.

2.4. Fipronil and fipronil sulfone assay

In rats, plasma fipronil and fipronil sulfone concentrations were determined by HPLC coupled with a UV/MS detection method as previously described [15]. In mice, the extraction method was unchanged but fipronil and fipronil sulfone plasma concentrations were assayed by LC/MS with an Acquity ultra performance liquid chromatography (UPLC[®]) coupled to a Xevo[®] triple quadrupole mass spectrometer (Waters, Milford, MA, USA). The mean within and between day precisions were below 15% for both fipronil (three different quality controls (QC) pools) and fipronil sulfone

(five different QC pools) for the two methods. The limit of quantification (LOQ) was 2.5 ng/mL for both fipronil and fipronil sulfone.

2.5. Thyroid hormone assays

Total T₄, free T₄, total T₃ and free T₃ plasma concentrations were determined using radioimmunoassay kits from Siemens (Coat-a-count[®] kit, Siemens Healthcare Diagnostics, Los Angeles, CA, USA). TSH plasma concentrations were determined using radioimmunoassay kits from Biocode-Hyclon (Massy, France). All the assays were performed according to the manufacturer's instructions. For all assays, the mean within and between day precisions for QC pools were below 15%. The limits of quantification for the total T₄ and the total T₃ assays were validated at 5 ng/mL and 0.2 ng/mL, respectively. The limits of detection of the free T₄, the free T₃ and the TSH assays were set at the lowest value of the standard curves, i.e. 1 pg/mL, 0.52 pg/mL and 2.1 ng/mL, respectively.

¹³C₆-LT₄ was assayed by LC/MS with UPLC[®] coupled to a Xevo[®] triple quadrupole mass spectrometer. Samples spiked with T₄-d₅ as an internal standard were purified by solid phase extraction (SPE) with Strata X-C cartridges (Phenomenex, LePecq, France). The extracted samples were separated on an Acquity BEH[®] RPC18 column (2.1 mm × 100 mm, 1.7 μm, Waters, Milford, MA, USA) with an acidified (0.05% formic acid) H₂O/AcN gradient elution. Samples were ionized in positive electrospray ionization mode (ESI⁺) and detected with the multiple following reaction monitoring (MRM) transitions: ¹³C₆-LT₄ m/z 784 < 738 and T₄-d₅ m/z 783 < 201. The mean within and between day precisions of three QC pools were below 15%. The calibration curve ranged from 0.2 to 100 ng/mL.

2.6. Pharmacokinetic analysis

The pharmacokinetic analysis following ¹³C₆-LT₄ injection was performed by least-square regression analysis using WinNonlin[®] software (WinNonlin[®] 5.3, Pharsight Corporation, CA, USA). The time course of plasma ¹³C₆-LT₄ concentrations were fitted using a

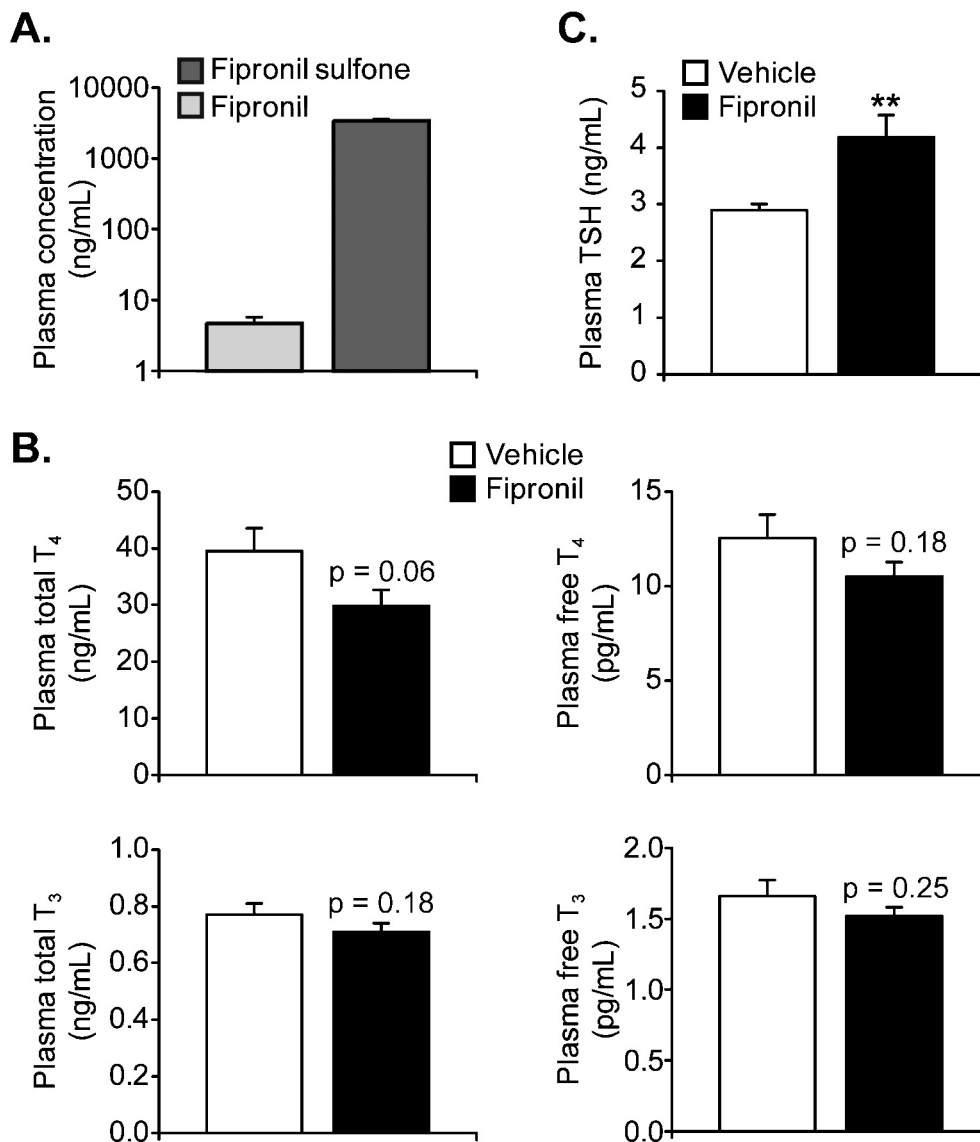


Fig. 1. Plasma concentrations of fipronil and fipronil sulfone and thyroid hormone profiles in rat treated with 3 mg/kg per day of fipronil for 14 days. (A) Fipronil (light gray) and fipronil sulfone (dark gray) concentrations were assayed in plasma samples from female rats treated with fipronil (3 mg/kg per day for 14 days, $n = 10$). (B and C) Total T₄, free T₄, total T₃, free T₃ and TSH (C) concentrations were assayed in plasma samples from female rats treated with fipronil (black bars, 3 mg/kg per day for 14 days, $n = 10$) or the vehicle alone (white bars, $n = 14$). Significantly different from the vehicle group: ** $p < 0.01$.

Table 2
Genes significantly upregulated in rat liver following fipronil treatment (q -value < 0.1).

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p -value	q -value	Description
A_42_P785801	Cyp3a23/3a1	ENSRNOT00000051244	4.08	0.0000	0.0000	ens Cytochrome P450 3A1 [Source:UniProtKB/Swiss-Prot;Acc:P04800] [ENSRNOT00000051244]
A_43_P12924	Abcg5	NM_053754	3.43	0.0000	0.0000	ref Rattus norvegicus ATP-binding cassette, subfamily G (WHITE), member 5 (Abcg5), mRNA [NM_053754]
A_44_P102588	Ces2c	NM_133586	2.76	0.0000	0.0000	ref Rattus norvegicus carboxylesterase 2C (Ces2c), mRNA [NM_133586]
A_44_P242938	Ces2a	NM_144743	2.56	0.0000	0.0000	ref Rattus norvegicus carboxylesterase 2A (Ces2a), mRNA [NM_144743]
A_44_P421809	Ugt2a3	NM_001135869	2.46	0.0000	0.0000	ref Rattus norvegicus UDP glucuronosyltransferase 2 family, polypeptide A3 (Ugt2a3), mRNA [NM_001135869]
A_44_P203532	Slco1a4	NM_131906	2.45	0.0000	0.0000	ref Rattus norvegicus solute carrier organic anion transporter family, member 1a4 (Slco1a4), mRNA [NM_131906]
A_42_P708480	Slco1a4	NM_131906	2.31	0.0000	0.0000	ref Rattus norvegicus solute carrier organic anion transporter family, member 1a4 (Slco1a4), mRNA [NM_131906]
A_43_P16529	Gadd45b	NM_001008321	2.22	0.0000	0.0000	ref Rattus norvegicus growth arrest and DNA-damage-inducible, beta (Gadd45b), mRNA [NM_001008321]
A_44_P446578	Ugt1a1	NM_012683	2.08	0.0000	0.0000	ref Rattus norvegicus UDP glucuronosyltransferase 1 family, polypeptide A1 (Ugt1a1), mRNA [NM_012683]
A_42_P813567	Scd	NM_031841	2.01	0.0038	0.0929	ref Rattus norvegicus stearyl-CoA desaturase (delta-9-desaturase) (Scd), mRNA [NM_031841]
A_44_P541213	LOC681383	NM_001109441	1.99	0.0000	0.0001	ref Rattus norvegicus similar to Protein C10orf11 homolog (LOC681383), mRNA [NM_001109441]
A_44_P320677	Slco1a6	NM_130736	1.95	0.0000	0.0000	ref Rattus norvegicus solute carrier organic anion transporter family, member 1a6 (Slco1a6), mRNA [NM_130736]
A_44_P311322	Cyp2b2	NM_001198676	1.94	0.0000	0.0046	ref Rattus norvegicus cytochrome P450, family 2, subfamily b, polypeptide 2 (Cyp2b2), mRNA [NM_001198676]
A_42_P679814	Cyp3a18	NM_145782	1.89	0.0000	0.0000	ref Rattus norvegicus cytochrome P450, family 3, subfamily a, polypeptide 18 (Cyp3a18), mRNA [NM_145782]
A_44_P109562	Akr1c13	NM_001014240	1.79	0.0008	0.0520	ref Rattus norvegicus aldo-keto reductase family 1, member C13 (Akr1c13), mRNA [NM_001014240]
A_44_P1046787	Rpesp	XM_001063197	1.68	0.0000	0.0115	ref PREDICTED: Rattus norvegicus RPE-spondin (Rpesp), mRNA [XM_001063197]
A_44_P126355	Rbm38	NM_001108965	1.66	0.0001	0.0180	ref Rattus norvegicus RNA binding motif protein 38 (Rbm38), mRNA [NM_001108965]
A_44_P402641	Ugt1a2	NM_201423	1.64	0.0000	0.0000	ref Rattus norvegicus UDP glucuronosyltransferase 1 family, polypeptide A2 (Ugt1a2), mRNA [NM_201423]
A_43_P23115	Inmt	NM_001109022	1.58	0.0000	0.0051	ref Rattus norvegicus indolethylamine N-methyltransferase (Inmt), mRNA [NM_001109022]
A_44_P311323	Cyp2b2	NM_001198676	1.58	0.0001	0.0162	ref Rattus norvegicus cytochrome P450, family 2, subfamily b, polypeptide 2 (Cyp2b2), mRNA [NM_001198676]
A_44_P209854	FQ077343	FQ077343	1.58	0.0001	0.0201	gb FQ077343 Rattus norvegicus brain Sprague–Dawley Rattus norvegicus cDNA 3', mRNA sequence [FQ077343]
A_44_P470794	Abcg8	NM_130414	1.57	0.0000	0.0001	ref Rattus norvegicus ATP-binding cassette, subfamily G (WHITE), member 8 (Abcg8), mRNA [NM_130414]
A_44_P124335	ENSRNOT00000067476	ENSRNOT00000067476	1.54	0.0005	0.0400	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZR8] [ENSRNOT00000067476]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P200539	Cbl11	NM_001108018	1.47	0.0021	0.0763	ref Rattus norvegicus Cas-Br-M (murine) ecotropic retroviral transforming sequence-like 1 (Cbl11), mRNA [NM_001108018]
A_44_P828941	TC596530	TC596530	1.42	0.0000	0.0016	Unknown
A_44_P372277	Ugt2b1	NM_173295	1.41	0.0000	0.0000	ref Rattus norvegicus UDP glucuronosyltransferase 2 family, polypeptide B1 (Ugt2b1), mRNA [NM_173295]
A_44_P432355	Ugt1a2	NM_201423	1.38	0.0000	0.0000	ref Rattus norvegicus UDP glucuronosyltransferase 1 family, polypeptide A2 (Ugt1a2), mRNA [NM_201423]
A_44_P313452	Spink1	NM_152936	1.37	0.0015	0.0666	ref Rattus norvegicus serine peptidase inhibitor, Kazal type 1 (Spink1), mRNA [NM_152936]
A_44_P113879	Slco1a5	NM_030838	1.35	0.0000	0.0000	ref Rattus norvegicus solute carrier organic anion transporter family, member 1a5 (Slco1a5), mRNA [NM_030838]
A_43_P19879	LOC689770	NM_001142304	1.30	0.0012	0.0599	ref Rattus norvegicus similar to osteoclast inhibitory lectin (LOC689770), mRNA [NM_001142304]
A_44_P156850	Akr1c12l1	NM_001135744	1.25	0.0006	0.0452	ref Rattus norvegicus aldo-keto reductase family 1, member C12-like 1 (Akr1c12l1), mRNA [NM_001135744]
A_44_P365286	Aldh1a1	NM_022407	1.22	0.0000	0.0121	ref Rattus norvegicus aldehyde dehydrogenase 1 family, member A1 (Aldh1a1), mRNA [NM_022407]
A_44_P967547	FQ161612	FQ161612	1.18	0.0007	0.0473	gb FQ161612 Rattus norvegicus spleen Sprague–Dawley Rattus norvegicus cDNA clone TL0AEA25YG21 3', mRNA sequence [FQ161612]
A_44_P1002360	Cryl1	NM_175757	1.18	0.0000	0.0011	ref Rattus norvegicus crystallin, lambda 1 (Cryl1), mRNA [NM_175757]
A_44_P311326	Cyp2b2	NM_001198676	1.17	0.0003	0.0300	ref Rattus norvegicus cytochrome P450, family 2, subfamily b, polypeptide 2 (Cyp2b2), mRNA [NM_001198676]
A_43_P11512	Spink3	M35299	1.17	0.0031	0.0876	gb Rat pancreatic secretory trypsin inhibitor-like protein (PSTI) mRNA, complete cds. [M35299]
A_42_P754888	Dlk1	NM_053744	1.15	0.0010	0.0545	ref Rattus norvegicus delta-like 1 homolog (Drosophila) (Dlk1), mRNA [NM_053744]
A_44_P349781	Nfe2	NM_001012224	1.15	0.0022	0.0777	ref Rattus norvegicus nuclear factor, erythroid derived 2 (Nfe2), mRNA [NM_001012224]
A_44_P1037342	Cyp3a9	NM_147206	1.14	0.0003	0.0287	ref Rattus norvegicus cytochrome P450, family 3, subfamily a, polypeptide 9 (Cyp3a9), mRNA [NM_147206]
A_44_P174374	Ephx1	NM_012844	1.12	0.0001	0.0166	ref Rattus norvegicus epoxide hydrolase 1, microsomal (Ephx1), transcript variant 2, mRNA [NM_012844]
A_44_P623578	TC600277	TC600277	1.04	0.0002	0.0274	Unknown
A_44_P370267	Ethe1	NM_001106234	1.04	0.0040	0.0945	ref Rattus norvegicus ethylmalonic encephalopathy 1 (Ethe1), nuclear gene encoding mitochondrial protein, mRNA [NM_001106234]
A_43_P11484	Mme	NM_012608	1.03	0.0001	0.0201	ref Rattus norvegicus membrane metallo-endopeptidase (Mme), mRNA [NM_012608]
A_44_P513360	ENSRNOT00000012985	ENSRNOT00000012985	1.01	0.0034	0.0896	ens Cyclin-dependent kinase inhibitor 3 [Source:UniProtKB/Swiss-Prot;Acc:B2RZ50] [ENSRNOT00000012985]
A_42_P703647	Cda	NM_001108688	0.98	0.0000	0.0011	ref Rattus norvegicus cytidine deaminase (Cda), mRNA [NM_001108688]
A_42_P573296	Hdc	NM_017016	0.97	0.0000	0.0090	ref Rattus norvegicus histidine decarboxylase (Hdc), mRNA [NM_017016]
A_43_P15534	Slco1a1	NM_017111	0.96	0.0000	0.0000	ref Rattus norvegicus solute carrier organic anion transporter family, member 1a1 (Slco1a1), mRNA [NM_017111]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P210202	Polg	NM_053528	0.96	0.0001	0.0149	ref Rattus norvegicus polymerase (DNA directed), gamma (Polg), mRNA [NM_053528]
A_43_P11754	Akr7a3	NM_013215	0.95	0.0002	0.0275	ref Rattus norvegicus aldo-keto reductase family 7, member A3 (aflatoxin aldehyde reductase) (Akr7a3), mRNA [NM_013215]
A_44_P128201	U25282	U25282	0.95	0.0006	0.0418	gb Rattus norvegicus brush border myosin I (BBMI) mRNA, alternatively spliced testis-specific variant, partial cds. [U25282]
A_44_P470892	ENSRNOT00000029787	ENSRNOT00000029787	0.93	0.0001	0.0201	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1LTS8] [ENSRNOT00000029787]
A_44_P210198	Polg	NM_053528	0.90	0.0000	0.0121	ref Rattus norvegicus polymerase (DNA directed), gamma (Polg), mRNA [NM_053528]
A_43_P13967	Gsta2	NM_017013	0.89	0.0010	0.0559	ref Rattus norvegicus glutathione S-transferase A2 (Gsta2), mRNA [NM_017013]
A_44_P371125	Sult1b1	NM_022513	0.89	0.0000	0.0114	ref Rattus norvegicus sulfotransferase family, cytosolic, 1B, member 1 (Sult1b1), mRNA [NM_022513]
A_43_P17939	TC644990	TC644990	0.87	0.0000	0.0001	tc BC007785 SNX8 protein {Homo sapiens} (exp=-1; wgp=0; cg=0), partial (33%) [TC644990]
A_44_P604927	FQ217318	FQ217318	0.86	0.0000	0.0005	gb Rattus norvegicus TL0ACA2YC11 mRNA sequence. [FQ217318]
A_42_P580844	Cdk1	NM_019296	0.84	0.0007	0.0468	ref Rattus norvegicus cyclin-dependent kinase 1 (Cdk1), mRNA [NM_019296]
A_44_P987040	Insig2	ENSRNOT00000003391	0.82	0.0001	0.0135	ens Insulin-induced gene 2 protein [Source:UniProtKB/Swiss-Prot;Acc:Q80UA9] [ENSRNOT00000003391]
A_44_P231243	Insig2	NM_178091	0.82	0.0000	0.0106	ref Rattus norvegicus insulin induced gene 2 (Insig2), mRNA [NM_178091]
A_43_P12233	Sult1b1	NM_022513	0.80	0.0001	0.0138	ref Rattus norvegicus sulfotransferase family, cytosolic, 1B, member 1 (Sult1b1), mRNA [NM_022513]
A_44_P544661	Cyp3a2	NM_153312	0.80	0.0007	0.0484	ref Rattus norvegicus cytochrome P450, family 3, subfamily a, polypeptide 2 (Cyp3a2), mRNA [NM_153312]
A_44_P864923	FQ214383	FQ214383	0.80	0.0001	0.0180	gb Rattus norvegicus TL0AAA41YP21 mRNA sequence. [FQ214383]
A_44_P219628	Ggt1	NM_053840	0.80	0.0002	0.0244	ref Rattus norvegicus gamma-glutamyltransferase 1 (Ggt1), mRNA [NM_053840]
A_44_P808295	TC612707	TC612707	0.76	0.0010	0.0545	tc 2008147A protein RAKb. {Rattus norvegicus} (exp=-1; wgp=-1; cg=-1), partial (13%) [TC612707]
A_44_P115886	RGD1309534	NM_001014206	0.75	0.0005	0.0405	ref Rattus norvegicus similar to RIKEN cDNA 4931406C07 (RGD1309534), mRNA [NM_001014206]
A_43_P11776	Gstm1	NM_017014	0.75	0.0018	0.0716	ref Rattus norvegicus glutathione S-transferase mu 1 (Gstm1), mRNA [NM_017014]
A_44_P1009594	Cyp3a62	NM_001024232	0.75	0.0003	0.0298	ref Rattus norvegicus cytochrome P450, family 3, subfamily a, polypeptide 62 (Cyp3a62), mRNA [NM_001024232]
A_44_P1071390	AY156086	AY156086	0.74	0.0000	0.0032	gb Rattus norvegicus INSIG2a (Insig2) mRNA, 5' untranslated region, alternatively spliced. [AY156086]
A_43_P17743	Pir	NM_001009474	0.74	0.0001	0.0138	ref Rattus norvegicus pirin (iron-binding nuclear protein) (Pir), mRNA [NM_001009474]
A_44_P109455	Gstm2	NM_177426	0.73	0.0003	0.0304	ref Rattus norvegicus glutathione S-transferase mu 2 (Gstm2), mRNA [NM_177426]
A_44_P638952	TC604219	TC604219	0.71	0.0023	0.0777	tc Q6XJV6_MOUSE (Q6XJV6) CD200 cell surface glycoprotein receptor isoform 2, partial (15%) [TC604219]
A_44_P605947	Ces2h	NM_001044258	0.70	0.0000	0.0008	ref Rattus norvegicus carboxylesterase 2H (Ces2h), transcript variant 1, mRNA [NM_001044258]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_43_P11481	Me1	NM_012600	0.69	0.0027	0.0815	ref Rattus norvegicus malic enzyme 1, NADP(+)-dependent, cytosolic (Me1), mRNA [NM_012600]
A_43_P22556	Cidea	NM_001170467	0.69	0.0028	0.0834	ref Rattus norvegicus cell death-inducing DFFA-like effector a (Cidea), mRNA [NM_001170467]
A_44_P1056309	Snx8	NM_001105912	0.66	0.0000	0.0027	ref Rattus norvegicus sorting nexin 8 (Snx8), mRNA [NM_001105912]
A_44_P287250	Oat	NM_022521	0.64	0.0025	0.0792	ref Rattus norvegicus ornithine aminotransferase (Oat), nuclear gene encoding mitochondrial protein, mRNA [NM_022521]
A_44_P452797	RGD1309534	NM_001014206	0.64	0.0009	0.0538	ref Rattus norvegicus similar to RIKEN cDNA 4931406C07 (RGD1309534), mRNA [NM_001014206]
A_44_P899264	Lhfp12	NM_001106402	0.63	0.0009	0.0539	ref Rattus norvegicus lipoma HMGIC fusion partner-like 2 (Lhfp12), mRNA [NM_001106402]
A_43_P16697	TC584707	TC584707	0.63	0.0000	0.0014	tc Q6PGC7_MOUSE (Q6PGC7) Solute carrier family 35, member E3, partial (45%) [TC584707]
A_44_P639283	TC627850	TC627850	0.63	0.0003	0.0298	Unknown
A_44_P1042952	Hrk	NM_057130	0.62	0.0001	0.0198	ref Rattus norvegicus harakiri, BCL2 interacting protein (contains only BH3 domain) (Hrk), mRNA [NM_057130]
A_43_P12029	Rgs5	NM_019341	0.62	0.0001	0.0151	ref Rattus norvegicus regulator of G-protein signaling 5 (Rgs5), mRNA [NM_019341]
A_42_P572725	Abcc3	NM_080581	0.61	0.0032	0.0876	ref Rattus norvegicus ATP-binding cassette, subfamily C (CFTR/MRP), member 3 (Abcc3), mRNA [NM_080581]
A_44_P287842	Cyp2c22	NM_138512	0.61	0.0002	0.0235	ref Rattus norvegicus cytochrome P450, family 2, subfamily c, polypeptide 22 (Cyp2c22), mRNA [NM_138512]
A_44_P898999	A_44_P898999	A_44_P898999	0.61	0.0000	0.0093	Unknown
A_44_P212189	BF291149	BF291149	0.59	0.0000	0.0056	gb EST455740 Rat Gene Index, normalized rat, Rattus norvegicus cDNA Rattus norvegicus cDNA clone RGIIJ36 3' sequence, mRNA sequence [BF291149]
A_42_P585328	Xrcc1	NM_053435	0.59	0.0000	0.0056	ref Rattus norvegicus X-ray repair complementing defective repair in Chinese hamster cells 1 (Xrcc1), mRNA [NM_053435]
A_44_P129053	TC645262	TC645262	0.59	0.0025	0.0792	gb AA848383 EST191143 Normalized rat kidney, Bento Soares Rattus sp. cDNA clone RKIAB83 5' end, mRNA sequence [AA848383]
A_44_P114184	Ccdc80	NM_022543	0.58	0.0005	0.0388	ref Rattus norvegicus coiled-coil domain containing 80 (Ccdc80), mRNA [NM_022543]
A_44_P273777	Masp1	NM_022257	0.58	0.0001	0.0160	ref Rattus norvegicus mannan-binding lectin serine peptidase 1 (Masp1), mRNA [NM_022257]
A_44_P1042711	Kif20a	NM_001108426	0.57	0.0009	0.0533	ref Rattus norvegicus kinesin family member 20A (Kif20a), mRNA [NM_001108426]
A_42_P763522	Cypr1	NM_001013980	0.57	0.0007	0.0463	ref Rattus norvegicus cysteine/tyrosine-rich 1 (Cypr1), mRNA [NM_001013980]
A_44_P179787	Panx2	NM_199409	0.56	0.0011	0.0574	ref Rattus norvegicus pannexin 2 (Panx2), mRNA [NM_199409]
A_44_P634946	Mdm2	NM_001108099	0.56	0.0000	0.0009	ref Rattus norvegicus Mdm2 p53 binding protein homolog (mouse) (Mdm2), mRNA [NM_001108099]
A_44_P141897	Abcb1b	NM_012623	0.56	0.0000	0.0002	ref Rattus norvegicus ATP-binding cassette, subfamily B (MDR/TAP), member 1B (Abcb1b), mRNA [NM_012623]
A_44_P319238	Cpne4	NM_001109003	0.56	0.0002	0.0234	ref Rattus norvegicus copine IV (Cpne4), mRNA [NM_001109003]
A_44_P500880	App	NM_019288	0.55	0.0000	0.0116	ref Rattus norvegicus amyloid beta (A4) precursor protein (App), mRNA [NM_019288]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P201117	Fndc5	ENSRNOT00000047152	0.55	0.0002	0.0268	ens Fibronectin type III domain-containing protein 5 [Source:UniProtKB/Swiss-Prot;Acc:Q8K3V5] [ENSRNOT00000047152]
A_44_P104483	Ccdc64	NM_001191667	0.55	0.0001	0.0176	ref Rattus norvegicus coiled-coil domain containing 64 (Ccdc64), mRNA [NM_001191667]
A_44_P140092	Myh14	NM_001100690	0.53	0.0004	0.0354	ref Rattus norvegicus myosin, heavy chain 14, non-muscle (Myh14), mRNA [NM_001100690]
A_42_P460340	Mal2	NM_198786	0.53	0.0003	0.0317	ref Rattus norvegicus mal, T-cell differentiation protein 2 (Mal2), mRNA [NM_198786]
A_44_P401165	Stmn1	NM_017166	0.53	0.0011	0.0580	ref Rattus norvegicus stathmin 1 (Stmn1), mRNA [NM_017166]
A_42_P735417	Fcgr2b	NM_175756	0.53	0.0032	0.0884	ref Rattus norvegicus Fc fragment of IgG, low affinity IIb, receptor (CD32) (Fcgr2b), mRNA [NM_175756]
A_43_P11891	Adh4	NM_017270	0.52	0.0044	0.0998	ref Rattus norvegicus alcohol dehydrogenase 4 (class II), pi polypeptide (Adh4), mRNA [NM_017270]
A_42_P654578	Cyp2a1	NM_012692	0.52	0.0018	0.0712	ref Rattus norvegicus cytochrome P450, family 2, subfamily a, polypeptide 1 (Cyp2a1), mRNA [NM_012692]
A_44_P674018	Acer2	NM_001107943	0.51	0.0016	0.0697	ref Rattus norvegicus alkaline ceramidase 2 (Acer2), mRNA [NM_001107943]
A_44_P1018147	Isoc1	NM_001014242	0.51	0.0022	0.0772	ref Rattus norvegicus isochorismatase domain containing 1 (Isoc1), mRNA [NM_001014242]
A_42_P491707	FQ226403	FQ226403	0.51	0.0044	0.0992	gb Rattus norvegicus TL0AEA2YE23 mRNA sequence. [FQ226403]
A_44_P809374	Clcf1	NM_207615	0.51	0.0002	0.0257	ref Rattus norvegicus cardiostrophin-like cytokine factor 1 (Clcf1), mRNA [NM_207615]
A_44_P325666	Cyp2d2	NM_012730	0.51	0.0002	0.0243	ref Rattus norvegicus cytochrome P450, family 2, subfamily d, polypeptide 2 (Cyp2d2), mRNA [NM_012730]
A_44_P715425	TC588735	TC588735	0.51	0.0000	0.0009	Unknown
A_44_P168405	Fcgr2a	NM_053843	0.51	0.0034	0.0896	ref Rattus norvegicus Fc fragment of IgG, low affinity IIa, receptor (CD32) (Fcgr2a), mRNA [NM_053843]
A_44_P930534	Gas2	NM_001127504	0.50	0.0038	0.0929	ref Rattus norvegicus growth arrest-specific 2 (Gas2), mRNA [NM_001127504]
A_44_P126381	ENSRNOT00000035265	ENSRNOT00000035265	0.49	0.0005	0.0405	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1M4F9] [ENSRNOT00000035265]
A_44_P993370	Fermt2	NM_001011915	0.49	0.0001	0.0184	ref Rattus norvegicus fermitin family member 2 (Fermt2), mRNA [NM_001011915]
A_44_P365358	Tusc3	NM_001004212	0.49	0.0001	0.0148	ref Rattus norvegicus tumor suppressor candidate 3 (Tusc3), mRNA [NM_001004212]
A_44_P700498	Angptl3	NM_001025065	0.48	0.0002	0.0224	ref Rattus norvegicus angiopoietin-like 3 (Angptl3), mRNA [NM_001025065]
A_44_P517880	Fgf1	NM_012846	0.48	0.0001	0.0135	ref Rattus norvegicus fibroblast growth factor 1 (Fgf1), mRNA [NM_012846]
A_44_P743168	AI412180	AI412180	0.48	0.0001	0.0160	gb AI412180 EST240474 Normalized rat kidney, Bento Soares Rattus sp. cDNA clone RKIEP46 3' end, mRNA sequence [AI412180]
A_43_P16515	TC579683	TC579683	0.48	0.0004	0.0326	tc Q6K0P5_RAT (Q6K0P5) PRP2, complete [TC579683]
A_44_P135224	Plk3	NM_022187	0.48	0.0009	0.0538	ref Rattus norvegicus polo-like kinase 3 (Plk3), mRNA [NM_022187]
A_44_P405443	Manba	NM_001031655	0.48	0.0001	0.0160	ref Rattus norvegicus mannosidase, beta A, lysosomal (Manba), mRNA [NM_001031655]
A_44_P992535	Gpr116	NM_139110	0.48	0.0003	0.0298	ref Rattus norvegicus G protein-coupled receptor 116 (Gpr116), mRNA [NM_139110]
A_44_P519251	Cd14	NM_021744	0.48	0.0032	0.0884	ref Rattus norvegicus CD14 molecule (Cd14), mRNA [NM_021744]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P883793	TC611717	TC611717	0.48	0.0009	0.0536	Unknown
A_44_P226832	Rasgrf1	NM_001170531	0.47	0.0027	0.0827	ref Rattus norvegicus RAS protein-specific guanine nucleotide-releasing factor 1 (Rasgrf1), transcript variant 1, mRNA [NM_001170531]
A_44_P805242	TC588735	TC588735	0.47	0.0000	0.0106	gb AW917651 EST348955 Rat gene index, normalized rat, norvegicus, Bento Soares Rattus norvegicus cDNA clone RGIEG45 5' end, mRNA sequence [AW917651]
A_44_P509500	Akap2	NM_001011974	0.47	0.0002	0.0235	ref Rattus norvegicus A kinase (PRKA) anchor protein 2 (Akap2), mRNA [NM_001011974]
A_44_P1043208	Snx14	NM_001108174	0.46	0.0005	0.0385	ref Rattus norvegicus sorting nexin 14 (Snx14), mRNA [NM_001108174]
A_43_P17763	Scrn3	ENSRNOT00000025255	0.46	0.0006	0.0418	ens secernin-3 [Source:RefSeq peptide;Acc:NP_001013180] [ENSRNOT00000025255]
A_44_P228874	Gclc	NM_012815	0.46	0.0005	0.0393	ref Rattus norvegicus glutamate-cysteine ligase, catalytic subunit (Gclc), mRNA [NM_012815]
A_44_P356027	Sc5dl	NM_053642	0.46	0.0034	0.0896	ref Rattus norvegicus sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, S. cerevisiae)-like (Sc5dl), mRNA [NM_053642]
A_44_P296924	Rdh10	NM_181478	0.45	0.0000	0.0094	ref Rattus norvegicus retinol dehydrogenase 10 (all-trans) (Rdh10), mRNA [NM_181478]
A_43_P14566	Aatf	NM_053720	0.45	0.0015	0.0680	ref Rattus norvegicus apoptosis antagonizing transcription factor (Aatf), mRNA [NM_053720]
A_44_P398167	Prdx1	NM_057114	0.45	0.0001	0.0133	ref Rattus norvegicus peroxiredoxin 1 (Prdx1), mRNA [NM_057114]
A_44_P604787	TC586784	TC586784	0.45	0.0010	0.0547	gb AW917268 EST348572 Rat gene index, normalized rat, norvegicus, Bento Soares Rattus norvegicus cDNA clone RGIEB53 5' end, mRNA sequence [AW917268]
A_44_P575340	Hprt1	NM_012583	0.45	0.0001	0.0160	ref Rattus norvegicus hypoxanthine phosphoribosyltransferase 1 (Hprt1), mRNA [NM_012583]
A_43_P11580	Abcc2	NM_012833	0.45	0.0010	0.0546	ref Rattus norvegicus ATP-binding cassette, subfamily C (CFTR/MRP), member 2 (Abcc2), mRNA [NM_012833]
A_44_P319080	Car8	NM_001009662	0.45	0.0005	0.0393	ref Rattus norvegicus carbonic anhydrase 8 (Car8), mRNA [NM_001009662]
A_44_P728623	TC634460	TC634460	0.45	0.0007	0.0463	tc Q6NS70_MOUSE (Q6NS70) LOC547091 protein, partial (46%) [TC634460]
A_44_P249990	Mal2	NM_198786	0.44	0.0006	0.0421	ref Rattus norvegicus mal, T-cell differentiation protein 2 (Mal2), mRNA [NM_198786]
A_43_P11861	Dio3	NM_017210	0.44	0.0028	0.0831	ref Rattus norvegicus deiodinase, iodothyronine, type III (Dio3), mRNA [NM_017210]
A_42_P631122	Cd302	NM_001013916	0.44	0.0005	0.0408	ref Rattus norvegicus CD302 molecule (Cd302), mRNA [NM_001013916]
A_44_P543096	Serpina10	NM_133617	0.44	0.0026	0.0814	ref Rattus norvegicus serine (or cysteine) peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 10 (Serpina10), mRNA [NM_133617]
A_44_P536832	Dennd2a	XM_231654	0.44	0.0003	0.0298	gb Rattus norvegicus similar to RIKEN cDNA B930096L08 (LOC312257), mRNA [XM_231654]
A_43_P21402	CB546753	CB546753	0.44	0.0001	0.0180	gb CB546753 AMGNNUC:NRPC1-00004-D7-A nrpc1 (10212) Rattus norvegicus cDNA clone nrpc1-00004-d7 5', mRNA sequence [CB546753]
A_44_P714816	TC612754	TC612754	0.43	0.0008	0.0507	Unknown
A_42_P455982	Pgm2	NM_001106007	0.43	0.0013	0.0631	ref Rattus norvegicus phosphoglucomutase 2 (Pgm2), mRNA [NM_001106007]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_43_P13409	Zdhhc2	NM_145096	0.43	0.0033	0.0889	ref Rattus norvegicus zinc finger, DHHC-type containing 2 (Zdhhc2), mRNA [NM_145096]
A_44_P365155	Hprt1	NM_012583	0.43	0.0003	0.0290	ref Rattus norvegicus hypoxanthine phosphoribosyltransferase 1 (Hprt1), mRNA [NM_012583]
A_44_P512828	Nup210	NM_053322	0.42	0.0010	0.0546	ref Rattus norvegicus nucleoporin 210 (Nup210), mRNA [NM_053322]
A_44_P342334	A_44_P342334	A_44_P342334	0.42	0.0003	0.0319	Unknown
A_42_P623688	Gatm	NM_031031	0.42	0.0012	0.0622	ref Rattus norvegicus glycine amidinotransferase (ι -arginine:glycine amidinotransferase) (Gatm), nuclear gene encoding mitochondrial protein, mRNA [NM_031031]
A_44_P340434	Ttc38	NM_001130499	0.42	0.0002	0.0275	ref Rattus norvegicus tetratricopeptide repeat domain 38 (Ttc38), mRNA [NM_001130499]
A_44_P293948	Ghitm	NM_001005908	0.41	0.0025	0.0800	ref Rattus norvegicus growth hormone inducible transmembrane protein (Ghitm), mRNA [NM_001005908]
A_44_P1057690	Dnase113	NM_053907	0.41	0.0006	0.0424	ref Rattus norvegicus deoxyribonuclease 1-like 3 (Dnase113), mRNA [NM_053907]
A_42_P550172	Hip1r	NM_001134763	0.41	0.0038	0.0931	ref Rattus norvegicus huntingtin interacting protein 1 related (Hip1r), transcript variant 1, mRNA [NM_001134763]
A_44_P499327	Ggct	NM_001108629	0.41	0.0000	0.0027	ref Rattus norvegicus gamma-glutamyl cyclotransferase (Ggct), mRNA [NM_001108629]
A_44_P534089	Ccnb1	NM_171991	0.41	0.0033	0.0889	ref Rattus norvegicus cyclin B1 (Ccnb1), mRNA [NM_171991]
A_44_P227286	XM_234810	XM_234810	0.41	0.0008	0.0520	gb Rattus norvegicus similar to glutathione S-transferase 8 (GST 8-8) (CHAIN 8) (GST CLASS-ALPHA) (LOC314570), mRNA [XM_234810]
A_42_P518462	Hmgn3	NM_001007020	0.41	0.0042	0.0966	ref Rattus norvegicus high mobility group nucleosomal binding domain 3 (Hmgn3), transcript variant 2, mRNA [NM_001007020]
A_44_P236068	Ugt2b36	NM_001004271	0.41	0.0002	0.0252	ref Rattus norvegicus UDP glucuronosyltransferase 2 family, polypeptide B36 (Ugt2b36), mRNA [NM_001004271]
A_43_P14688	FQ211316	FQ211316	0.41	0.0016	0.0685	gb Rattus norvegicus TL0ABA13YA24 mRNA sequence. [FQ211316]
A_44_P1014862	Ubxn8	NM_001106086	0.41	0.0001	0.0160	ref Rattus norvegicus UBX domain protein 8 (Ubxn8), mRNA [NM_001106086]
A_44_P1019407	Rnf103	NM_053438	0.41	0.0004	0.0351	ref Rattus norvegicus ring finger protein 103 (Rnf103), mRNA [NM_053438]
A_44_P591548	Papd7	NM_001107333	0.41	0.0001	0.0200	ref Rattus norvegicus PAP associated domain containing 7 (Papd7), mRNA [NM_001107333]
A_44_P1022458	Tubb6	NM_001025675	0.40	0.0034	0.0896	ref Rattus norvegicus tubulin, beta 6 (Tubb6), mRNA [NM_001025675]
A_44_P493606	Camk2n1	NM_173337	0.40	0.0020	0.0748	ref Rattus norvegicus calcium/calmodulin-dependent protein kinase II inhibitor 1 (Camk2n1), mRNA [NM_173337]
A_44_P274526	RGD1311378	NM_001106547	0.40	0.0006	0.0421	ref Rattus norvegicus similar to RIKEN cDNA 2010011120 (RGD1311378), mRNA [NM_001106547]
A_44_P233963	Mras	NM_012981	0.40	0.0020	0.0752	ref Rattus norvegicus muscle RAS oncogene homolog (Mras), mRNA [NM_012981]
A_44_P851230	TC587902	TC587902	0.40	0.0021	0.0765	gb BF558478 UI-R-C1-la-e-02-0-UI.r1 UI-R-C1 Rattus norvegicus cDNA clone UI-R-C1-la-e-02-0-UI 5', mRNA sequence [BF558478]
A_42_P519868	Gsr	NM_053906	0.40	0.0005	0.0385	ref Rattus norvegicus glutathione reductase (Gsr), mRNA [NM_053906]
A_42_P505393	Serpnb6a	NM_199085	0.40	0.0016	0.0697	ref Rattus norvegicus serine (or cysteine) peptidase inhibitor, clade B, member 6a (Serpnb6a), mRNA [NM_199085]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P215253	N4bp2l1	NM_001035222	0.39	0.0017	0.0705	ref Rattus norvegicus NEDD4 binding protein 2-like 1 (N4bp2l1), mRNA [NM_001035222]
A_44_P837036	A_44_P837036	A_44_P837036	0.39	0.0014	0.0657	Unknown
A_44_P293944	Ghitm	NM_001005908	0.39	0.0014	0.0648	ref Rattus norvegicus growth hormone inducible transmembrane protein (Ghitm), mRNA [NM_001005908]
A_43_P19850	TC622988	TC622988	0.39	0.0001	0.0201	tc Q6NS70_MOUSE (Q6NS70) LOC547091 protein, partial (10%) [TC622988]
A_44_P423662	Sh3bp5	NM_054011	0.39	0.0021	0.0765	ref Rattus norvegicus SH3-domain binding protein 5 (BTK-associated) (Sh3bp5), mRNA [NM_054011]
A_44_P506017	ENSRNOT00000024276	ENSRNOT00000024276	0.39	0.0021	0.0763	ens Histone H2B type 1 [Source:UniProtKB/Swiss-Prot;Acc:Q00715] [ENSRNOT00000024276]
A_44_P113933	Tyms	NM_019179	0.39	0.0006	0.0427	ref Rattus norvegicus thymidylate synthetase (Tyms), mRNA [NM_019179]
A_44_P769872	ENSRNOT00000038817	ENSRNOT00000038817	0.39	0.0017	0.0699	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZFH5] [ENSRNOT00000038817]
A_42_P531078	Gsta4	NM_001106840	0.39	0.0002	0.0257	ref Rattus norvegicus glutathione S-transferase alpha 4 (Gsta4), mRNA [NM_001106840]
A_44_P370015	Pgrmc1	NM_021766	0.39	0.0000	0.0065	ref Rattus norvegicus progesterone receptor membrane component 1 (Pgrmc1), mRNA [NM_021766]
A_44_P1043302	Crb3	NM_001025661	0.39	0.0017	0.0697	ref Rattus norvegicus crumbs homolog 3 (Drosophila) (Crb3), mRNA [NM_001025661]
A_44_P1001963	TC595761	TC595761	0.39	0.0001	0.0160	tc Q7R8P9_PLAYO (Q7R8P9) Homeobox-containing protein (Fragment), partial (5%) [TC595761]
A_44_P400211	Sgpl1	NM_173116	0.39	0.0023	0.0777	ref Rattus norvegicus sphingosine-1-phosphate lyase 1 (Sgpl1), mRNA [NM_173116]
A_43_P20296	Ppp2r3c	NM_001014196	0.39	0.0023	0.0777	ref Rattus norvegicus protein phosphatase 2, regulatory subunit B', gamma (Ppp2r3c), mRNA [NM_001014196]
A_44_P496572	Kmo	NM_021593	0.38	0.0000	0.0032	ref Rattus norvegicus kynurenine 3-monooxygenase (kynurenine 3-hydroxylase) (Kmo), mRNA [NM_021593]
A_44_P461187	St3gal4	NM_203337	0.38	0.0001	0.0201	ref Rattus norvegicus ST3 beta-galactoside alpha-2,3-sialyltransferase 4 (St3gal4), mRNA [NM_203337]
A_44_P698199	A_44_P698199	A_44_P698199	0.38	0.0016	0.0684	Unknown
A_44_P389389	Ttl19	NM_001014051	0.38	0.0026	0.0813	ref Rattus norvegicus tubulin tyrosine ligase-like family, member 9 (Ttl19), mRNA [NM_001014051]
A_44_P501204	Nup54	NM_017361	0.38	0.0021	0.0766	ref Rattus norvegicus nucleoporin 54 (Nup54), mRNA [NM_017361]
A_44_P374586	Cyb5a	NM_022245	0.38	0.0000	0.0033	ref Rattus norvegicus cytochrome b5 type A (microsomal) (Cyb5a), mRNA [NM_022245]
A_44_P948250	Il13ra1	NM_145789	0.38	0.0008	0.0508	ref Rattus norvegicus interleukin 13 receptor, alpha 1 (Il13ra1), mRNA [NM_145789]
A_44_P869774	Clec1b	NM_001191978	0.38	0.0010	0.0553	ref Rattus norvegicus C-type lectin domain family 1, member B (Clec1b), mRNA [NM_001191978]
A_44_P298064	Gas2	NM_001127504	0.38	0.0004	0.0326	ref Rattus norvegicus growth arrest-specific 2 (Gas2), mRNA [NM_001127504]
A_44_P269697	ENSRNOT00000042005	ENSRNOT00000042005	0.38	0.0014	0.0664	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1LP73] [ENSRNOT00000042005]
A_44_P281482	Chchd6	NM_001106608	0.38	0.0013	0.0637	ref Rattus norvegicus coiled-coil-helix-coiled-coil-helix domain containing 6 (Chchd6), mRNA [NM_001106608]
A_44_P466614	Lactb2	NM_001024247	0.37	0.0020	0.0752	ref Rattus norvegicus lactamase, beta 2 (Lactb2), mRNA [NM_001024247]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P369493	Ccdc17	NM_001014067	0.37	0.0034	0.0896	ref Rattus norvegicus coiled-coil domain containing 17 (Ccdc17), mRNA [NM_001014067]
A_44_P133650	Trim37	NM_001108288	0.37	0.0009	0.0545	ref Rattus norvegicus tripartite motif-containing 37 (Trim37), mRNA [NM_001108288]
A_44_P1034879	RGD1564865	NM_001164396	0.37	0.0016	0.0683	ref Rattus norvegicus similar to 20-alpha-hydroxysteroid dehydrogenase (RGD1564865), mRNA [NM_001164396]
A_43_P11848	Bmp2	NM_017178	0.36	0.0001	0.0180	ref Rattus norvegicus bone morphogenetic protein 2 (Bmp2), mRNA [NM_017178]
A_44_P400346	ENSRNOT00000059540	ENSRNOT00000059540	0.36	0.0030	0.0854	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1LZZ5] [ENSRNOT00000059540]
A_44_P177793	A_44_P177793	A_44_P177793	0.36	0.0009	0.0538	Unknown
A_44_P1034068	LOC100364126	XM_002726281	0.36	0.0005	0.0385	ref PREDICTED: Rattus norvegicus sorting nexin 21-like (LOC100364126), partial mRNA [XM_002726281]
A_44_P380218	RGD1564906	ENSRNOT00000000233	0.36	0.0005	0.0400	ens Glutathione S-transferase [Source:UniProtKB/TrEMBL;Acc:D3ZBD6] [ENSRNOT00000000233]
A_43_P12460	Lrrn3	NM_030856	0.36	0.0004	0.0375	ref Rattus norvegicus leucine rich repeat neuronal 3 (Lrrn3), mRNA [NM_030856]
A_44_P579594	Dse	NM_001108933	0.36	0.0031	0.0876	ref Rattus norvegicus dermatan sulfate epimerase (Dse), mRNA [NM_001108933]
A_44_P399459	Col4a3bp	NM_001108935	0.36	0.0019	0.0729	ref Rattus norvegicus collagen, type IV, alpha 3 (Goodpasture antigen) binding protein (Col4a3bp), mRNA [NM_001108935]
A_44_P526425	Selt	NM_001014253	0.36	0.0016	0.0692	ref Rattus norvegicus selenoprotein T (Selt), mRNA [NM_001014253]
A_44_P1032898	ENSRNOT00000006995	ENSRNOT00000006995	0.36	0.0011	0.0591	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZH11] [ENSRNOT00000006995]
A_43_P12007	Slc3a2	NM_019283	0.35	0.0022	0.0768	ref Rattus norvegicus solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2 (Slc3a2), mRNA [NM_019283]
A_44_P553751	Avpi1	NM_134373	0.35	0.0030	0.0859	ref Rattus norvegicus arginine vasopressin-induced 1 (Avpi1), mRNA [NM_134373]
A_44_P382363	Amn1	NM_001008333	0.35	0.0019	0.0735	ref Rattus norvegicus antagonist of mitotic exit network 1 homolog (S. cerevisiae) (Amn1), mRNA [NM_001008333]
A_44_P745027	A_44_P745027	A_44_P745027	0.35	0.0014	0.0660	Unknown
A_44_P531727	LOC367195	NM_001047920	0.35	0.0031	0.0876	ref Rattus norvegicus similar to 60S RIBOSOMAL PROTEIN L7 (LOC367195), mRNA [NM_001047920]
A_42_P816767	Nt5c3	NM_001107862	0.35	0.0015	0.0673	ref Rattus norvegicus 5'-nucleotidase, cytosolic III (Nt5c3), mRNA [NM_001107862]
A_44_P509129	Tex2	ENSRNOT00000055114	0.35	0.0009	0.0538	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZZA4] [ENSRNOT00000055114]
A_44_P369389	Capn5	FQ223532	0.35	0.0002	0.0229	gb Rattus norvegicus TLOADA10YB20 mRNA sequence. [FQ223532]
A_44_P229597	ENSRNOT00000020358	ENSRNOT00000020358	0.35	0.0005	0.0418	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1M3C9] [ENSRNOT00000020358]
A_44_P981679	Fam118a	NM_001173336	0.34	0.0012	0.0611	ref Rattus norvegicus family with sequence similarity 118, member A (Fam118a), mRNA [NM_001173336]
A_44_P775631	RGD1564854	NM_001109341	0.34	0.0007	0.0474	ref Rattus norvegicus similar to divalent cation tolerant protein CUTA (RGD1564854), mRNA [NM_001109341]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P274762	Cpped1	NM_001013963	0.34	0.0013	0.0631	ref Rattus norvegicus calcineurin-like phosphoesterase domain containing 1 (Cpped1), mRNA [NM_001013963]
A_44_P461314	Gucy1b2	NM_012770	0.34	0.0006	0.0418	ref Rattus norvegicus guanylate cyclase 1, soluble, beta 2 (Gucy1b2), mRNA [NM_012770]
A_44_P777928	Ttc38	FQ210197	0.34	0.0005	0.0418	gb Rattus norvegicus TL0ABA32YM14 mRNA sequence. [FQ210197]
A_44_P975601	Phf111	NM_001014235	0.34	0.0026	0.0814	ref Rattus norvegicus PHD finger protein 11-like (Phf111), mRNA [NM_001014235]
A_44_P424335	Ces2g	NM_001106175	0.34	0.0015	0.0665	ref Rattus norvegicus carboxylesterase 2G (Ces2g), mRNA [NM_001106175]
A_44_P136679	Isoc1	NM_001014242	0.34	0.0026	0.0814	ref Rattus norvegicus isochorismatase domain containing 1 (Isoc1), mRNA [NM_001014242]
A_44_P432937	TC592288	TC592288	0.34	0.0004	0.0345	tc Q5XI04_RAT (Q5XI04) Stomatin (Predicted), complete [TC592288]
A_44_P989111	TC590171	TC590171	0.34	0.0006	0.0453	tc Q91842_XENLA (Q91842) Xenopus laevis U2 snRNA gene, partial (6%) [TC590171]
A_44_P541378	Isoc1	NM_001014242	0.33	0.0013	0.0640	ref Rattus norvegicus isochorismatase domain containing 1 (Isoc1), mRNA [NM_001014242]
A_44_P965553	CA503908	CA503908	0.33	0.0016	0.0684	gb UI-R-FS1-cqe-a-24-0-UI.s1 UI-R-FS1 Rattus norvegicus cDNA clone UI-R-FS1-cqe-a-24-0-UI 3', mRNA sequence [CA503908]
A_43_P11622	Cd59	NM_012925	0.32	0.0012	0.0599	ref Rattus norvegicus CD59 molecule, complement regulatory protein (Cd59), mRNA [NM_012925]
A_44_P159430	Calml4	NM_001127575	0.32	0.0002	0.0266	ref Rattus norvegicus calmodulin-like 4 (Calml4), mRNA [NM_001127575]
A_44_P184865	Ptp4a1	L27843	0.32	0.0019	0.0735	gb Rattus norvegicus tyrosine phosphatase (PRL-1) mRNA, complete cds. [L27843]
A_44_P299282	Shank2	NM_133441	0.32	0.0015	0.0665	ref Rattus norvegicus SH3 and multiple ankyrin repeat domains 2 (Shank2), transcript variant 4, mRNA [NM_133441]
A_44_P513385	Dab2	NM_024159	0.32	0.0017	0.0707	ref Rattus norvegicus disabled homolog 2 (Drosophila) (Dab2), mRNA [NM_024159]
A_44_P420225	RGD1563982	NM_001110491	0.32	0.0039	0.0932	ref Rattus norvegicus similar to F-box only protein 27 (RGD1563982), mRNA [NM_001110491]
A_44_P603871	TC587235	TC587235	0.32	0.0019	0.0727	tc Q5C7U4_SCHJA (Q5C7U4) SJCHGC08389 protein (Fragment), partial (9%) [TC587235]
A_44_P715164	CB557922	CB557922	0.32	0.0008	0.0497	gb AMGNNUC:NRHY5-00137-F10-A W Rat hypothalamus (10471) Rattus norvegicus cDNA clone nrhy5-00137-f10 5', mRNA sequence [CB557922]
A_44_P410000	Stx18	NM_001012151	0.32	0.0019	0.0729	ref Rattus norvegicus syntaxin 18 (Stx18), mRNA [NM_001012151]
A_44_P513251	XM_222985	XM_222985	0.32	0.0004	0.0326	gb Rattus norvegicus similar to protein-tyrosine-phosphatase (EC 3.1.3.48) isoenzyme AcP2-rat (LOC289297), mRNA [XM_222985]
A_44_P160550	Capn2	NM_017116	0.32	0.0026	0.0813	ref Rattus norvegicus calpain 2 (Capn2), mRNA [NM_017116]
A_44_P190229	Fam58b	NM_001025412	0.32	0.0014	0.0650	ref Rattus norvegicus family with sequence similarity 58, member B (Fam58b), mRNA [NM_001025412]
A_44_P458319	TC590099	TC590099	0.31	0.0025	0.0795	gb AW918893 EST350197 Rat gene index, normalized rat, norvegicus, Bento Soares Rattus norvegicus cDNA clone RGIFA03 5' end, mRNA sequence [AW918893]
A_44_P196824	Serpinb9	NM_001007732	0.31	0.0024	0.0789	ref Rattus norvegicus serpin peptidase inhibitor, clade B (ovalbumin), member 9 (Serpinb9), mRNA [NM_001007732]
A_44_P837602	TC645764	TC645764	0.31	0.0026	0.0804	tc AF284830 carboxypeptidase D isoform CPD-N (Rattus norvegicus) (exp=-1; wgp=0; cg=0), complete [TC581295]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P853102	Dusp16	NM_001106624	0.31	0.0011	0.0580	gb Rattus norvegicus dual specificity phosphatase 16 (Dusp16), mRNA [NM_001106624]
A_44_P792470	RGD1563482	FQ211547	0.31	0.0038	0.0931	gb Rattus norvegicus TL0AAA88YM11 mRNA sequence. [FQ211547]
A_44_P269925	Acer2	NM_001107943	0.31	0.0031	0.0876	ref Rattus norvegicus alkaline ceramidase 2 (Acer2), mRNA [NM_001107943]
A_44_P802937	FQ213704	FQ213704	0.31	0.0003	0.0295	gb Rattus norvegicus TL0AAA46YD19 mRNA sequence. [FQ213704]
A_44_P620208	FQ221790	FQ221790	0.31	0.0035	0.0896	gb Rattus norvegicus TL0ADA31YM21 mRNA sequence. [FQ221790]
A_44_P298730	TC581937	TC581937	0.31	0.0012	0.0599	tc Q99LR9_MOUSE (Q99LR9) Riok3 protein (Fragment), partial (13%) [TC581937]
A_44_P501797	ENSRNOT00000059335	ENSRNOT00000059335	0.31	0.0003	0.0280	ens RCG61997Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZVK5] [ENSRNOT00000059335]
A_42_P658815	Atp6v1e1	NM_198745	0.31	0.0013	0.0623	ref Rattus norvegicus ATPase, H+ transporting, lysosomal V1 subunit E1 (Atp6v1e1), mRNA [NM_198745]
A_44_P270658	TC598704	TC598704	0.31	0.0004	0.0376	tc Q6A808_PROAC (Q6A808) Peptide chain release factor 2, partial (6%) [TC598704]
A_44_P201385	Psmc6	NM_001100509	0.30	0.0035	0.0900	ref Rattus norvegicus proteasome (prosome, macropain) 26S subunit, ATPase, 6 (Psmc6), mRNA [NM_001100509]
A_44_P265911	Cnr2	NM_001164143	0.30	0.0008	0.0520	ref Rattus norvegicus cannabinoid receptor 2 (macrophage) (Cnr2), transcript variant 1, mRNA [NM_001164143]
A_43_P20587	Gypc	NM_001013233	0.30	0.0011	0.0571	ref Rattus norvegicus glycophorin C (Gerbich blood group) (Gypc), mRNA [NM_001013233]
A_42_P478706	LOC361990	NM_001014175	0.30	0.0021	0.0763	ref Rattus norvegicus similar to DKFZP547E1010 protein (LOC361990), mRNA [NM_001014175]
A_44_P398587	Usp9x	NM_001135893	0.30	0.0018	0.0713	ref Rattus norvegicus ubiquitin specific peptidase 9, X-linked (Usp9x), transcript variant 1, mRNA [NM_001135893]
A_42_P768355	Hrk	NM_057130	0.30	0.0023	0.0777	ref Rattus norvegicus harakiri, BCL2 interacting protein (contains only BH3 domain) (Hrk), mRNA [NM_057130]
A_44_P378514	TC637536	TC637536	0.30	0.0028	0.0829	tc Q1ZZX1_MUSPR (Q1ZZX1) DELLA protein (Fragment), partial (7%) [TC637536]
A_42_P668972	Acp1	NM_021262	0.30	0.0003	0.0275	ref Rattus norvegicus acid phosphatase 1, soluble (Acp1), transcript variant 1, mRNA [NM_021262]
A_42_P477732	Slc10a1	NM_017047	0.30	0.0022	0.0777	ref Rattus norvegicus solute carrier family 10 (sodium/bile acid cotransporter family), member 1 (Slc10a1), mRNA [NM_017047]
A_44_P125145	CF109884	CF109884	0.30	0.0008	0.0520	gb Shultzomica03135 Rat lung airway and parenchyma cDNA libraries Rattus norvegicus cDNA clone Contig2758 5', mRNA sequence [CF109884]
A_42_P743301	Psm1	NM_017278	0.30	0.0018	0.0712	ref Rattus norvegicus proteasome (prosome, macropain) subunit, alpha type 1 (Psm1), mRNA [NM_017278]
A_44_P105310	Elov2	NM_001109118	0.30	0.0030	0.0854	ref Rattus norvegicus elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 2 (Elov2), mRNA [NM_001109118]
A_44_P177333	TC633253	TC633253	0.29	0.0010	0.0545	tc Q8R1U0_MOUSE (Q8R1U0) Cflar protein, partial (82%) [TC632248]
A_44_P491831	Gsta5	NM_001009920	0.29	0.0017	0.0711	ref Rattus norvegicus glutathione S-transferase Yc2 subunit (Gsta5), transcript variant 1, mRNA [NM_001009920]
A_44_P284642	Ccdc104	NM_001024866	0.29	0.0031	0.0869	ref Rattus norvegicus coiled-coil domain containing 104 (Ccdc104), mRNA [NM_001024866]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P168112	Skp1	NM_001007608	0.29	0.0014	0.0664	ref Rattus norvegicus S-phase kinase-associated protein 1 (Skp1), mRNA [NM_001007608]
A_44_P226601	F8	NM_183331	0.29	0.0018	0.0712	ref Rattus norvegicus coagulation factor VIII, procoagulant component (F8), mRNA [NM_183331]
A_44_P929247	Cyp4f17	NM_001191986	0.29	0.0013	0.0640	ref Rattus norvegicus cytochrome P450, family 4, subfamily f, polypeptide 17 (Cyp4f17), mRNA [NM_001191986]
A_44_P741723	Il13ra1	NM_145789	0.29	0.0013	0.0640	ref Rattus norvegicus interleukin 13 receptor, alpha 1 (Il13ra1), mRNA [NM_145789]
A_44_P325744	Nap111	NM_053561	0.29	0.0037	0.0927	ref Rattus norvegicus nucleosome assembly protein 1-like 1 (Nap111), mRNA [NM_053561]
A_43_P19545	Meis3	NM_001108472	0.29	0.0032	0.0884	ref Rattus norvegicus Meis homeobox 3 (Meis3), mRNA [NM_001108472]
A_44_P793558	TC599526	TC599526	0.29	0.0000	0.0114	Unknown
A_44_P103020	Dbnnd2	NM_001047111	0.29	0.0002	0.0275	ref Rattus norvegicus dysbindin (dystrobrevin binding protein 1) domain containing 2 (Dnnd2), mRNA [NM_001047111]
A_44_P304667	Slc35b3	ENSRNOT00000021669	0.29	0.0039	0.0941	ens Solute carrier family 35, member B3 (Predicted), isoform CRA_bUncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D4AAG3] [ENSRNOT00000021669]
A_44_P562251	BF545174	BF545174	0.29	0.0002	0.0239	gb U1-R-C2p-rx-c-04-0-U1.r1 U1-R-C2p Rattus norvegicus cDNA clone U1-R-C2p-rx-c-04-0-U1 5', mRNA sequence [BF545174]
A_43_P11552	Ptpra	NM_012763	0.29	0.0009	0.0541	ref Rattus norvegicus protein tyrosine phosphatase, receptor type, A (Ptpra), mRNA [NM_012763]
A_42_P462987	Vangl1	NM_001109584	0.29	0.0043	0.0984	ref Rattus norvegicus vang-like 1 (van gogh, Drosophila) (Vangl1), mRNA [NM_001109584]
A_42_P637618	Fopnl	NM_001108261	0.29	0.0022	0.0777	ref Rattus norvegicus FGFR1OP N-terminal like (Fopnl), mRNA [NM_001108261]
A_44_P1031034	Clip1	NM_031745	0.28	0.0005	0.0416	ref Rattus norvegicus CAP-GLY domain containing linker protein 1 (Clip1), mRNA [NM_031745]
A_42_P541784	RGD1566099	NM_001108347	0.28	0.0015	0.0673	ref Rattus norvegicus similar to novel protein (RGD1566099), mRNA [NM_001108347]
A_44_P260268	Tinf2	NM_001006962	0.28	0.0044	0.0998	ref Rattus norvegicus TRF1 (TRF1)-interacting nuclear factor 2 (Tinf2), mRNA [NM_001006962]
A_44_P713299	LOC684862	XM_001072231	0.28	0.0039	0.0935	ref PREDICTED: Rattus norvegicus hypothetical protein LOC684862 (LOC684862), mRNA [XM_001072231]
A_44_P463899	ENSRNOT00000067247	ENSRNOT00000067247	0.28	0.0039	0.0933	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1LZ30] [ENSRNOT00000067247]
A_44_P472974	Masp1	NM_022257	0.28	0.0005	0.0394	ref Rattus norvegicus mannan-binding lectin serine peptidase 1 (Masp1), mRNA [NM_022257]
A_44_P510188	TC618566	TC618566	0.28	0.0014	0.0659	gb AW143279 EST293575 Normalized rat brain, Bento Soares Rattus sp. cDNA clone RGIBJ29 5' end, mRNA sequence [AW143279]
A_42_P485589	Map2k5	NM_017246	0.28	0.0035	0.0905	ref Rattus norvegicus mitogen activated protein kinase 5 (Map2k5), transcript variant 2, mRNA [NM_017246]
A_44_P804257	FQ214033	FQ214033	0.28	0.0017	0.0707	gb Rattus norvegicus TLOAAA44YD13 mRNA sequence. [FQ214033]
A_44_P245087	RGD1565247	FQ211597	0.28	0.0006	0.0421	gb Rattus norvegicus TLOAAA86YF16 mRNA sequence. [FQ211597]
A_44_P433157	Clip1	NM_031745	0.27	0.0041	0.0950	ref Rattus norvegicus CAP-GLY domain containing linker protein 1 (Clip1), mRNA [NM_031745]
A_44_P524922	NP072211	NP072211	0.27	0.0020	0.0747	tc GB M35258.1 AAA41564.1 malic enzyme (EC 1.1.1.40) [NP072211]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P313838	Lipc	NM_012597	0.27	0.0033	0.0890	ref Rattus norvegicus lipase, hepatic (Lipc), mRNA [NM_012597]
A_44_P335703	Toag1	NM_001110838	0.27	0.0030	0.0863	ref Rattus norvegicus tolerance-associated gene 1 (Toag1), mRNA [NM_001110838]
A_42_P707992	Tspan18	NM_001107750	0.27	0.0002	0.0247	ref Rattus norvegicus tetraspanin 18 (Tspan18), mRNA [NM_001107750]
A_44_P149734	Hat1	NM_001009657	0.27	0.0010	0.0554	ref Rattus norvegicus histone acetyltransferase 1 (Hat1), mRNA [NM_001009657]
A_44_P363229	Grk5	NM_030829	0.27	0.0012	0.0599	ref Rattus norvegicus G protein-coupled receptor kinase 5 (Grk5), mRNA [NM_030829]
A_43_P10301	Esd	NM_001106051	0.27	0.0006	0.0418	ref Rattus norvegicus esterase D (Esd), mRNA [NM_001106051]
A_44_P453874	Rpl7	NM_001100534	0.27	0.0012	0.0623	ref Rattus norvegicus ribosomal protein L7 (Rpl7), mRNA [NM_001100534]
A_44_P253108	Spc25	NM_001009654	0.27	0.0037	0.0920	ref Rattus norvegicus SPC25, NDC80 kinetochore complex component, homolog (<i>S. cerevisiae</i>) (Spc25), mRNA [NM_001009654]
A_44_P142029	Nenf	NM_001002851	0.27	0.0026	0.0814	ref Rattus norvegicus neudesin neurotrophic factor (Nenf), mRNA [NM_001002851]
A_42_P552341	Sorl1	NM_053519	0.27	0.0006	0.0418	ref Rattus norvegicus sortilin-related receptor, LDLR class A repeats-containing (Sorl1), mRNA [NM_053519]
A_44_P1046097	RGD1306063	NM_001106026	0.27	0.0024	0.0784	ref Rattus norvegicus similar to HT021 (RGD1306063), mRNA [NM_001106026]
A_44_P338864	Nap111	NM_053561	0.27	0.0005	0.0408	ref Rattus norvegicus nucleosome assembly protein 1-like 1 (Nap111), mRNA [NM_053561]
A_44_P1051042	C8g	NM_001106555	0.27	0.0029	0.0851	ref Rattus norvegicus complement component 8, gamma polypeptide (C8g), mRNA [NM_001106555]
A_44_P382727	RGD1566215	NM_001106929	0.27	0.0031	0.0876	ref Rattus norvegicus similar to Coatomer gamma-2 subunit (Gamma-2 COP) (RGD1566215), mRNA [NM_001106929]
A_44_P900672	Robo2	NM_032106	0.27	0.0016	0.0684	ref Rattus norvegicus roundabout homolog 2 (<i>Drosophila</i>) (Robo2), mRNA [NM_032106]
A_43_P18526	Atp11c-ps1	ENSRNOT00000049120	0.27	0.0039	0.0932	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3Z9J3] [ENSRNOT00000049120]
A_44_P554799	Rab11a	NM_031152	0.27	0.0002	0.0268	ref Rattus norvegicus RAB11a, member RAS oncogene family (Rab11a), mRNA [NM_031152]
A_44_P784011	TC639313	TC639313	0.26	0.0020	0.0752	Unknown
A_44_P430989	Fbnp1	NM_138914	0.26	0.0003	0.0307	ref Rattus norvegicus formin binding protein 1 (Fbnp1), mRNA [NM_138914]
A_44_P411919	Psm1	NM_031978	0.26	0.0009	0.0541	ref Rattus norvegicus proteasome (prosome, macropain) 26S subunit, non-ATPase, 1 (Psm1), mRNA [NM_031978]
A_44_P337699	Mnd1	ENSRNOT00000031179	0.26	0.0019	0.0735	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1LWN6] [ENSRNOT00000031179]
A_44_P407849	Nphp1	NM_001106506	0.26	0.0002	0.0223	ref Rattus norvegicus nephronophthisis 1 (juvenile) homolog (human) (Nphp1), mRNA [NM_001106506]
A_44_P415177	ENSRNOT00000049967	ENSRNOT00000049967	0.26	0.0029	0.0851	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3Z822] [ENSRNOT00000049967]
A_44_P220256	Prtfdc1	NM_001106127	0.26	0.0036	0.0911	ref Rattus norvegicus phosphoribosyl transferase domain containing 1 (Prtfdc1), mRNA [NM_001106127]
A_44_P389072	Il13ra1	NM_145789	0.26	0.0000	0.0106	ref Rattus norvegicus interleukin 13 receptor, alpha 1 (Il13ra1), mRNA [NM_145789]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P351898	Mad211	NM_001106594	0.26	0.0015	0.0665	ref Rattus norvegicus MAD2 mitotic arrest deficient-like 1 (yeast) (Mad211), mRNA [NM_001106594]
A_44_P915588	LOC365723	XR_086165	0.26	0.0030	0.0854	ref PREDICTED: Rattus norvegicus similar to zinc finger protein 458 (LOC365723), miscRNA [XR_086165]
A_43_P17528	Akr1e2	NM_001008342	0.26	0.0031	0.0872	ref Rattus norvegicus aldo-keto reductase family 1, member E2 (Akr1e2), mRNA [NM_001008342]
A_44_P226881	Pde2a	NM_031079	0.26	0.0035	0.0896	ref Rattus norvegicus phosphodiesterase 2A, cGMP-stimulated (Pde2a), transcript variant 2, mRNA [NM_031079]
A_44_P991376	Orc3	NM_001025282	0.26	0.0023	0.0777	ref Rattus norvegicus origin recognition complex, subunit 3 (Orc3), mRNA [NM_001025282]
A_44_P538921	Cetn4	ENSRNOT00000065384	0.26	0.0002	0.0243	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:FILTY0][ENSRNOT00000065384]
A_44_P747071	Vav3	NM_001191714	0.26	0.0025	0.0802	ref Rattus norvegicus vav 3 guanine nucleotide exchange factor (Vav3), mRNA [NM_001191714]
A_42_P726132	Tmem62	XM_230497	0.26	0.0020	0.0748	ref PREDICTED: Rattus norvegicus transmembrane protein 62 (Tmem62), mRNA [XM_230497]
A_44_P540126	Pros1	NM_031086	0.25	0.0032	0.0884	ref Rattus norvegicus protein S (alpha) (Pros1), mRNA [NM_031086]
A_42_P639047	RGD1309350	NM_001134507	0.25	0.0016	0.0689	ref Rattus norvegicus similar to transthyretin (4L369) (RGD1309350), mRNA [NM_001134507]
A_44_P242756	Pcna	NM_022381	0.25	0.0014	0.0657	ref Rattus norvegicus proliferating cell nuclear antigen (Pcna), mRNA [NM_022381]
A_44_P1014445	Zfp259	NM_001137646	0.25	0.0009	0.0538	ref Rattus norvegicus zinc finger protein 259 (Zfp259), mRNA [NM_001137646]
A_42_P670901	Ccdc120	FQ211363	0.25	0.0011	0.0593	gb Rattus norvegicus TLOABA12YD13 mRNA sequence. [FQ211363]
A_44_P445359	Pex7	NM_001034147	0.25	0.0007	0.0467	ref Rattus norvegicus peroxisomal biogenesis factor 7 (Pex7), mRNA [NM_001034147]
A_43_P19101	RGD1562626	ENSRNOT00000067712	0.25	0.0008	0.0520	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZNN9][ENSRNOT00000067712]
A_44_P231719	Tmem9b	NM_001106289	0.25	0.0009	0.0545	ref Rattus norvegicus TMEM9 domain family, member B (Tmem9b), mRNA [NM_001106289]
A_43_P13342	Gstp1	NM_012577	0.25	0.0036	0.0909	ref Rattus norvegicus glutathione S-transferase pi 1 (Gstp1), mRNA [NM_012577]
A_44_P508924	LOC691594	XM_001078957	0.25	0.0010	0.0547	ref PREDICTED: Rattus norvegicus similar to hypothetical protein LOC501396 (LOC691594), mRNA [XM_001078957]
A_43_P18931	RGD1304982	NM_001113775	0.25	0.0027	0.0821	ref Rattus norvegicus similar to RIKEN cDNA 2810025M15 (RGD1304982), mRNA [NM_001113775]
A_44_P260055	Gyg1	NM_031043	0.25	0.0021	0.0763	ref Rattus norvegicus glycogenin 1 (Gyg1), mRNA [NM_031043]
A_44_P792333	TC598219	TC598219	0.25	0.0004	0.0359	tc CD59_RAT (P27274) CD59 glycoprotein precursor (Membrane attack complex inhibition factor) (MACIF) (MAC-inhibitory protein) (MAC-IP) (Protectin), complete [TC598219]
A_44_P237220	Ttc13	NM_001136162	0.24	0.0036	0.0911	ref Rattus norvegicus tetra-tricopeptide repeat domain 13 (Ttc13), mRNA [NM_001136162]
A_42_P586064	Pacs1	NM_134406	0.24	0.0020	0.0752	ref Rattus norvegicus phosphofurin acidic cluster sorting protein 1 (Pacs1), mRNA [NM_134406]
A_43_P16992	Auh	NM_001108407	0.24	0.0005	0.0406	ref Rattus norvegicus AU RNA binding protein/enoyl-CoA hydratase (Auh), nuclear gene encoding mitochondrial protein, mRNA [NM_001108407]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P380343	XM_217443	XM_217443	0.24	0.0003	0.0275	gb Rattus norvegicus similar to 4833408P15Rik protein (LOC301525), mRNA [XM_217443]
A_44_P689118	CO402250	CO402250	0.24	0.0040	0.0941	gb AGENCOURT_27852273 NIH_MGC_252 Rattus norvegicus cDNA clone IMAGE:7306766 5', mRNA sequence [CO402250]
A_44_P434893	Hspb11	NM_001131002	0.24	0.0023	0.0777	ref Rattus norvegicus heat shock protein family B (small), member 11 (Hspb11), mRNA [NM_001131002]
A_44_P405360	Spryd7	NM_001009635	0.24	0.0011	0.0582	ref Rattus norvegicus SPRY domain containing 7 (Spryd7), mRNA [NM_001009635]
A_44_P792035	Mcart1	NM_001024785	0.24	0.0018	0.0716	ref Rattus norvegicus mitochondrial carrier triple repeat 1 (Mcart1), nuclear gene encoding mitochondrial protein, mRNA [NM_001024785]
A_43_P17839	Prkra	NM_001024780	0.24	0.0012	0.0623	ref Rattus norvegicus protein kinase, interferon inducible double stranded RNA dependent activator (Prkra), mRNA [NM_001024780]
A_44_P379951	Rnf170	XM_344558	0.23	0.0030	0.0862	ref PREDICTED: Rattus norvegicus ring finger protein 170 (Rnf170), mRNA [XM_344558]
A_43_P22401	Lrrc51	NM_001106284	0.23	0.0010	0.0546	ref Rattus norvegicus leucine rich repeat containing 51 (Lrrc51), mRNA [NM_001106284]
A_44_P154436	Tnfaip8	NM_001107387	0.23	0.0038	0.0931	ref Rattus norvegicus tumor necrosis factor, alpha-induced protein 8 (Tnfaip8), mRNA [NM_001107387]
A_42_P547027	Fuca2	NM_001004218	0.23	0.0044	0.0991	ref Rattus norvegicus fucosidase, alpha-L-2, plasma (Fuca2), mRNA [NM_001004218]
A_44_P534249	Ociad1	NM_001013874	0.23	0.0010	0.0553	ref Rattus norvegicus OCIA domain containing 1 (Ociad1), mRNA [NM_001013874]
A_44_P362380	RGD1559612	ENSRNOT00000058581	0.23	0.0022	0.0768	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1LVC4] [ENSRNOT00000058581]
A_44_P435016	Nudt2	NM_207596	0.23	0.0004	0.0354	ref Rattus norvegicus nudix (nucleoside diphosphate linked moiety X)-type motif 2 (Nudt2), mRNA [NM_207596]
A_44_P311969	XM_342996	XM_342996	0.23	0.0015	0.0665	gb Rattus norvegicus similar to hypothetical protein FLJ90811 (LOC362681), mRNA [XM_342996]
A_44_P286259	Fbxl4	ENSRNOT00000061128	0.23	0.0024	0.0786	ens F-box/LRR-repeat protein 4 [Source:RefSeq peptide;Acc:NP_001101389] [ENSRNOT00000061128]
A_43_P16611	Usp9x	NM_001135893	0.23	0.0010	0.0554	ref Rattus norvegicus ubiquitin specific peptidase 9, X-linked (Usp9x), transcript variant 1, mRNA [NM_001135893]
A_44_P1044046	Ndufaf1	NM_001106500	0.23	0.0040	0.0941	ref Rattus norvegicus NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 1 (Ndufaf1), mRNA [NM_001106500]
A_44_P235462	AI029293	AI029293	0.22	0.0018	0.0713	gb AI029293 UI-R-CO-iq-f-03-0-UI.s1 UI-R-CO Rattus norvegicus cDNA clone UI-R-CO-iq-f-03-0-UI 3', mRNA sequence [AI029293]
A_43_P17077	Mettl10	NM_001108504	0.22	0.0035	0.0899	ref Rattus norvegicus methyltransferase like 10 (Mettl10), mRNA [NM_001108504]
A_44_P432452	Akr1b1	NM_012498	0.22	0.0008	0.0520	ref Rattus norvegicus aldo-keto reductase family 1, member B1 (aldose reductase) (Akr1b1), mRNA [NM_012498]
A_44_P175751	Dip2a	NM_001191564	0.22	0.0020	0.0752	ref Rattus norvegicus DIP2 disco-interacting protein 2 homolog A (Drosophila) (Dip2a), mRNA [NM_001191564]
A_44_P540944	Plekha5	ENSRNOT00000011770	0.22	0.0033	0.0889	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZSV9] [ENSRNOT00000011770]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_44_P500653	Nicn1	NM_001034999	0.22	0.0024	0.0789	ref Rattus norvegicus nicolin 1 (Nicn1), mRNA [NM_001034999]
A_43_P20902	Donson	NM_001008287	0.22	0.0003	0.0298	ref Rattus norvegicus downstream neighbor of SON (Donson), mRNA [NM_001008287]
A_44_P160545	DV725496	DV725496	0.22	0.0033	0.0891	gb RVL17676 Wackym-Soares normalized rat vestibular cDNA library Rattus norvegicus cDNA 5', mRNA sequence [DV725496]
A_44_P971443	TC623207	TC623207	0.22	0.0025	0.0792	gb AW918781 EST350085 Rat gene index, normalized rat, norvegicus, Bento Soares Rattus norvegicus cDNA clone RGIEY05 5' end, mRNA sequence [AW918781]
A_44_P299500	Gmpr2	NM_001013036	0.22	0.0037	0.0928	ref Rattus norvegicus guanosine monophosphate reductase 2 (Gmpr2), mRNA [NM_001013036]
A_44_P434541	Ada	NM_130399	0.22	0.0040	0.0943	ref Rattus norvegicus adenosine deaminase (Ada), mRNA [NM_130399]
A_44_P1025802	Metap1	NM_001106476	0.21	0.0018	0.0713	ref Rattus norvegicus methionyl aminopeptidase 1 (Metap1), mRNA [NM_001106476]
A_42_P756393	TC589591	TC589591	0.21	0.0025	0.0795	gb AW920459 EST351763 Rat gene index, normalized rat, norvegicus, Bento Soares Rattus norvegicus cDNA clone RGIGW54 5' end, mRNA sequence [AW920459]
A_44_P1058112	Yars2	NM_001009627	0.21	0.0041	0.0956	ref Rattus norvegicus tyrosyl-tRNA synthetase 2 (mitochondrial) (Yars2), nuclear gene encoding mitochondrial protein, mRNA [NM_001009627]
A_44_P147426	Nt5dc1	NM_001106393	0.21	0.0021	0.0762	ref Rattus norvegicus 5'-nucleotidase domain containing 1 (Nt5dc1), mRNA [NM_001106393]
A_44_P1036696	Napg	NM_001107384	0.21	0.0011	0.0591	ref Rattus norvegicus N-ethylmaleimide-sensitive factor attachment protein, gamma (Napg), mRNA [NM_001107384]
A_44_P499318	LOC294154	NM_001039607	0.21	0.0021	0.0763	ref Rattus norvegicus similar to chromosome 6 open reading frame 106 isoform a (LOC294154), mRNA [NM_001039607]
A_44_P537250	RGD1562626	ENSRNOT00000003369	0.21	0.0037	0.0929	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZNN9] [ENSRNOT00000003369]
A_44_P329925	Vps37b	NM_001105928	0.21	0.0007	0.0490	ref Rattus norvegicus vacuolar protein sorting 37 homolog B (<i>S. cerevisiae</i>) (Vps37b), mRNA [NM_001105928]
A_44_P144871	Coq4	NM_001031662	0.21	0.0028	0.0840	ref Rattus norvegicus coenzyme Q4 homolog (<i>S. cerevisiae</i>) (Coq4), nuclear gene encoding mitochondrial protein, mRNA [NM_001031662]
A_44_P377731	Pef1	NM_001007651	0.21	0.0008	0.0521	ref Rattus norvegicus penta-EF hand domain containing 1 (Pef1), mRNA [NM_001007651]
A_43_P20851	Ppfibp2	NM_001100582	0.21	0.0034	0.0896	ref Rattus norvegicus PTPRF interacting protein, binding protein 2 (liprin beta 2) (Ppfibp2), mRNA [NM_001100582]
A_44_P249902	Vps29	NM_001105932	0.21	0.0006	0.0436	ref Rattus norvegicus vacuolar protein sorting 29 homolog (<i>S. cerevisiae</i>) (Vps29), mRNA [NM_001105932]
A_44_P182336	Tanc1	NM_001002854	0.21	0.0006	0.0436	ref Rattus norvegicus tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 1 (Tanc1), mRNA [NM_001002854]
A_44_P105304	Dapp1	NM_001108568	0.21	0.0036	0.0917	ref Rattus norvegicus dual adaptor of phosphotyrosine and 3-phosphoinositides (Dapp1), mRNA [NM_001108568]
A_44_P505694	Cyp20a1	NM_199401	0.20	0.0042	0.0966	ref Rattus norvegicus cytochrome P450, family 20, subfamily a, polypeptide 1 (Cyp20a1), mRNA [NM_199401]
A_43_P15601	Mat2a	NM_134351	0.20	0.0038	0.0931	ref Rattus norvegicus methionine adenosyltransferase II, alpha (Mat2a), mRNA [NM_134351]

Table 2 (Continued)

ProbeName	GeneName	SystematicName	log2(FIP/CTRL)	p-value	q-value	Description
A_44_P1008284	TC575338	TC575338	0.20	0.0031	0.0876	tc DCTN4_RAT (Q9QUR2) Dynactin subunit 4 (Dynactin subunit p62), complete [TC575338]
A_44_P463679	Zpbp2	NM_001007011	0.20	0.0016	0.0684	ref Rattus norvegicus zona pellucida binding protein 2 (Zpbp2), mRNA [NM_001007011]
A_44_P457833	Trim32	NM_001012103	0.20	0.0013	0.0631	ref Rattus norvegicus tripartite motif-containing 32 (Trim32), mRNA [NM_001012103]
A_44_P330197	Srpk3	NM_184045	0.19	0.0032	0.0876	ref Rattus norvegicus SRSF protein kinase 3 (Srpk3), mRNA [NM_184045]
A_42_P513580	ENSRNOT00000036634	ENSRNOT00000036634	0.19	0.0041	0.0950	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1LVY9] [ENSRNOT00000036634]
A_43_P18283	March6	XM_215517	0.18	0.0019	0.0739	ref PREDICTED: Rattus norvegicus membrane-associated ring finger (C3HC4) 6 (March6), mRNA [XM_215517]
A_44_P234212	Olfml3	NM_001107708	0.18	0.0014	0.0649	ref Rattus norvegicus olfactomedin-like 3 (Olfml3), mRNA [NM_001107708]
A_44_P152017	FQ227332	FQ227332	0.18	0.0037	0.0919	gb Rattus norvegicus TLOAEA13YL20 mRNA sequence. [FQ227332]
A_44_P409232	Cyp2e1	NM_031543	0.17	0.0025	0.0796	ref Rattus norvegicus cytochrome P450, family 2, subfamily e, polypeptide 1 (Cyp2e1), mRNA [NM_031543]
A_44_P1042504	Rg9mtd2	NM_001044232	0.16	0.0031	0.0876	ref Rattus norvegicus RNA (guanine-9-) methyltransferase domain containing 2 (Rg9mtd2), mRNA [NM_001044232]
A_44_P161579	Haus2	XM_001053441	0.16	0.0037	0.0928	ref PREDICTED: Rattus norvegicus HAUS augmin-like complex, subunit 2, transcript variant 1 (Haus2), mRNA [XM_001053441]
A_42_P521006	ENSRNOT00000025574	ENSRNOT00000025574	0.14	0.0028	0.0829	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:E9PTB3] [ENSRNOT00000025574]

one-compartment model with a first-order absorption rate using the following equation:

$$C(t) = \frac{F \times D \times K_{01}}{V \times (K_{01} - K_{10})} \times (\exp(-K_{10} \times t) - \exp(-K_{01} \times t)),$$

where $C(t)$ is the plasma concentration at time t (ng/mL), F is the bioavailability of the drug, D is the drug dose ($\mu\text{g}/\text{kg}$), V is the volume of distribution (mL/kg), K_{01} is the first-order rate constant of absorption (h^{-1}) and K_{10} is the first-order rate constant of elimination (h^{-1}). The data were weighted by the inverse of the fitted values. The apparent clearance was defined as dose/AUC.

2.7. Statistical analysis

Data were analyzed under R (R[®] 2.13.0, www.r-project.org). Microarray data were analyzed using packages from Bioconductor (www.bioconductor.org). Details of microarray data analysis, together with raw and processed microarray data can be found in GEO entry GSE39378. Differentially expressed probes were identified using the limma and q -value packages. Probes with a q -value ≤ 0.1 were considered significant. All other data were analyzed by ANOVA with the appropriate factors as fixed effects (depending on the experimental design: treatment, genotype and their interaction) followed by Student's t -test with a pooled variance estimate to compare the group's means. Data are presented as mean \pm SEM.

3. Results

3.1. Impact of fipronil on rat liver transcriptome

Consistent with our previous observations [5], female rats treated with fipronil *via* oral route (3 mg/kg per day, 14 days)

displayed plasma concentrations of its main metabolite fipronil sulfone at least 700-fold higher than those of fipronil itself (Fig. 1A). Fipronil had no effect on body weight gain throughout the experiment (data not shown) and the animals did not display any overt sign of toxicity. As previously reported [4], fipronil treatment was associated with reduced plasma thyroid hormone (TH) levels (Fig. 1B) although only the decrease in total T_4 clearly approached significance ($p = 0.06$). We have previously shown using a model of T_3 -supplemented thyroidectomized rats that this effect of fipronil is linked to an increase in TH clearance [4]. Consistent with an increased TH clearance which could be compensated by feedback induction of TH synthesis, fipronil treatment led to a significant increase in plasma TSH ($p < 0.05$, Fig. 1C).

The liver plays a central role in the metabolism of fipronil [7,16] and of thyroid hormones [17,18]. To explore the main impacts of fipronil treatment in the liver, we used Agilent microarrays to analyze the hepatic transcriptome of vehicle- ($n = 7$) and fipronil-treated rats ($n = 8$). Following fipronil treatment we found 402 upregulated probes (377 unique genes, Table 2) and 310 downregulated probes (292 unique genes, Table 3) using a FDR threshold of 10% (q -value < 0.1 , which corresponds to raw p -value < 0.0045). The clear impact of fipronil on the liver transcriptome is illustrated by the heatmap and hierarchical clustering obtained from these 712 probes which captured differential gene expression (Fig. 2A). The tests for the enrichment of gene ontology (GO) biological processes revealed that functions linked to the metabolism and transport of xenobiotics, hormones and endogenous compounds such as bile acids or steroids were over-represented among the upregulated genes (Fig. 2A and Table 4). Interestingly, this analysis also identified the over-representation of thyroid hormone transporters among the upregulated genes. Conversely, functions linked

Table 3
Genes significantly downregulated in rat liver following fipronil treatment (q -value < 0.1).

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p -value	q -value	Description
A_44_P204758	Sult4a1	NM_031641	-1.82	0.0000	0.0014	ref Rattus norvegicus sulfotransferase family 4A, member 1 (Sult4a1), mRNA [NM_031641]
A_44_P822061	ENSRNOT00000041850	ENSRNOT00000041850	-0.75	0.0000	0.0016	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZAW7][ENSRNOT00000041850]
A_43_P17890	Fam198a	ENSRNOT00000014323	-0.48	0.0000	0.0027	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1M8H1][ENSRNOT00000014323]
A_44_P904150	TC617637	TC617637	-0.59	0.0000	0.0051	Unknown
A_44_P323951	ENSRNOT00000041800	ENSRNOT00000041800	-0.94	0.0000	0.0051	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1LVH0][ENSRNOT00000041800]
A_44_P236670	LOC691410	XM_001078125	-0.59	0.0000	0.0056	ref PREDICTED: Rattus norvegicus similar to Discs large homolog 5 (Placenta and prostate DLG) (Discs large protein P-dlg) (LOC691410), mRNA [XM_001078125]
A_44_P168755	LOC100360315	XM_002730116	-0.43	0.0000	0.0072	ref PREDICTED: Rattus norvegicus spermatogenesis associated glutamate (E)-rich protein 4e-like (LOC100360315), mRNA [XM_002730116]
A_44_P757007	Bmp1	NM_031323	-0.44	0.0000	0.0074	ref Rattus norvegicus bone morphogenetic protein 1 (Bmp1), mRNA [NM_031323]
A_44_P378799	Igfbp6	NM_013104	-0.72	0.0000	0.0075	ref Rattus norvegicus insulin-like growth factor binding protein 6 (Igfbp6), mRNA [NM_013104]
A_44_P468902	XM_226288	XM_226288	-0.50	0.0000	0.0093	gb Rattus norvegicus similar to RIKEN cDNA 1700081O22 (LOC307681), mRNA [XM_226288]
A_43_P22318	Prss32	NM_001106983	-0.47	0.0000	0.0094	ref Rattus norvegicus protease, serine, 32 (Prss32), mRNA [NM_001106983]
A_44_P541505	XM_226288	XM_226288	-0.92	0.0000	0.0104	gb Rattus norvegicus similar to RIKEN cDNA 1700081O22 (LOC307681), mRNA [XM_226288]
A_44_P247219	Cited4	NM_053699	-0.75	0.0000	0.0116	ref Rattus norvegicus Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 4 (Cited4), mRNA [NM_053699]
A_44_P253380	RGD1563738	XM_345920	-0.80	0.0000	0.0116	gb Rattus norvegicus similar to RIKEN cDNA 1700081O22 (LOC367059), mRNA [XM_345920]
A_43_P13418	Kcnk2	NM_172042	-1.62	0.0000	0.0120	ref Rattus norvegicus potassium channel, subfamily K, member 2 (Kcnk2), transcript variant 2, mRNA [NM_172042]
A_44_P727508	TC594987	TC594987	-0.43	0.0001	0.0135	gb BF281819 EST446410 Rat Gene Index, normalized rat, Rattus norvegicus cDNA Rattus norvegicus cDNA clone RGIBD05, mRNA sequence [BF281819]
A_44_P515978	ENSRNOT00000041850	ENSRNOT00000041850	-0.61	0.0001	0.0135	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZAW7][ENSRNOT00000041850]
A_44_P220821	AW532611	AW532611	-0.26	0.0001	0.0149	gb AW532611 UI-R-BS0-amp-e-02-0-UI.s1 UI-R-BS0 Rattus norvegicus cDNA clone UI-R-BS0-amp-e-02-0-UI 3', mRNA sequence [AW532611]
A_44_P1042234	Stmn3	NM_024346	-0.41	0.0001	0.0151	ref Rattus norvegicus stathmin-like 3 (Stmn3), mRNA [NM_024346]
A_44_P210486	Atp5g1	NM_017311	-0.31	0.0001	0.0160	ref Rattus norvegicus ATP synthase, H ⁺ -transporting, mitochondrial F0 complex, subunit C1 (subunit 9) (Atp5g1), nuclear gene encoding mitochondrial protein, mRNA [NM_017311]
A_42_P808456	Disp1	NM_001105983	-0.41	0.0001	0.0160	ref Rattus norvegicus dispatched homolog 1 (Drosophila) (Disp1), mRNA [NM_001105983]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_44_P865620	TC591379	TC591379	-0.74	0.0001	0.0160	tc Q9JJ03_RAT (Q9JJ03) Angiotensin II type 1A receptor associated protein, complete [TC591379]
A_44_P268395	AA943735	AA943735	-0.33	0.0001	0.0164	gb AA943735 EST199234 Normalized rat brain, Bento Soares Rattus sp. cDNA clone RBRAP04 3' end, mRNA sequence [AA943735]
A_44_P148699	AA955748	AA955748	-0.27	0.0001	0.0180	gb AA955748 UI-R-E1-fg-d-10-0-UI.s1 UI-R-E1 Rattus norvegicus cDNA clone UI-R-E1-fg-d-10-0-UI 3' similar to gi [AA955748]
A_44_P884766	RGD1561849	NM_001109260	-0.76	0.0001	0.0180	ref Rattus norvegicus similar to RIKEN cDNA 3110035E14 (RGD1561849), mRNA [NM_001109260]
A_42_P540711	Rasd2	NM_133568	-1.16	0.0001	0.0201	ref Rattus norvegicus RASD family, member 2 (Rasd2), mRNA [NM_133568]
A_44_P126564	Mon1a	NM_001126284	-0.35	0.0001	0.0209	ref Rattus norvegicus MON1 homolog A (yeast) (Mon1a), mRNA [NM_001126284]
A_42_P820829	Oaf	NM_001014090	-0.44	0.0001	0.0217	ref Rattus norvegicus OAF homolog (Drosophila) (Oaf), mRNA [NM_001014090]
A_44_P112527	Megf11	ENSRNOT00000058007	-0.58	0.0001	0.0217	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1M1S8] [ENSRNOT00000058007]
A_43_P15784	Cyp4a3	NM_175760	-0.73	0.0002	0.0229	ref Rattus norvegicus cytochrome P450, family 4, subfamily a, polypeptide 3 (Cyp4a3), mRNA [NM_175760]
A_44_P466189	Angptl2	NM_133569	-0.92	0.0002	0.0231	ref Rattus norvegicus angiopoietin-like 2 (Angptl2), mRNA [NM_133569]
A_44_P295408	ENSRNOT00000041850	ENSRNOT00000041850	-0.58	0.0002	0.0235	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZAW7] [ENSRNOT00000041850]
A_44_P175349	Crispld2	NM_138518	-0.69	0.0002	0.0235	ref Rattus norvegicus cysteine-rich secretory protein LCCL domain containing 2 (Crispld2), mRNA [NM_138518]
A_44_P118531	AW919008	AW919008	-0.22	0.0002	0.0235	gb AW919008 EST350312 Rat gene index, normalized rat, norvegicus, Bento Soares Rattus norvegicus cDNA clone RGIFB53 5' end, mRNA sequence [AW919008]
A_44_P283985	ENSRNOT00000052385	ENSRNOT00000052385	-0.54	0.0002	0.0240	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZWL2] [ENSRNOT00000052385]
A_44_P169574	AI045802	AI045802	-0.22	0.0002	0.0247	gb AI045802 UI-R-C0-jq-c-07-0-UI.s2 UI-R-C0 Rattus norvegicus cDNA clone UI-R-C0-jq-c-07-0-UI 3', mRNA sequence [AI045802]
A_43_P11040	Tppp3	NM_001009639	-0.81	0.0002	0.0247	ref Rattus norvegicus tubulin polymerization-promoting protein family member 3 (Tppp3), mRNA [NM_001009639]
A_44_P523028	XM_344727	XM_344727	-0.45	0.0002	0.0266	gb Rattus norvegicus similar to RIKEN cDNA 4933431D05 (LOC364949), mRNA [XM_344727]
A_44_P426478	XM_239603	XM_239603	-0.33	0.0002	0.0266	gb Rattus norvegicus similar to RIKEN cDNA 1300006M19 (LOC304282), mRNA [XM_239603]
A_44_P370229	Fam20c	NM_001012238	-0.47	0.0002	0.0266	ref Rattus norvegicus family with sequence similarity 20, member C (Fam20c), mRNA [NM_001012238]
A_44_P422134	ENSRNOT00000041850	ENSRNOT00000041850	-0.60	0.0002	0.0266	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZAW7] [ENSRNOT00000041850]
A_44_P356738	LOC501080	XM_576492	-0.51	0.0002	0.0275	ref PREDICTED: Rattus norvegicus similar to Discs large homolog 5 (Placenta and prostate DLG) (Discs large protein P-dlg) (LOC501080), mRNA [XM_576492]
A_44_P1034201	Lamb3	NM_001100841	-0.52	0.0002	0.0275	ref Rattus norvegicus laminin, beta 3 (Lamb3), mRNA [NM_001100841]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_44_P365516	Tsc22d1	NM_013043	-0.75	0.0002	0.0275	ref Rattus norvegicus TSC22 domain family, member 1 (Tsc22d1), transcript variant 2, mRNA [NM_013043]
A_42_P721270	Nfix	NM_030866	-0.36	0.0003	0.0275	ref Rattus norvegicus nuclear factor I/X (CCAAT-binding transcription factor) (Nfix), mRNA [NM_030866]
A_44_P298934	BE116552	BE116552	-0.49	0.0003	0.0275	gb BE116552 UI-R-BS1-ayj-e-12-0-UI.s1 UI-R-BS1 Rattus norvegicus cDNA clone UI-R-BS1-ayj-e-12-0-UI 3', mRNA sequence [BE116552]
A_44_P1038885	Slc16a13	NM_001005530	-1.05	0.0003	0.0287	ref Rattus norvegicus solute carrier family 16, member 13 (monocarboxylic acid transporter 13) (Slc16a13), mRNA [NM_001005530]
A_44_P390265	AA858718	AA858718	-0.25	0.0003	0.0298	gb AA858718 UI-R-A0-be-b-04-0-UI.s1 UI-R-A0 Rattus norvegicus cDNA clone UI-R-A0-be-b-04-0-UI 3' similar to emb [AA858718]
A_44_P861558	Ncor2	NM_001108334	-0.29	0.0003	0.0298	ref Rattus norvegicus nuclear receptor co-repressor 2 (Ncor2), mRNA [NM_001108334]
A_42_P706831	RGD1562079	NM_001177687	-0.31	0.0003	0.0298	ref Rattus norvegicus RGD1562079 (RGD1562079), mRNA [NM_001177687]
A_44_P397472	BQ205131	BQ205131	-0.37	0.0003	0.0298	gb BQ205131 UI-R-DZ1-cn-h-f-09-0-UI.s1 NCI_CGAP_DZ1 Rattus norvegicus cDNA clone IMAGE:7345643 3', mRNA sequence [BQ205131]
A_44_P204001	ENSRNOT00000041850	ENSRNOT00000041850	-0.60	0.0003	0.0298	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZAW7] [ENSRNOT00000041850]
A_43_P14977	Tsc22d1	NM_001109912	-0.68	0.0003	0.0298	ref Rattus norvegicus TSC22 domain family, member 1 (Tsc22d1), transcript variant 1, mRNA [NM_001109912]
A_42_P533312	Pc	NM_012744	-0.46	0.0003	0.0305	ref Rattus norvegicus pyruvate carboxylase (Pc), nuclear gene encoding mitochondrial protein, mRNA [NM_012744]
A_44_P553424	Pnpla5	NM_001130497	-1.45	0.0003	0.0319	ref Rattus norvegicus patatin-like phospholipase domain containing 5 (Pnpla5), mRNA [NM_001130497]
A_44_P482700	Ttyh1	NM_001106225	-0.18	0.0004	0.0326	ref Rattus norvegicus tweety homolog 1 (Drosophila) (Ttyh1), mRNA [NM_001106225]
A_44_P277923	AI072634	AI072634	-0.49	0.0004	0.0326	gb AI072634 UI-R-C2-nn-f-11-0-UI.s1 UI-R-C2 Rattus norvegicus cDNA clone UI-R-C2-nn-f-11-0-UI 3', mRNA sequence [AI072634]
A_43_P18256	LOC100158225	NM_001127606	-0.25	0.0004	0.0336	ref Rattus norvegicus hypothetical protein LOC100158225 (LOC100158225), mRNA [NM_001127606]
A_43_P18344	Ripk2	NM_001191865	-0.27	0.0004	0.0375	ref Rattus norvegicus receptor-interacting serine-threonine kinase 2 (Ripk2), mRNA [NM_001191865]
A_44_P653701	Mybl2	NM_001106536	-0.29	0.0004	0.0375	ref Rattus norvegicus myeloblastosis oncogene-like 2 (Mybl2), mRNA [NM_001106536]
A_44_P121790	ENSRNOT00000041850	ENSRNOT00000041850	-0.42	0.0004	0.0375	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZAW7] [ENSRNOT00000041850]
A_44_P1033661	Prpf3	NM_001108559	-0.25	0.0005	0.0396	ref Rattus norvegicus PRP3 pre-mRNA processing factor 3 homolog (S. cerevisiae) (Prpf3), mRNA [NM_001108559]
A_42_P735495	Cyp4a8	NM_031605	-0.83	0.0005	0.0400	ref Rattus norvegicus cytochrome P450, family 4, subfamily a, polypeptide 8 (Cyp4a8), mRNA [NM_031605]
A_44_P776188	Actr1b	NM_001039028	-0.29	0.0005	0.0406	ref Rattus norvegicus ARP1 actin-related protein 1 homolog B (yeast) (Actr1b), mRNA [NM_001039028]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_44_P516940	BF281337	BF281337	-0.34	0.0005	0.0406	gb BF281337 EST445928 Rat Gene Index, normalized rat, Rattus norvegicus cDNA Rattus norvegicus cDNA clone RGIAD41 3' sequence, mRNA sequence [BF281337]
A_42_P462379	TC593865	TC593865	-0.39	0.0005	0.0409	tc Q3H6G1_9ACTO (Q3H6G1) Regulatory protein, LuxR: Metal-dependent phosphohydrolase, HD subdomain, partial (3%) [TC593865]
A_44_P200630	AA851208	AA851208	-0.31	0.0006	0.0418	gb AA851208 EST193976 Normalized rat placenta, Bento Soares Rattus sp. cDNA clone RPLAD82 3' end, mRNA sequence [AA851208]
A_44_P699211	A_44_P699211	A_44_P699211	-0.32	0.0006	0.0420	Unknown
A_44_P447222	AA956633	AA956633	-0.36	0.0006	0.0421	gb AA956633 UI-R-E1-fn-g-02-0-UI.s1 UI-R-E1 Rattus norvegicus cDNA clone UI-R-E1-fn-g-02-0-UI 3' similar to gi [AA956633]
A_44_P330847	ENSRNOT00000038605	ENSRNOT00000038605	-0.87	0.0006	0.0436	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1M2G1]
A_44_P433431	Hist1h2an	NM_001107354	-0.28	0.0006	0.0444	ref Rattus norvegicus histone cluster 1, H2an (Hist1h2an), mRNA [NM_001107354]
A_43_P11369	RGD1304792	NM_001134554	-0.28	0.0006	0.0452	ref Rattus norvegicus similar to chromosome 2 open reading frame 3; transcription factor 9 (binds GC-rich sequences) (RGD1304792), mRNA [NM_001134554]
A_44_P146616	Hist3h2a	NM_021840	-0.32	0.0007	0.0463	gb Rattus norvegicus histone 2a (H2a), mRNA [NM_021840]
A_44_P342451	Rpp38	NM_001033063	-0.51	0.0007	0.0463	ref Rattus norvegicus ribonuclease P/ MRP 38 subunit (human) (Rpp38), mRNA [NM_001033063]
A_44_P226050	BM391860	BM391860	-0.27	0.0007	0.0469	gb BM391860 UI-R-DO1-cmk-j-12-0-UI.s1 UI-R-DO1 Rattus norvegicus cDNA clone UI-R-DO1-cmk-j-12-0-UI 3', mRNA sequence [BM391860]
A_44_P949357	TC637337	TC637337	-0.32	0.0007	0.0486	tc Q3JMD5_BURP1 (Q3JMD5) Hydrogenase 4 membrane component, partial (7%) [TC637337]
A_44_P552849	Ctsh	NM_012939	-0.30	0.0007	0.0490	ref Rattus norvegicus cathepsin H (Ctsh), mRNA [NM_012939]
A_44_P219516	AW252650	AW252650	-0.43	0.0008	0.0520	gb AW252650 UI-R-BJ0-aeb-a-05-0-UI.s1 UI-R-BJ0 Rattus norvegicus cDNA clone UI-R-BJ0-aeb-a-05-0-UI 3', mRNA sequence [AW252650]
A_44_P711071	Smg7	NM_001191549	-0.27	0.0008	0.0526	ref Rattus norvegicus Smg-7 homolog, nonsense mediated mRNA decay factor (C. elegans) (Smg7), mRNA [NM_001191549]
A_44_P520700	FQ234328	FQ234328	-0.37	0.0008	0.0531	gb Rattus norvegicus TL0AEA59YG01 mRNA sequence. [FQ234328]
A_44_P995058	Cope	ENSRNOT00000027381	-0.25	0.0009	0.0533	ens coatamer subunit epsilon [Source:RefSeq peptide;Acc:NP_001099546]
A_43_P18422	Zcchc24	NM_001108394	-0.26	0.0009	0.0538	ref Rattus norvegicus zinc finger, CCHC domain containing 24 (Zcchc24), mRNA [NM_001108394]
A_43_P21520	Lrp8	ENSRNOT00000017575	-0.29	0.0009	0.0538	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZE47]
A_44_P869639	Setd5	NM_001106614	-0.31	0.0009	0.0538	ref Rattus norvegicus SET domain containing 5 (Setd5), mRNA [NM_001106614]
A_42_P504077	Pdpx	NM_001135819	-0.56	0.0009	0.0538	ref Rattus norvegicus pyridoxal (pyridoxine, vitamin B6) phosphatase (Pdpx), mRNA [NM_001135819]
A_44_P503251	Nov	NM_030868	-1.92	0.0009	0.0538	ref Rattus norvegicus nephroblastoma overexpressed gene (Nov), mRNA [NM_030868]
A_42_P600817	Trpv4	NM_023970	-0.24	0.0009	0.0540	ref Rattus norvegicus transient receptor potential cation channel, subfamily V, member 4 (Trpv4), mRNA [NM_023970]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_44_P375553	Lrp1	NM_001130490	-0.58	0.0009	0.0541	ref Rattus norvegicus low density lipoprotein receptor-related protein 1 (Lrp1), mRNA [NM_001130490]
A_44_P593422	FQ226701	FQ226701	-0.21	0.0010	0.0545	gb Rattus norvegicus TLOAEA1YL10 mRNA sequence. [FQ226701]
A_44_P649046	Lrrc20	NM_001109171	-0.33	0.0009	0.0545	ref Rattus norvegicus leucine rich repeat containing 20 (Lrrc20), mRNA [NM_001109171]
A_44_P423365	TC590043	TC590043	-0.39	0.0010	0.0545	gb AW143634 EST293930 Normalized rat embryo, Bento Soares Rattus sp. cDNA clone RGIBX04 5' end, mRNA sequence [AW143634]
A_44_P334157	AI176460	AI176460	-0.64	0.0010	0.0546	gb AI176460 EST220045 Normalized rat ovary, Bento Soares Rattus sp. cDNA clone ROVBS08 3' end, mRNA sequence [AI176460]
A_44_P1031421	Akap13	NM_001106271	-0.25	0.0010	0.0553	ref Rattus norvegicus A kinase (PRKA) anchor protein 13 (Akap13), mRNA [NM_001106271]
A_44_P194256	Gstt2	NM_012796	-0.36	0.0010	0.0553	ref Rattus norvegicus glutathione S-transferase, theta 2 (Gstt2), mRNA [NM_012796]
A_44_P222551	ENSRNOT00000047696	ENSRNOT00000047696	-0.28	0.0010	0.0556	ens Histone H2A type 2-A [Source:UniProtKB/Swiss-Prot;Acc:P0CC09] [ENSRNOT00000047696]
A_44_P761302	TC597117	TC597117	-0.57	0.0011	0.0589	tc Q60AM1_METCA (Q60AM1) CheW domain protein, partial (7%) [TC597117]
A_44_P617381	Rnf216	NM_001107122	-0.27	0.0011	0.0592	ref Rattus norvegicus ring finger protein 216 (Rnf216), mRNA [NM_001107122]
A_44_P1034209	Lamb3	NM_001100841	-0.33	0.0011	0.0593	ref Rattus norvegicus laminin, beta 3 (Lamb3), mRNA [NM_001100841]
A_44_P558992	AI137488	AI137488	-0.33	0.0012	0.0611	gb AI137488 UI-R-C2p-ol-g-11-0-UI.s1 UI-R-C2p Rattus norvegicus cDNA clone UI-R-C2p-ol-g-11-0-UI 3', mRNA sequence [AI137488]
A_44_P115192	Slc5a5	NM_052983	-0.37	0.0012	0.0613	ref Rattus norvegicus solute carrier family 5 (sodium iodide symporter), member 5 (Slc5a5), mRNA [NM_052983]
A_44_P508845	XM_216190	XM_216190	-0.30	0.0012	0.0614	gb Rattus norvegicus similar to SEPIAPTERIN REDUCTASE (SPR) (LOC297402), mRNA [XM_216190]
A_44_P258949	Pde4b	NM_017031	-0.21	0.0012	0.0620	ref Rattus norvegicus phosphodiesterase 4B, cAMP specific (Pde4b), mRNA [NM_017031]
A_44_P1014163	Gsn	NM_001004080	-0.36	0.0012	0.0623	ref Rattus norvegicus gelsolin (Gsn), mRNA [NM_001004080]
A_42_P463675	Itga7	NM_030842	-0.45	0.0012	0.0623	ref Rattus norvegicus integrin, alpha 7 (Itga7), mRNA [NM_030842]
A_44_P1036534	Paqr4	NM_001017377	-0.63	0.0013	0.0625	ref Rattus norvegicus progesterin and adipoQ receptor family member IV (Paqr4), mRNA [NM_001017377]
A_44_P387934	AI070791	AI070791	-0.45	0.0013	0.0626	gb UI-R-C2-mr-d-11-0-UI.s1 UI-R-C2 Rattus norvegicus cDNA clone UI-R-C2-mr-d-11-0-UI 3', mRNA sequence [AI070791]
A_44_P484512	AA924735	AA924735	-0.44	0.0013	0.0631	gb AA924735 UI-R-A1-ed-g-01-0-UI.s1 UI-R-A1 Rattus norvegicus cDNA clone UI-R-A1-ed-g-01-0-UI 3' similar to gi [AA924735]
A_44_P165039	Zfp1	NM_001242627	-0.36	0.0013	0.0635	ref Rattus norvegicus zinc finger protein, multitype 1 (Zfp1), mRNA [NM_001242627]
A_44_P138355	LOC100362689	ENSRNOT00000002214	-0.29	0.0013	0.0637	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1M9R9] [ENSRNOT00000002214]
A_42_P562635	Tmem115	NM_001108779	-0.23	0.0013	0.0640	ref Rattus norvegicus transmembrane protein 115 (Tmem115), mRNA [NM_001108779]
A_43_P22719	Pla2g2e	NM_001106696	-0.25	0.0014	0.0660	ref Rattus norvegicus phospholipase A2, group IIE (Pla2g2e), mRNA [NM_001106696]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_42_P475340	Fbxw5	NM_001025730	−0.26	0.0014	0.0660	ref Rattus norvegicus F-box and WD repeat domain containing 5 (Fbxw5), mRNA [NM_001025730]
A_44_P490265	RGD1564730	ENSRNOT00000047012	−0.28	0.0014	0.0660	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZH62] [ENSRNOT00000047012]
A_44_P911187	AA858651	AA858651	−0.43	0.0014	0.0660	gb UI-R-A0-bf-d-04-0-UI.s1 UI-R-A0 Rattus norvegicus cDNA clone UI-R-A0-bf-d-04-0-UI 3' similar to gb [AA858651]
A_44_P800548	A_44_P800548	A_44_P800548	−0.45	0.0014	0.0660	Unknown
A_43_P12227	Crip2	NM_022501	−0.50	0.0014	0.0663	ref Rattus norvegicus cysteine-rich protein 2 (Crip2), mRNA [NM_022501]
A_44_P1004142	Lime1	NM_001108614	−0.23	0.0015	0.0665	ref Rattus norvegicus Lck interacting transmembrane adaptor 1 (Lime1), mRNA [NM_001108614]
A_44_P503552	Macrocl1	NM_139337	−0.37	0.0015	0.0673	ref Rattus norvegicus MACRO domain containing 1 (Macrocl1), mRNA [NM_139337]
A_44_P463345	Vkorc1	AW253787	−0.50	0.0015	0.0673	gb AW253787 UI-R-BJ0-acz-d-05-0-UI.s1 UI-R-BJ0 Rattus norvegicus cDNA clone UI-R-BJ0-acz-d-05-0-UI 3', mRNA sequence [AW253787]
A_43_P16535	Mrps34	NM_001105771	−0.19	0.0015	0.0682	ref Rattus norvegicus mitochondrial ribosomal protein S34 (Mrps34), nuclear gene encoding mitochondrial protein, mRNA [NM_001105771]
A_44_P417303	RGD1560784	XM_343770	−0.24	0.0015	0.0683	gb Rattus norvegicus similar to hypothetical protein MGC31104 (LOC363449), mRNA [XM_343770]
A_44_P868495	TC590801	TC590801	−0.27	0.0016	0.0684	tc Q6TMY0_SCHBO (Q6TMY0) Nicotinic acetylcholine receptor non-alpha subunit precursor, partial (3%) [TC590801]
A_44_P305636	AA955197	AA955197	−0.22	0.0016	0.0697	gb AA955197 UI-R-A1-du-d-02-0-UI.s1 UI-R-A1 Rattus norvegicus cDNA clone UI-R-A1-du-d-02-0-UI 3', mRNA sequence [AA955197]
A_44_P905275	BG381647	BG381647	−0.34	0.0017	0.0697	gb BG381647 UI-R-CT0-bud-g-05-0-UI.s1 UI-R-CT0 Rattus norvegicus cDNA clone UI-R-CT0-bud-g-05-0-UI 3', mRNA sequence [BG381647]
A_44_P638654	Ihh	NM_053384	−0.49	0.0016	0.0697	ref Rattus norvegicus Indian hedgehog (Ihh), mRNA [NM_053384]
A_44_P175376	Aldh1b1	NM_001011975	−0.49	0.0016	0.0697	ref Rattus norvegicus aldehyde dehydrogenase 1 family, member B1 (Aldh1b1), nuclear gene encoding mitochondrial protein, mRNA [NM_001011975]
A_44_P210994	ENSRNOT00000041850	ENSRNOT00000041850	−0.56	0.0016	0.0697	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZAW7] [ENSRNOT00000041850]
A_44_P178561	LOC100302372	NM_001162897	−0.30	0.0017	0.0698	ref Rattus norvegicus hypothetical protein LOC100302372 (LOC100302372), mRNA [NM_001162897]
A_43_P10865	Ube2e2	NM_001108371	−0.30	0.0017	0.0698	ref Rattus norvegicus ubiquitin-conjugating enzyme E2E 2 (Ube2e2), mRNA [NM_001108371]
A_44_P674035	AW522880	AW522880	−0.39	0.0017	0.0698	gb UI-R-BO0-ahn-g-09-0-UI.s1 UI-R-BO0 Rattus norvegicus cDNA clone UI-R-BO0-ahn-g-09-0-UI 3', mRNA sequence [AW522880]
A_44_P1048380	Fam46a	NM_001106844	−0.45	0.0017	0.0698	ref Rattus norvegicus family with sequence similarity 46, member A (Fam46a), mRNA [NM_001106844]
A_44_P329712	S63167	S63167	−0.72	0.0017	0.0698	gb 3 beta-hydroxysteroid dehydrogenase isomerase type II.2 [rats, liver, mRNA, 2675 nt]. [S63167]
A_44_P386664	ENSRNOT00000046191	ENSRNOT00000046191	−0.27	0.0017	0.0707	ens Histone H2A type 1-F [Source:UniProtKB/Swiss-Prot;Acc:Q64598] [ENSRNOT00000046191]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_44_P387410	AA963282	AA963282	-0.16	0.0018	0.0711	gb AA963282 UI-R-E1-gh-h-06-0-UI.s1 UI-R-E1 Rattus norvegicus cDNA clone UI-R-E1-gh-h-06-0-UI 3', mRNA sequence [AA963282]
A_44_P283444	Slc19a1	NM_017299	-0.21	0.0018	0.0711	ref Rattus norvegicus solute carrier family 19 (folate transporter), member 1 (Slc19a1), transcript variant 1, mRNA [NM_017299]
A_43_P22141	Foxo4	NM_001106943	-0.22	0.0018	0.0711	ref Rattus norvegicus forkhead box O4 (Foxo4), mRNA [NM_001106943]
A_44_P167638	AW534176	AW534176	-0.28	0.0018	0.0711	gb AW534176 UI-R-C4-alq-b-02-0-UI.s1 UI-R-C4 Rattus norvegicus cDNA clone UI-R-C4-alq-b-02-0-UI 3', mRNA sequence [AW534176]
A_44_P116346	Soat2	NM_153728	-0.34	0.0017	0.0711	ref Rattus norvegicus sterol O-acyltransferase 2 (Soat2), mRNA [NM_153728]
A_44_P433147	Gnat3	NM_173139	-0.38	0.0018	0.0711	ref Rattus norvegicus guanine nucleotide binding protein, alpha transducing 3 (Gnat3), mRNA [NM_173139]
A_44_P592983	FM122635	FM122635	-0.44	0.0018	0.0711	gb FM122635 etnohea Rattus norvegicus cDNA clone etnoheaP0058C05 5', mRNA sequence [FM122635]
A_44_P325285	Tymp	NM_001012122	-1.12	0.0017	0.0711	ref Rattus norvegicus thymidine phosphorylase (Tymp), mRNA [NM_001012122]
A_44_P999653	Tsen54	NM_001109576	-0.23	0.0018	0.0713	ref Rattus norvegicus tRNA splicing endonuclease 54 homolog (S. cerevisiae) (Tsen54), mRNA [NM_001109576]
A_44_P554782	BF564475	BF564475	-0.24	0.0019	0.0729	gb UI-R-BU0-amt-h-03-0-UI.r1 UI-R-BU0 Rattus norvegicus cDNA clone UI-R-BU0-amt-h-03-0-UI 5', mRNA sequence [BF564475]
A_44_P975167	Hist1h2an	NM_001107354	-0.26	0.0019	0.0729	ref Rattus norvegicus histone cluster 1, H2an (Hist1h2an), mRNA [NM_001107354]
A_44_P151759	Cdig2	NM_153624	-0.29	0.0019	0.0735	ref Rattus norvegicus Cdig2 protein (Cdig2), mRNA [NM_153624]
A_44_P179814	Gas6	NM_057100	-0.48	0.0019	0.0735	ref Rattus norvegicus growth arrest specific 6 (Gas6), mRNA [NM_057100]
A_44_P620356	Cstf2t	NM_001107586	-0.22	0.0019	0.0735	ref Rattus norvegicus cleavage stimulation factor, 3' pre-RNA subunit 2, tau (Cstf2t), mRNA [NM_001107586]
A_44_P454763	Pcdh18	NM_001100524	-0.44	0.0020	0.0747	ref Rattus norvegicus protocadherin 18 (Pcdh18), mRNA [NM_001100524]
A_44_P476936	TC574523	TC574523	-0.36	0.0020	0.0752	tc AGTRA_RAT (P25095) Type-1A angiotensin II receptor (AT1) (AT1A), complete [TC574523]
A_44_P180980	TC621691	TC621691	-0.39	0.0020	0.0752	gb BQ209232 UI-R-DY1-cnt-c-16-0-UI.s1 NCI_CGAP_DY1 Rattus norvegicus cDNA clone IMAGE:7334442 3', mRNA sequence [BQ209232]
A_44_P1040503	Pctp	ENSRNOT00000003295	-0.42	0.0020	0.0758	ens Phosphatidylcholine transfer protein [Source:UniProtKB/Swiss-Prot;Acc:P53809] [ENSRNOT00000003295]
A_44_P615345	Llgl2	NM_001127549	-0.23	0.0020	0.0758	ref Rattus norvegicus lethal giant larvae homolog 2 (Drosophila) (Llgl2), mRNA [NM_001127549]
A_44_P976212	TC630316	TC630316	-0.28	0.0021	0.0760	Unknown
A_44_P336925	CA510266	CA510266	-0.26	0.0021	0.0763	gb CA510266 UI-R-FS0-cqr-h-07-0-UI.s1 NCI_CGAP_FS0 Rattus norvegicus cDNA clone IMAGE:7357209 3', mRNA sequence [CA510266]
A_44_P207383	AI013472	AI013472	-0.36	0.0021	0.0763	gb AI013472 EST208147 Normalized rat spleen, Bento Soares Rattus sp. cDNA clone RSPBL95 3' end, mRNA sequence [AI013472]
A_44_P1038341	Hal	NM_017159	-0.47	0.0021	0.0765	ref Rattus norvegicus histidine ammonia lyase (Hal), mRNA [NM_017159]
A_44_P575890	TC602730	TC602730	-0.40	0.0021	0.0765	tc Q7TQ12_RAT (Q7TQ12) Aa1114, partial (9%) [TC602730]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_44_P352912	AI575434	AI575434	-0.22	0.0021	0.0765	gb AI575434 UI-R-Y0-vg-c-11-0-UI.s1 UI-R-Y0 Rattus norvegicus cDNA clone UI-R-Y0-vg-c-11-0-UI 3', mRNA sequence [AI575434]
A_42_P710309	FQ216592	FQ216592	-0.23	0.0022	0.0768	gb Rattus norvegicus TL0ACA41YP14 mRNA sequence. [FQ216592]
A_42_P823706	Wdtdc1	NM_001107908	-0.27	0.0022	0.0768	ref Rattus norvegicus WD and tetratricopeptide repeats 1 (Wdtdc1), mRNA [NM_001107908]
A_44_P503215	AA799326	AA799326	-0.57	0.0022	0.0768	gb AA799326 EST188823 Normalized rat heart, Bento Soares Rattus sp. cDNA clone RHEAA33 3' end similar to fatty acid transport protein, mRNA sequence [AA799326]
A_44_P1045734	Stac3	NM_001130558	-2.94	0.0022	0.0768	ref Rattus norvegicus SH3 and cysteine rich domain 3 (Stac3), mRNA [NM_001130558]
A_44_P1004218	Gne	NM_053765	-0.31	0.0022	0.0771	ref Rattus norvegicus glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (Gne), mRNA [NM_053765]
A_43_P11350	Nt5dc2	NM_001009271	-0.26	0.0022	0.0771	ref Rattus norvegicus 5'-nucleotidase domain containing 2 (Nt5dc2), mRNA [NM_001009271]
A_44_P659386	A_44_P659386	A_44_P659386	-0.23	0.0022	0.0777	Unknown
A_44_P388545	BM986478	BM986478	-0.25	0.0022	0.0777	gb BM986478 EST594072 Rat gene index, normalized rat, norvegicus Rattus norvegicus cDNA clone RGOAC57 3' end, mRNA sequence [BM986478]
A_43_P14265	TC608958	TC608958	-0.28	0.0022	0.0777	tc Q2G7V7_NOVAD (Q2G7V7) Glycosyl transferase, group 1, partial (4%) [TC608958]
A_44_P921786	AI072054	AI072054	-0.18	0.0023	0.0777	gb AI072054 UI-R-C2-nf-a-03-0-UI.s1 UI-R-C2 Rattus norvegicus cDNA clone UI-R-C2-nf-a-03-0-UI 3', mRNA sequence [AI072054]
A_44_P329944	AA945177	AA945177	-0.23	0.0023	0.0777	gb AA945177 EST200676 Normalized rat liver, Bento Soares Rattus sp. cDNA clone RLI AH53 3' end, mRNA sequence [AA945177]
A_44_P413821	AA956104	AA956104	-0.23	0.0023	0.0777	gb AA956104 UI-R-E1-fi-e-03-0-UI.s1 UI-R-E1 Rattus norvegicus cDNA clone UI-R-E1-fi-e-03-0-UI 3' similar to gi [AA956104]
A_44_P484393	Ptma	NM_021740	-0.29	0.0023	0.0777	ref Rattus norvegicus prothymosin alpha (Ptma), mRNA [NM_021740]
A_44_P163957	XM_343681	XM_343681	-0.22	0.0023	0.0777	gb Rattus norvegicus LOC363343 (LOC363343), mRNA [XM_343681]
A_43_P12332	Nolc1	NM_022869	-0.26	0.0023	0.0777	ref Rattus norvegicus nucleolar and coiled-body phosphoprotein 1 (Nolc1), mRNA [NM_022869]
A_44_P257135	Slc29a3	NM_181639	-0.28	0.0023	0.0777	ref Rattus norvegicus solute carrier family 29 (nucleoside transporters), member 3 (Slc29a3), mRNA [NM_181639]
A_44_P704817	A_44_P704817	A_44_P704817	-0.29	0.0023	0.0777	Unknown
A_44_P104221	BQ194442	BQ194442	-0.34	0.0023	0.0777	gb BQ194442 UI-R-CN1-cma-f-24-0-UI.s1 UI-R-CN1 Rattus norvegicus cDNA clone UI-R-CN1-cma-f-24-0-UI 3', mRNA sequence [BQ194442]
A_44_P165037	Zfpm1	NM_001242627	-0.35	0.0023	0.0777	ref Rattus norvegicus zinc finger protein, multitype 1 (Zfpm1), mRNA [NM_001242627]
A_44_P198304	AW527961	AW527961	-0.42	0.0023	0.0777	gb AW527961 UI-R-BT1-akg-b-05-0-UI.s1 UI-R-BT1 Rattus norvegicus cDNA clone UI-R-BT1-akg-b-05-0-UI 3', mRNA sequence [AW527961]
A_44_P374638	Hsd17b2	NM_024391	-0.49	0.0023	0.0777	ref Rattus norvegicus hydroxysteroid (17-beta) dehydrogenase 2 (Hsd17b2), mRNA [NM_024391]
A_44_P473223	XM_344209	XM_344209	-0.62	0.0023	0.0777	gb Rattus norvegicus similar to RIKEN cDNA 1700081022 (LOC364100), mRNA [XM_344209]
A_44_P487856	Tymp	NM_001012122	-1.07	0.0023	0.0777	ref Rattus norvegicus thymidine phosphorylase (Tymp), mRNA [NM_001012122]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_44_P750262	TC610217	TC610217	-0.27	0.0024	0.0781	Unknown
A_44_P341204	AA997107	AA997107	-0.29	0.0024	0.0786	gb AA997107 UI-R-C0-hr-d-04-0-UI.s1 UI-R-C0 Rattus norvegicus cDNA clone UI-R-C0-hr-d-04-0-UI 3', mRNA sequence [AA997107]
A_44_P361465	Odf3b	NM_001191992	-0.70	0.0024	0.0786	ref Rattus norvegicus outer dense fiber of sperm tails 3B (Odf3b), mRNA [NM_001191992]
A_44_P496853	A_44_P496853	A_44_P496853	-0.31	0.0024	0.0789	Unknown
A_44_P324189	AI235446	AI235446	-0.42	0.0024	0.0789	gb AI235446 EST232008 Normalized rat ovary, Bento Soares Rattus sp. cDNA clone ROVCR88 3' end, mRNA sequence [AI235446]
A_44_P1071170	M16349	M16349	-0.44	0.0024	0.0789	gb Rat asialoglycoprotein receptor RHL1 mRNA, 5' end. [M16349]
A_43_P11857	Avpr1b	NM_017205	-0.18	0.0024	0.0792	ref Rattus norvegicus arginine vasopressin receptor 1B (Avpr1b), mRNA [NM_017205]
A_44_P791057	A_44_P791057	A_44_P791057	-0.20	0.0025	0.0792	Unknown
A_44_P351452	Bmp1	NM_031323	-0.34	0.0025	0.0795	ref Rattus norvegicus bone morphogenetic protein 1 (Bmp1), mRNA [NM_031323]
A_44_P653879	TC596924	TC596924	-0.22	0.0025	0.0797	Unknown
A_44_P1018129	TC610213	TC610213	-0.55	0.0025	0.0800	Unknown
A_44_P435381	Agxt	NM_030656	-0.36	0.0025	0.0800	ref Rattus norvegicus alanine-glyoxylate aminotransferase (Agxt), mRNA [NM_030656]
A_44_P450258	Fitm2	NM_001107799	-0.18	0.0025	0.0802	ref Rattus norvegicus fat storage-inducing transmembrane protein 2 (Fitm2), mRNA [NM_001107799]
A_44_P539597	AA818108	AA818108	-0.19	0.0025	0.0802	gb UI-R-A0-am-f-08-0-UI.s1 UI-R-A0 Rattus norvegicus cDNA clone UI-R-A0-am-f-08-0-UI 3' similar to gb [AA818108]
A_42_P570300	Depdc5	NM_001107229	-0.23	0.0026	0.0802	ref Rattus norvegicus DEP domain containing 5 (Depdc5), mRNA [NM_001107229]
A_43_P11285	Apitd1	NM_001204879	-0.64	0.0026	0.0804	ref Rattus norvegicus apoptosis-inducing, TAF9-like domain 1 (Apitd1), mRNA [NM_001204879]
A_42_P589201	Slc15a4	NM_144758	-0.19	0.0026	0.0814	ref Rattus norvegicus solute carrier family 15, member 4 (Slc15a4), mRNA [NM_144758]
A_44_P555638	Prickle3	NM_001014110	-0.25	0.0027	0.0814	ref Rattus norvegicus prickle homolog 3 (Drosophila) (Prickle3), mRNA [NM_001014110]
A_42_P647072	Mapkapk2	NM_178102	-0.31	0.0027	0.0814	ref Rattus norvegicus mitogen-activated protein kinase-activated protein kinase 2 (Mapkapk2), mRNA [NM_178102]
A_43_P17569	Sel113	XM_341223	-0.52	0.0026	0.0814	ref PREDICTED: Rattus norvegicus similar to RIKEN cDNA 2310045A20 (RGD1562860), mRNA [XM_341223]
A_43_P15779	Hapln2	NM_022285	-0.16	0.0027	0.0815	ref Rattus norvegicus hyaluronan and proteoglycan link protein 2 (Hapln2), mRNA [NM_022285]
A_44_P209949	BQ211506	BQ211506	-0.20	0.0027	0.0827	gb BQ211506 UI-R-DY1-cnq-h-17-0-UI.s1 NCI_CGAP_DY1 Rattus norvegicus cDNA clone IMAGE:7333411 3', mRNA sequence [BQ211506]
A_44_P166418	Samd11	ENSRNOT00000027564	-0.24	0.0027	0.0827	ens RCG31097, isoform CRA_aUncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZMX5] [ENSRNOT00000027564]
A_43_P12474	Ap2a2	NM_031008	-0.27	0.0027	0.0827	ref Rattus norvegicus adaptor-related protein complex 2, alpha 2 subunit (Ap2a2), mRNA [NM_031008]
A_44_P384260	Ninj2	NM_021595	-0.66	0.0027	0.0827	ref Rattus norvegicus ninjurin 2 (Ninj2), mRNA [NM_021595]
A_44_P164947	AI177413	AI177413	-0.35	0.0027	0.0829	gb AI177413 EST221033 Normalized rat placenta, Bento Soares Rattus sp. cDNA clone RPLBY89 3' end, mRNA sequence [AI177413]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_44_P482267	Elov15	NM_134382	-0.28	0.0028	0.0832	ref Rattus norvegicus ELOVL family member 5, elongation of long chain fatty acids (yeast) (Elov15), mRNA [NM_134382]
A_44_P715517	RGD1309228	NM_001017451	-0.26	0.0028	0.0834	ref Rattus norvegicus similar to putative protein, with at least 9 transmembrane domains, of eukaryotic origin (43.9 kDa) (2G415) (RGD1309228), mRNA [NM_001017451]
A_44_P423458	AI100773	AI100773	-0.23	0.0028	0.0839	gb AI100773 EST210062 Normalized rat brain, Bento Soares Rattus sp. cDNA clone RBRBA09 3' end, mRNA sequence [AI100773]
A_44_P869863	TC606533	TC606533	-0.44	0.0028	0.0839	Unknown
A_44_P840751	TC635476	TC635476	-0.18	0.0029	0.0840	Unknown
A_44_P334900	Gdf6	NM_001013038	-0.24	0.0029	0.0840	ref Rattus norvegicus growth differentiation factor 6 (Gdf6), mRNA [NM_001013038]
A_44_P494310	Bri3	NM_001009604	-0.30	0.0028	0.0840	ref Rattus norvegicus brain protein I3 (Bri3), mRNA [NM_001009604]
A_44_P374375	TC648121	TC648121	-0.43	0.0028	0.0840	tc APOM_RAT (P14630) Apolipoprotein M precursor (Apo-M) (ApoM) (Protein Px), partial (41%) [TC648121]
A_44_P825985	TC625236	TC625236	-0.45	0.0028	0.0840	Unknown
A_44_P920467	FQ221509	FQ221509	-0.38	0.0029	0.0841	gb Rattus norvegicus TL0ADA35YE20 mRNA sequence. [FQ221509]
A_43_P11951	Ucn	NM_019150	-0.21	0.0029	0.0851	ref Rattus norvegicus urocortin (Ucn), mRNA [NM_019150]
A_44_P668704	TC585807	TC585807	-0.30	0.0029	0.0851	Unknown
A_43_P14751	Aqp9	NM_022960	-0.43	0.0029	0.0851	ref Rattus norvegicus aquaporin 9 (Aqp9), mRNA [NM_022960]
A_42_P676630	Gpld1	NM_001100512	-0.35	0.0029	0.0853	ref Rattus norvegicus glycosylphosphatidylinositol specific phospholipase D1 (Gpld1), mRNA [NM_001100512]
A_44_P1059556	Cyp4a1	NM_175837	-0.65	0.0029	0.0853	ref Rattus norvegicus cytochrome P450, family 4, subfamily a, polypeptide 1 (Cyp4a1), mRNA [NM_175837]
A_44_P428166	AW527148	AW527148	-0.16	0.0030	0.0853	gb AW527148 UI-R-BO1-ajm-a-12-0-UI.s1 UI-R-BO1 Rattus norvegicus cDNA clone UI-R-BO1-ajm-a-12-0-UI 3', mRNA sequence [AW527148]
A_44_P377520	A_44_P377520	A_44_P377520	-0.29	0.0030	0.0853	Unknown
A_44_P996268	Rasd2	NM_133568	-0.35	0.0030	0.0853	ref Rattus norvegicus RASD family, member 2 (Rasd2), mRNA [NM_133568]
A_44_P761492	Perld1	NM_001143895	-0.16	0.0030	0.0854	ref Rattus norvegicus per1-like domain containing 1 (Perld1), mRNA [NM_001143895]
A_44_P879764	B4galt1	NM_053287	-0.20	0.0030	0.0866	ref Rattus norvegicus UDP-Gal:betaGlcNAc beta-1,4-galactosyltransferase, polypeptide 1 (B4galt1), mRNA [NM_053287]
A_44_P1048296	Osbpl1a	NM_172023	-0.33	0.0031	0.0867	ref Rattus norvegicus oxysterol binding protein-like 1A (Osbpl1a), mRNA [NM_172023]
A_44_P573155	CA508976	CA508976	-0.21	0.0031	0.0875	gb UI-R-FS0-cqm-n-08-0-UI.s1 UI-R-FS0 Rattus norvegicus cDNA clone UI-R-FS0-cqm-n-08-0-UI 3', mRNA sequence [CA508976]
A_44_P336753	AC096165	AC096165	-0.19	0.0031	0.0876	gb Rattus norvegicus clone CH230-11H2, *** SEQUENCING IN PROGRESS ***. 45 unordered pieces [AC096165]
A_44_P134672	Snapc3	NM_001013212	-0.31	0.0032	0.0884	ref Rattus norvegicus small nuclear RNA activating complex, polypeptide 3 (Snapc3), mRNA [NM_001013212]
A_44_P430033	AI231180	AI231180	-0.39	0.0032	0.0884	gb AI231180 EST227868 Normalized rat embryo, Bento Soares Rattus sp. cDNA clone REMDG81 3' end, mRNA sequence [AI231180]
A_43_P19500	Efcab6	ENSRNOT00000055945	-0.55	0.0032	0.0884	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D4AAW3] [ENSRNOT00000055945]
A_44_P793109	TC601680	TC601680	-0.18	0.0032	0.0887	Unknown

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_43_P12530	Suox	NM_031127	-0.27	0.0033	0.0889	ref Rattus norvegicus sulfite oxidase (Suox), nuclear gene encoding mitochondrial protein, mRNA [NM_031127]
A_43_P23361	Aen	NM_001108487	-0.27	0.0033	0.0889	ref Rattus norvegicus apoptosis enhancing nuclease (Aen), mRNA [NM_001108487]
A_44_P143896	BQ211430	BQ211430	-0.22	0.0033	0.0889	gb BQ211430 UI-R-DY1-cok-f-02-0-UI.s1 NCI_CGAP_DY1 Rattus norvegicus cDNA clone IMAGE:7336420 3', mRNA sequence [BQ211430]
A_44_P212835	ENSRNOT00000041929	ENSRNOT00000041929	-0.26	0.0033	0.0889	ens Histone H2A type 1-F [Source:UniProtKB/Swiss-Prot;Acc:Q64598] [ENSRNOT00000041929]
A_44_P301367	AA800240	AA800240	-0.29	0.0033	0.0889	gb AA800240 EST189737 Normalized rat heart, Bento Soares Rattus sp. cDNA clone RHEAM82 3' end, mRNA sequence [AA800240]
A_44_P235448	BE110597	BE110597	-0.32	0.0033	0.0891	gb BE110597 UI-R-BJ1-avt-h-02-0-UI.s1 UI-R-BJ1 Rattus norvegicus cDNA clone UI-R-BJ1-avt-h-02-0-UI 3', mRNA sequence [BE110597]
A_44_P390826	BF282632	BF282632	-0.31	0.0033	0.0893	gb BF282632 EST447223 Rat Gene Index, normalized rat, Rattus norvegicus cDNA Rattus norvegicus cDNA clone RGIDR08 3' sequence, mRNA sequence [BF282632]
A_44_P654096	TC600000	TC600000	-0.32	0.0034	0.0893	Unknown
A_44_P202434	AA819129	AA819129	-0.44	0.0033	0.0893	gb AA819129 UI-R-A0-ba-b-08-0-UI.s1 UI-R-A0 Rattus norvegicus cDNA clone UI-R-A0-ba-b-08-0-UI 3' similar to emb [AA819129]
A_44_P809199	TC614636	TC614636	-0.46	0.0033	0.0893	Unknown
A_44_P399038	TC624112	TC624112	-0.20	0.0034	0.0896	tc Q6L7M6_9DELA (Q6L7M6) P12, partial (15%) [TC624112]
A_43_P16962	LOC301128	BC098860	-0.24	0.0034	0.0896	gb Rattus norvegicus similar to jumonji domain containing 2B, mRNA (cDNA clone IMAGE:7380411), complete cds. [BC098860]
A_42_P490296	Itgb4	NM_013180	-0.24	0.0035	0.0896	ref Rattus norvegicus integrin, beta 4 (Itgb4), mRNA [NM_013180]
A_44_P1037493	Tssc4	NM_001013194	-0.25	0.0035	0.0896	ref Rattus norvegicus tumor suppressing subtransferable candidate 4 (Tssc4), mRNA [NM_001013194]
A_42_P456939	Slc35b4	NM_001106590	-0.26	0.0034	0.0896	ref Rattus norvegicus solute carrier family 35, member B4 (Slc35b4), mRNA [NM_001106590]
A_44_P1024739	Wipi2	NM_001007615	-0.27	0.0034	0.0896	ref Rattus norvegicus WD repeat domain, phosphoinositide interacting 2 (Wipi2), mRNA [NM_001007615]
A_44_P165513	Dfnb31	NM_181088	-0.28	0.0035	0.0896	ref Rattus norvegicus deafness, autosomal recessive 31 (Dfnb31), mRNA [NM_181088]
A_44_P174588	FQ213162	FQ213162	-0.35	0.0034	0.0896	gb Rattus norvegicus TL0AAA49YG06 mRNA sequence. [FQ213162]
A_44_P959251	A_44_P959251	A_44_P959251	-0.37	0.0035	0.0896	Unknown
A_44_P240156	BI281697	BI281697	-0.38	0.0034	0.0896	gb BI281697 UI-R-CT0s-cav-d-07-0-UI.s1 UI-R-CT0s Rattus norvegicus cDNA clone UI-R-CT0s-cav-d-07-0-UI 3', mRNA sequence [BI281697]
A_44_P491393	Nudt7	NM_001108450	-0.43	0.0035	0.0896	ref Rattus norvegicus nudix (nucleoside diphosphate linked moiety X)-type motif 7 (Nudt7), mRNA [NM_001108450]
A_44_P291028	Arhgef19	NM_001108692	-0.59	0.0034	0.0896	ref Rattus norvegicus Rho guanine nucleotide exchange factor (GEF) 19 (Arhgef19), mRNA [NM_001108692]
A_44_P339202	Ppp1r12c	NM_001191946	-0.20	0.0035	0.0899	ref Rattus norvegicus protein phosphatase 1, regulatory (inhibitor) subunit 12C (Ppp1r12c), mRNA [NM_001191946]
A_42_P483419	Oaz1	NM_139081	-0.29	0.0035	0.0901	ref Rattus norvegicus ornithine decarboxylase antizyme 1 (Oaz1), mRNA [NM_139081]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_44_P101960	BF408841	BF408841	-0.32	0.0036	0.0909	gb BF408841 UI-R-BS2-bet-a-09-0-UI.s1 UI-R-BS2 Rattus norvegicus cDNA clone UI-R-BS2-bet-a-09-0-UI 3', mRNA sequence [BF408841]
A_44_P239864	AI231358	AI231358	-0.33	0.0036	0.0909	gb AI231358 EST228046 Normalized rat embryo, Bento Soares Rattus sp. cDNA clone REMD]10 3' end, mRNA sequence [AI231358]
A_44_P977792	CF111812	CF111812	-0.32	0.0036	0.0910	gb Shultzomica05063 Rat lung airway and parenchyma cDNA libraries Rattus norvegicus cDNA clone Contig963 5', mRNA sequence [CF111812]
A_44_P149572	Rassf7	NM_001106317	-0.28	0.0036	0.0911	ref Rattus norvegicus Ras association (RalGDS/AF-6) domain family (N-terminal) member 7 (Rassf7), mRNA [NM_001106317]
A_44_P408026	LOC100363662	XM_002726659	-0.33	0.0036	0.0911	ref PREDICTED: Rattus norvegicus 6-phosphogluconate dehydrogenase, decarboxylating-like (LOC100363662), mRNA [XM_002726659]
A_44_P280376	AI009427	AI009427	-0.37	0.0037	0.0919	gb AI009427 EST203878 Normalized rat heart, Bento Soares Rattus sp. cDNA clone RHEB]81 3' end, mRNA sequence [AI009427]
A_44_P971681	AI169156	AI169156	-0.31	0.0037	0.0928	gb AI169156 EST214990 Normalized rat kidney, Bento Soares Rattus sp. cDNA clone RKIBO21 3' end, mRNA sequence [AI169156]
A_44_P134993	Agxt	NM_030656	-0.35	0.0037	0.0928	ref Rattus norvegicus alanine-glyoxylate aminotransferase (Agxt), mRNA [NM_030656]
A_42_P470649	Dio1	NM_021653	-0.38	0.0037	0.0928	ref Rattus norvegicus deiodinase, iodothyronine, type 1 (Dio1), mRNA [NM_021653]
A_44_P517033	LOC312502	XR_085818	-0.39	0.0037	0.0928	ref PREDICTED: Rattus norvegicus similar to RAB11 family interacting protein 5 (class 1) isoform 1 (LOC312502), miscRNA [XR_085818]
A_44_P333071	Lrp1	NM_001130490	-0.46	0.0037	0.0928	ref Rattus norvegicus low density lipoprotein receptor-related protein 1 (Lrp1), mRNA [NM_001130490]
A_43_P21931	Ncapd3	NM_001034000	-0.16	0.0038	0.0931	ref Rattus norvegicus non-SMC condensin II complex, subunit D3 (Ncapd3), mRNA [NM_001034000]
A_44_P191862	Hras	NM_001098241	-0.26	0.0038	0.0931	ref Rattus norvegicus Harvey rat sarcoma virus oncogene (Hras), transcript variant 2, mRNA [NM_001098241]
A_43_P21639	Plekhg3	ENSRNOT00000008721	-0.26	0.0038	0.0931	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZA21] [ENSRNOT00000008721]
A_44_P179114	AA943131	AA943131	-0.28	0.0038	0.0931	gb AA943131 EST198630 Normalized rat brain, Bento Soares Rattus sp. cDNA clone RBRAF44 3' end, mRNA sequence [AA943131]
A_44_P394332	FQ239759	FQ239759	-0.34	0.0038	0.0931	gb FQ239759 Rattus norvegicus liver Sprague-Dawley Rattus norvegicus cDNA clone TLOABA6YL07 3', mRNA sequence [FQ239759]
A_44_P359113	ENSRNOT00000040880	ENSRNOT00000040880	-0.38	0.0038	0.0931	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F1M381] [ENSRNOT00000040880]
A_43_P18016	TC608166	TC608166	-0.48	0.0038	0.0931	tc Q91ZX7_MOUSE (Q91ZX7) Lipoprotein receptor-related protein, partial (4%) [TC608166]
A_44_P375616	Slc16a11	NM_001105797	-1.02	0.0038	0.0931	ref Rattus norvegicus solute carrier family 16 (monocarboxylic acid transporters), member 11 (Slc16a11), mRNA [NM_001105797]
A_44_P244839	BF397813	BF397813	-0.29	0.0039	0.0931	gb BF397813 UI-R-BS2-bee-h-09-0-UI.s1 UI-R-BS2 Rattus norvegicus cDNA clone UI-R-BS2-bee-h-09-0-UI 3', mRNA sequence [BF397813]
A_44_P915992	TC601232	TC601232	-0.33	0.0039	0.0931	Unknown

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_43_P13801	TC607835	TC607835	-0.18	0.0039	0.0932	tc P70602_RAT (P70602) Protein tyrosine phosphatase 20, partial (9%) [TC607835]
A_44_P209911	Nolc1	NM_022869	-0.24	0.0039	0.0932	ref Rattus norvegicus nucleolar and coiled-body phosphoprotein 1 (Nolc1), mRNA [NM_022869]
A_44_P254201	BF398403	BF398403	-0.24	0.0039	0.0933	gb BF398403 UI-R-BS2-beo-d-10-0-UI.s1 UI-R-BS2 Rattus norvegicus cDNA clone UI-R-BS2-beo-d-10-0-UI 3', mRNA sequence [BF398403]
A_44_P273639	BF414043	BF414043	-0.27	0.0039	0.0935	gb BF414043 UI-R-BJ2-bol-g-02-0-UI.s1 UI-R-BJ2 Rattus norvegicus cDNA clone UI-R-BJ2-bol-g-02-0-UI 3', mRNA sequence [BF414043]
A_44_P523401	AI234078	AI234078	-0.26	0.0040	0.0941	gb EST230766 Normalized rat lung, Bento Soares Rattus sp. cDNA clone RLUCU81 3' end, mRNA sequence [AI234078]
A_44_P258855	Qsox1	NM_053431	-0.38	0.0040	0.0941	ref Rattus norvegicus quiescin Q6 sulfhydryl oxidase 1 (Qsox1), transcript variant 2, mRNA [NM_053431]
A_44_P347253	Zc3h12a	NM_001077671	-0.17	0.0040	0.0945	ref Rattus norvegicus zinc finger CCCH type containing 12A (Zc3h12a), mRNA [NM_001077671]
A_42_P775698	Prmt1	NM_024363	-0.19	0.0040	0.0945	ref Rattus norvegicus protein arginine methyltransferase 1 (Prmt1), mRNA [NM_024363]
A_44_P126597	Paqr4	NM_001017377	-0.25	0.0040	0.0945	ref Rattus norvegicus progesterin and adipoQ receptor family member IV (Paqr4), mRNA [NM_001017377]
A_44_P125399	AI172437	AI172437	-0.30	0.0040	0.0945	gb AI172437 EST218445 Normalized rat muscle, Bento Soares Rattus sp. cDNA clone RMUBZ59 3' end, mRNA sequence [AI172437]
A_44_P376545	AI136203	AI136203	-0.32	0.0040	0.0945	gb AI136203 UI-R-C2p-ns-f-05-0-UI.s1 UI-R-C2p Rattus norvegicus cDNA clone UI-R-C2p-ns-f-05-0-UI 3', mRNA sequence [AI136203]
A_44_P502696	AA875523	AA875523	-0.37	0.0040	0.0945	gb AA875523 UI-R-E0-cv-e-11-0-UI.s1 UI-R-E0 Rattus norvegicus cDNA clone UI-R-E0-cv-e-11-0-UI 3' similar to gi [AA875523]
A_44_P819950	AA924747	AA924747	-0.30	0.0041	0.0950	gb AA924747 UI-R-A1-ed-h-01-0-UI.s1 UI-R-A1 Rattus norvegicus cDNA clone UI-R-A1-ed-h-01-0-UI 3' similar to gi [AA924747]
A_42_P673212	Cad	NM_001105710	-0.24	0.0041	0.0954	ref Rattus norvegicus carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (Cad), mRNA [NM_001105710]
A_44_P105889	BF401054	BF401054	-0.18	0.0041	0.0956	gb BF401054 UI-R-CA0-bgh-b-01-0-UI.s1 UI-R-CA0 Rattus norvegicus cDNA clone UI-R-CA0-bgh-b-01-0-UI 3', mRNA sequence [BF401054]
A_44_P714729	TC590838	TC590838	-0.31	0.0041	0.0956	tc Q7TQ12_RAT (Q7TQ12) Aa1114, partial (9%) [TC590838]
A_44_P461932	XM_228533	XM_228533	-0.58	0.0041	0.0956	gb Rattus norvegicus similar to 40S ribosomal protein S8 (LOC302393), mRNA [XM_228533]
A_44_P423435	BF283419	BF283419	-0.18	0.0042	0.0960	gb BF283419 EST448010 Rat Gene Index, normalized rat, Rattus norvegicus cDNA Rattus norvegicus cDNA clone RGIEB77 3' sequence, mRNA sequence [BF283419]
A_44_P358582	ENSRNOT00000027236	ENSRNOT00000027236	-0.29	0.0042	0.0960	ens Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D3ZDD5] [ENSRNOT00000027236]
A_44_P232319	TC595327	TC595327	-0.27	0.0042	0.0961	tc HSU37689 RNA polymerase II subunit (Homo sapiens) (exp=-1; wgp=0; cg=0), partial (19%) [TC595327]
A_44_P508514	LOC100359550	XM_002727971	-0.16	0.0042	0.0966	ref PREDICTED: Rattus norvegicus protein S100-A11-like (LOC100359550), mRNA [XM_002727971]

Table 3 (Continued)

ProbeName	GeneName	SystematicName	log ₂ (FIP/CTRL)	p-value	q-value	Description
A_42_P643349	Myl4	NM_001109495	−0.21	0.0042	0.0966	ref Rattus norvegicus myosin, light chain 4 (Myl4), mRNA [NM_001109495]
A_44_P521946	FQ235081	FQ235081	−0.23	0.0042	0.0966	gb Rattus norvegicus TL0AEA56YI18 mRNA sequence. [FQ235081]
A_44_P902085	FQ217643	FQ217643	−0.24	0.0042	0.0966	gb Rattus norvegicus TL0ACA21YB15 mRNA sequence. [FQ217643]
A_44_P1053032	Rnf150	NM_001191093	−0.26	0.0042	0.0966	ref Rattus norvegicus ring finger protein 150 (Rnf150), mRNA [NM_001191093]
A_44_P409709	Phldb1	NM_001191578	−0.20	0.0043	0.0972	ref Rattus norvegicus pleckstrin homology-like domain, family B, member 1 (Phldb1), mRNA [NM_001191578]
A_44_P351032	AA944168	AA944168	−0.18	0.0043	0.0986	gb AA944168 EST199667 Normalized rat embryo, Bento Soares Rattus sp. cDNA clone REMAD20 3' end, mRNA sequence [AA944168]
A_44_P1025476	Krt18	NM_053976	−0.33	0.0044	0.0992	ref Rattus norvegicus keratin 18 (Krt18), mRNA [NM_053976]
A_44_P524583	AI232320	AI232320	−0.42	0.0044	0.0993	gb AI232320 EST229008 Normalized rat kidney, Bento Soares Rattus sp. cDNA clone RKICA20 3' end similar to similar to mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase, mRNA sequence [AI232320]
A_42_P654862	Fam189b	NM_001107690	−0.25	0.0044	0.0998	ref Rattus norvegicus family with sequence similarity 189, member B (Fam189b), mRNA [NM_001107690]
A_44_P262102	Pafah1b3	NM_053654	−0.32	0.0044	0.0998	ref Rattus norvegicus platelet-activating factor acetylhydrolase, isoform 1b, subunit 3 (Pafah1b3), mRNA [NM_053654]

to lipid metabolism were enriched among the downregulated genes (Fig. 2A and Table 5). Because these latter effects were only partially confirmed by qPCR and were poorly reproduced in fipronil-treated mice (Fig. 3), our subsequent investigations were mainly focused on genes with upregulated expression after fipronil treatment.

Our microarray results and a previous report showing that fipronil could activate, although relatively weakly, human PXR [13] led us to hypothesize that the nuclear receptors CAR and PXR, two major regulators of hepatic biotransformation systems, could mediate a substantial part of the effects of fipronil on liver gene expression. An analysis of our microarray data through the use of IPA (Ingenuity Systems, www.ingenuity.com) also suggested that CAR and PXR were the major upstream regulators of liver gene expression upon fipronil treatment (data not shown). We first evaluated this hypothesis by comparing our gene expression profiles to those obtained by Ren et al. [19, GEO record GSE14712] in female rats exposed to phenobarbital (CAR and PXR activator) or PCN (PXR activator). Despite a limited overlap between the contents screened by Affymetrix and Agilent rat microarrays, we could show that approximately half of the genes regulated by fipronil in rat liver were also regulated by PB and/or PCN (Fig. 2B). Finally, we confirmed by qPCR the upregulation by fipronil of several genes involved in the metabolism and transport of xenobiotics and endogenous compounds (Fig. 2C–E).

3.2. Comparable but reduced effects of fipronil on mouse liver gene expression

In order to evaluate *in vivo* the role of CAR and/or PXR on liver gene expression regulations induced by fipronil, we chose to use nuclear receptor-deficient mice. As a preliminary study, we evaluated the impact of fipronil treatment (5 mg/kg per day, 14 days) on liver gene expression in wild-type C57BL/6J male mice.

Fipronil treatment resulted in an 8% increase in liver weight (1.10 ± 0.03 g vs 1.18 ± 0.02 g for control and fipronil-treated groups respectively, $p = 0.047$) as well as a 5% decrease in mean body weight at the end of the experiment (24.4 ± 0.3 g vs 23.2 ± 0.3 g respectively, $p < 0.05$) linked to a reduced body weight gain during the study in the group treated with fipronil (4.4% vs 0.7% increase in body weight respectively, $p < 0.05$).

We assayed by qPCR the hepatic expression of several mouse orthologs of the genes that were found to be upregulated in rats following fipronil treatment. As shown in Fig. 4, fipronil treatment in mouse also led to the upregulation of genes involved in the different phases of xenobiotic metabolism. Among phase I hepatic enzymes, we found that the prototypical CAR/PXR target genes *Cyp2b10* and *Cyp3a11* together with the gene encoding carboxylesterase *Ces2a* (mouse ortholog of rat *Ces6*) were strongly induced following fipronil treatment (Fig. 4A). The expression of the phase II enzymes *Ugt1a1* and *Sult1b1* which are involved in the conjugation of thyroid hormones [20,21] were significantly increased upon fipronil treatment (Fig. 4B) but to a lower extent than their orthologs in rat liver (Fig. 2D). On the contrary, the expression of *Gsta2* was increased as robustly in mouse as in rat (Fig. 4B). Among the membrane transporters tested, the strongest increases in expression were observed for *Abcc3* and the thyroid hormone transporter *Slco1a4* (Fig. 4C). Interestingly, the expression of the sterol transporters *Abcg5* and *Abcg8* (Fig. 4C) was also increased by fipronil treatment in mouse liver although to a much lower extent than in rat (Fig. 2E). The expression of other genes involved in the metabolism of xenobiotics and endogenous compounds that we assayed by qPCR showed no or very limited changes (Fig. 5). Thus, overall, the effects of fipronil on hepatic gene expression related to biotransformation systems and membrane transporters were reproduced to a large extent in mouse but several modulations were of very limited amplitude in this model, including genes involved in thyroid hormone metabolism.

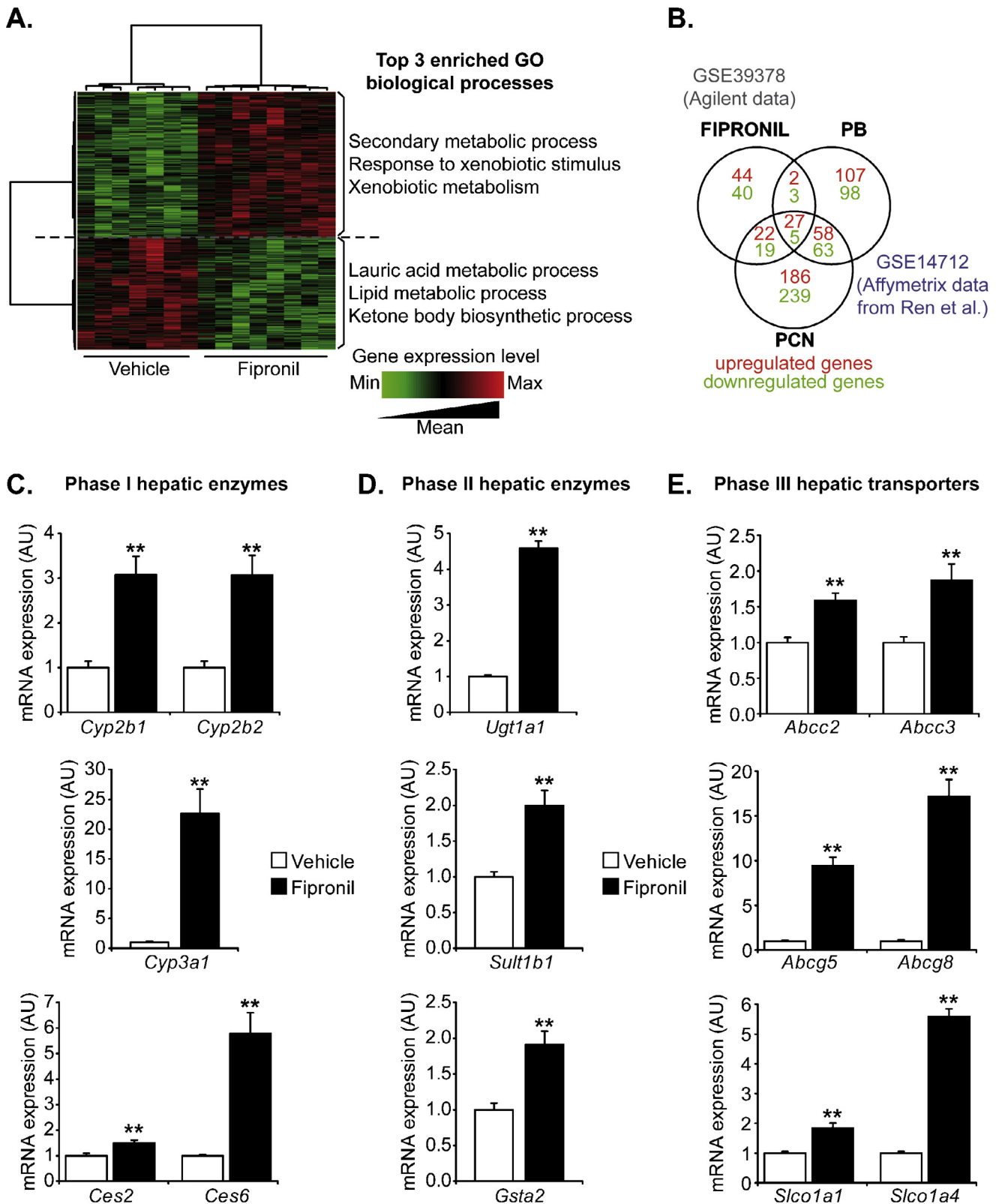


Fig. 2. Effects of fipronil on the rat hepatic transcriptome. (A) Gene expression profiles were obtained by microarray analysis (Agilent 4x44K whole rat genome) of liver samples from rats treated with fipronil (3 mg/kg per day, 14 days, $n = 8$) or the vehicle alone ($n = 7$). The heatmap represents the data obtained on all samples for the 712 differentially expressed probes (402 up- and 310 downregulated, q -value < 0.1). Hierarchical clustering was applied to the samples and the probes using 1-Pearson correlation coefficient as distance and the Ward's criterion for agglomeration. The top three GO biological processes most significantly enriched among the upregulated or downregulated genes are indicated. (B) Raw microarray data for female rats exposed to the PXR activator pregnenolone-16 α -carbonitrile (PCN), to the CAR and PXR activator phenobarbital (PB) or to the vehicle alone for 6 h, 24 h or 5 days were obtained from GEO [GSE14712, [19]]. Data were normalized using robust multi-array analysis (rma) and genes differentially expressed between PB or PCN and the control group at any time point were identified using limma. For the 3045 genes studied by both the Agilent and Affymetrix microarrays, the venn diagram illustrates the overlaps between the genes significantly up- (red) or downregulated (green) in the liver following fipronil (our study), PCN or PB exposure (study by Ren et al.). (C, D and E) mRNA expression of genes involved in hepatic xenobiotic metabolism, in particular phase I enzymes

Table 4
GO biological processes enriched in upregulated genes.

GOBPID	Pvalue	OddsRatio	ExpCount	Count	Size	Term
GO:0019748	1.63E-08	10.86	1.50	12	51	Secondary metabolic process
GO:0009410	1.10E-07	14.90	0.88	9	30	Response to xenobiotic stimulus
GO:0006805	6.44E-07	14.56	0.79	8	27	Xenobiotic metabolic process
GO:0055114	1.76E-05	2.58	14.02	31	478	Oxidation-reduction process
GO:0015721	1.31E-04	22.56	0.29	4	10	Bile acid and bile salt transport
GO:0042493	2.05E-04	2.65	8.95	21	305	Response to drug
GO:0019439	2.85E-04	10.62	0.62	5	21	Aromatic compound catabolic process
GO:0009812	4.65E-04	33.65	0.18	3	6	Flavonoid metabolic process
GO:0017144	7.58E-04	12.29	0.44	4	15	Drug metabolic process
GO:0010949	8.56E-04	Inf	0.06	2	2	Negative regulation of intestinal phytosterol absorption
GO:0045796	8.56E-04	Inf	0.06	2	2	Negative regulation of intestinal cholesterol absorption
GO:0070980	8.56E-04	Inf	0.06	2	2	Biphenyl catabolic process
GO:0009056	1.25E-03	1.85	23.29	38	794	Catabolic process
GO:0042398	1.59E-03	9.65	0.53	4	18	Cellular modified amino acid biosynthetic process
GO:0006720	1.84E-03	5.24	1.32	6	45	Isoprenoid metabolic process
GO:0006749	1.88E-03	6.52	0.91	5	31	Glutathione metabolic process
GO:0010033	2.29E-03	1.76	25.73	40	877	Response to organic substance
GO:0009822	2.52E-03	66.94	0.09	2	3	Alkaloid catabolic process
GO:0046101	2.52E-03	66.94	0.09	2	3	Hypoxanthine biosynthetic process
GO:0070233	2.52E-03	66.94	0.09	2	3	Negative regulation of T cell apoptosis
GO:0007052	2.56E-03	14.41	0.29	3	10	Mitotic spindle organization
GO:0009163	2.56E-03	14.41	0.29	3	10	Nucleoside biosynthetic process
GO:0042572	2.56E-03	14.41	0.29	3	10	Retinol metabolic process
GO:0046129	2.56E-03	14.41	0.29	3	10	Purine ribonucleoside biosynthetic process
GO:0042537	2.58E-03	4.86	1.41	6	48	Benzene-containing compound metabolic process
GO:0006855	3.44E-03	12.61	0.32	3	11	Drug transmembrane transport
GO:0050892	3.44E-03	12.61	0.32	3	11	Intestinal absorption
GO:0016101	3.46E-03	7.50	0.65	4	22	Diterpenoid metabolic process
GO:0043436	3.70E-03	1.96	13.47	24	459	Oxoacid metabolic process
GO:0044281	4.50E-03	1.63	31.86	46	1086	Small molecule metabolic process
GO:0008202	4.61E-03	2.71	4.43	11	151	Steroid metabolic process
GO:0006287	4.94E-03	33.46	0.12	2	4	Base-excision repair, gap-filling
GO:0009804	4.94E-03	33.46	0.12	2	4	Coumarin metabolic process
GO:0043101	4.94E-03	33.46	0.12	2	4	Purine-containing compound salvage
GO:0060045	4.94E-03	33.46	0.12	2	4	Positive regulation of cardiac muscle cell proliferation
GO:2000107	4.94E-03	33.46	0.12	2	4	Negative regulation of leukocyte apoptosis
GO:0006520	5.43E-03	2.42	5.84	13	199	Cellular amino acid metabolic process
GO:0050728	5.59E-03	6.43	0.73	4	25	Negative regulation of inflammatory response
GO:0030890	5.71E-03	10.08	0.38	3	13	Positive regulation of B cell proliferation
GO:0070988	5.71E-03	10.08	0.38	3	13	Demethylation
GO:0009719	5.91E-03	1.83	15.55	26	530	Response to endogenous stimulus
GO:0048589	6.39E-03	2.91	3.37	9	115	Developmental growth
GO:0046686	6.45E-03	6.13	0.76	4	26	Response to cadmium ion
GO:0002920	7.12E-03	9.17	0.41	3	14	Regulation of humoral immune response
GO:0050777	7.41E-03	5.87	0.79	4	27	Negative regulation of immune response
GO:0046700	7.51E-03	2.32	6.07	13	207	Heterocycle catabolic process
GO:0031100	7.88E-03	3.77	1.76	6	60	Organ regeneration
GO:0045454	8.01E-03	4.45	1.26	5	43	Cell redox homeostasis
GO:0010561	8.07E-03	22.30	0.15	2	5	Negative regulation of glycoprotein biosynthetic process
GO:0016098	8.07E-03	22.30	0.15	2	5	Monoterpenoid metabolic process
GO:0042474	8.07E-03	22.30	0.15	2	5	Middle ear morphogenesis
GO:0045916	8.07E-03	22.30	0.15	2	5	Negative regulation of complement activation
GO:0070327	8.07E-03	22.30	0.15	2	5	Thyroid hormone transport
GO:0009308	8.81E-03	2.07	8.33	16	284	Amine metabolic process
GO:0015711	9.70E-03	4.23	1.32	5	45	Organic anion transport

The enrichment of GO biological processes was evaluated with a conditional hypergeometric test as implemented in the GStats R package. GOBPID: gene ontology (GO) biological process (BP) identifier, Pvalue: *p*-value of the enrichment test, OddsRatio: odds ratio for the category tested, ExpCount: expected number of genes from the category in the selected genes, Count: observed number of genes from the category in the selected genes, Size: number of genes annotated with the category in the gene universe, Term: GO term.

3.3. Effects of fipronil on liver gene expression in CAR- and PXR-deficient mice

Based on these observations, we studied the expression of a selection of robustly regulated genes in wild-type, CAR and PXR-deficient mice treated with fipronil (3 mg/kg per day, 14 days) or vehicle (Fig. 6A). The increased expression of *Cyp2b10* and *Gsta2*

mRNAs upon fipronil treatment was not reproduced in this experiment (Fig. 6A), which could result from the use of older animals (15–22 week-old) in this study. However, an independent experiment using higher fipronil doses (10 mg/kg per day, 14 days) in younger mice (9 week-old) confirmed these modulations in wild-type mice (Fig. 6B). The induction of *Cyp2b10* mRNA expression by fipronil was completely absent in CAR-/- but not

(C), phase II enzymes (D) and phase III transporters (E) was assayed by RT-qPCR in liver samples from female rats treated with fipronil (black bars, 3 mg/kg per day for 14 days, *n* = 10 including the eight rats used in the microarray study) or the vehicle alone (white bars, *n* = 14 including the seven rats used in the microarray study). Abc: ATP-binding cassette transporter, Ces: carboxylesterase, Cyp: cytochrome P450, Gst: glutathione S-transferase, Slco: solute carrier organic anion transporter, Sult: sulfotransferase, Ugt: UDP-glucuronosyltransferase. Significantly different from the vehicle group: ***p* < 0.01.

Table 5
GO biological processes enriched in downregulated genes.

GOBPID	Pvalue	OddsRatio	ExpCount	Count	Size	Term
GO:0048252	2.49E-05	162.22	0.07	3	4	Lauric acid metabolic process
GO:0006629	2.17E-04	2.63	9.79	22	525	Lipid metabolic process
GO:0046951	1.02E-03	107.15	0.06	2	3	Ketone body biosynthetic process
GO:0043277	1.23E-03	18.00	0.22	3	12	Apoptotic cell clearance
GO:0010934	2.02E-03	53.56	0.07	2	4	Macrophage cytokine production
GO:0019369	2.96E-03	12.45	0.30	3	16	Arachidonic acid metabolic process
GO:0043651	3.32E-03	35.70	0.09	2	5	Linoleic acid metabolic process
GO:0071702	8.32E-03	2.49	4.81	11	258	Organic substance transport
GO:0010884	8.97E-03	17.84	0.15	2	8	Positive regulation of lipid storage
GO:0042756	8.97E-03	17.84	0.15	2	8	Drinking behavior

The enrichment of GO biological processes was evaluated as in Table 4.

in PXR^{-/-} mice (Fig. 6A and B). The modest induction of *Gsta2* upon treatment with high fipronil dose was not observed in CAR^{-/-} and PXR^{-/-} mice (Fig. 6B). The induction by fipronil of mRNA expression for *Cyp3a11*, as well as for *Ces2a*, *Abcc3* and *Slco1a4* was

completely absent in PXR^{-/-} mice (Fig. 6A and B). In CAR^{-/-} mice, these regulations were blunted at the moderate fipronil dose (3 mg/kg per day, Fig. 6A) but were globally maintained at the high fipronil dose (10 mg/kg per day, Fig. 6B). Thus, overall, the expression of PXR and to a lesser extent of CAR is required for a full induction by fipronil of the hepatic expression of genes involved in xenobiotic and TH metabolism and transport.

3.4. Effects of fipronil on TH clearance and fipronil metabolism in CAR and PXR-deficient mice

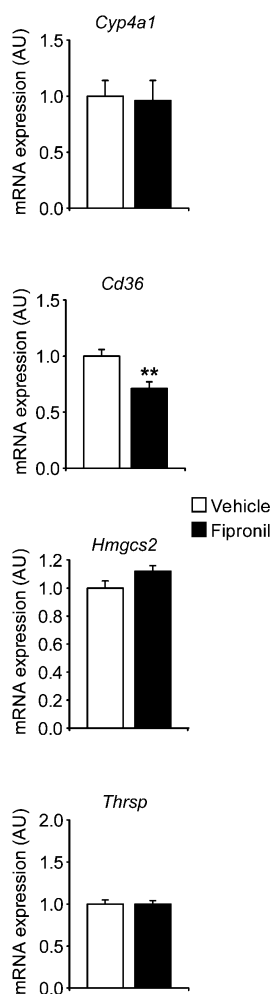
Next, we evaluated whether gene expression modulations induced by fipronil and their disruption in CAR^{-/-} and PXR^{-/-} mice were associated with functional consequences on the metabolism of fipronil itself and on its ability to modulate thyroid hormone clearance. The oral treatment with fipronil resulted in a predominant internal exposure to fipronil sulfone in all genotypes (Fig. 7A). Plasma fipronil sulfone concentrations reached levels within the same order of magnitude in all three genotypes (2621 ± 429, 1991 ± 445 and 1985 ± 644 ng/mL for the wild-type, CAR^{-/-} and PXR^{-/-} mice, respectively) but were significantly lower in CAR^{-/-} and PXR^{-/-} mice compared to wild-type mice (Fig. 7A). Next, we determined the disposition time course of the thyroxine stable isotope ¹³C₆-LT₄ in wild-type, CAR^{-/-} and PXR^{-/-} mice over a 24 h period following an ip bolus of ¹³C₆-LT₄ (Fig. 7B). For wild-type mice, fipronil treatment was associated to a very limited increase of the ¹³C₆-LT₄ apparent clearance. Similarly, for CAR^{-/-} mice a small increase in the ¹³C₆-LT₄ apparent clearance was observed. Moreover, these mice exhibited a constitutively lower clearance than wild-type mice. For PXR^{-/-} mice, the ¹³C₆-LT₄ apparent clearance was not affected at all by the treatment.

4. Discussion

Fipronil has been described as a thyroid disruptor in rat [3–5]. Treatment of rats with this widely used insecticide reduces plasma T₄ via increased T₄ clearance and increases plasma TSH levels (Fig. 1 and Ref. [4]). These effects on T₄ clearance were reproduced when rats were treated with fipronil sulfone [5], the main fipronil metabolite which is produced by cytochrome P450-mediated biotransformation in the liver [7,16]. It is thought that the induction of liver enzymes involved in the metabolism of thyroid hormones underlie the thyroid disrupting effects of fipronil [5,22].

Due to the central role of the liver in both fipronil [7,16] and thyroid hormone metabolism [17,18], we first evaluated the impact of fipronil treatment on the hepatic transcriptome in the rat. In accordance with previous observations in rat liver [5] and human hepatocytes [16] we found that fipronil induces the expression of hepatic phase I detoxification enzymes, in particular *Cyp2b1*, *Cyp2b2* and *Cyp3a1* which are involved in fipronil

A. Rat



B. Mouse

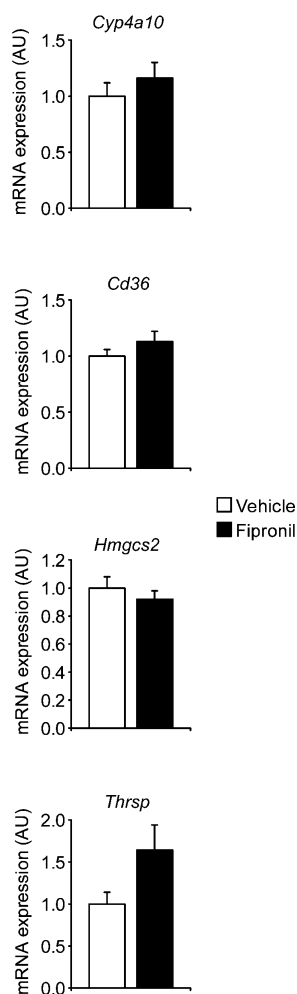


Fig. 3. Effect of fipronil on mRNA expression of genes involved in lipid metabolism in rat and mouse liver. mRNA expression of genes involved in lipid metabolism was assayed by RT-qPCR in liver samples obtained from rats (A) or mice (B) treated with fipronil (black bars, 3 mg/kg per day for rat and 5 mg/kg per day for mouse, 14 days, $n = 10$ rats including the eight rats used in the microarray study and $n = 8$ mice respectively) or the vehicle alone (white bars, $n = 14$ rats including the seven rats used in the microarray study and $n = 8$ mice respectively). Significantly different from the vehicle group: ** $p < 0.01$.

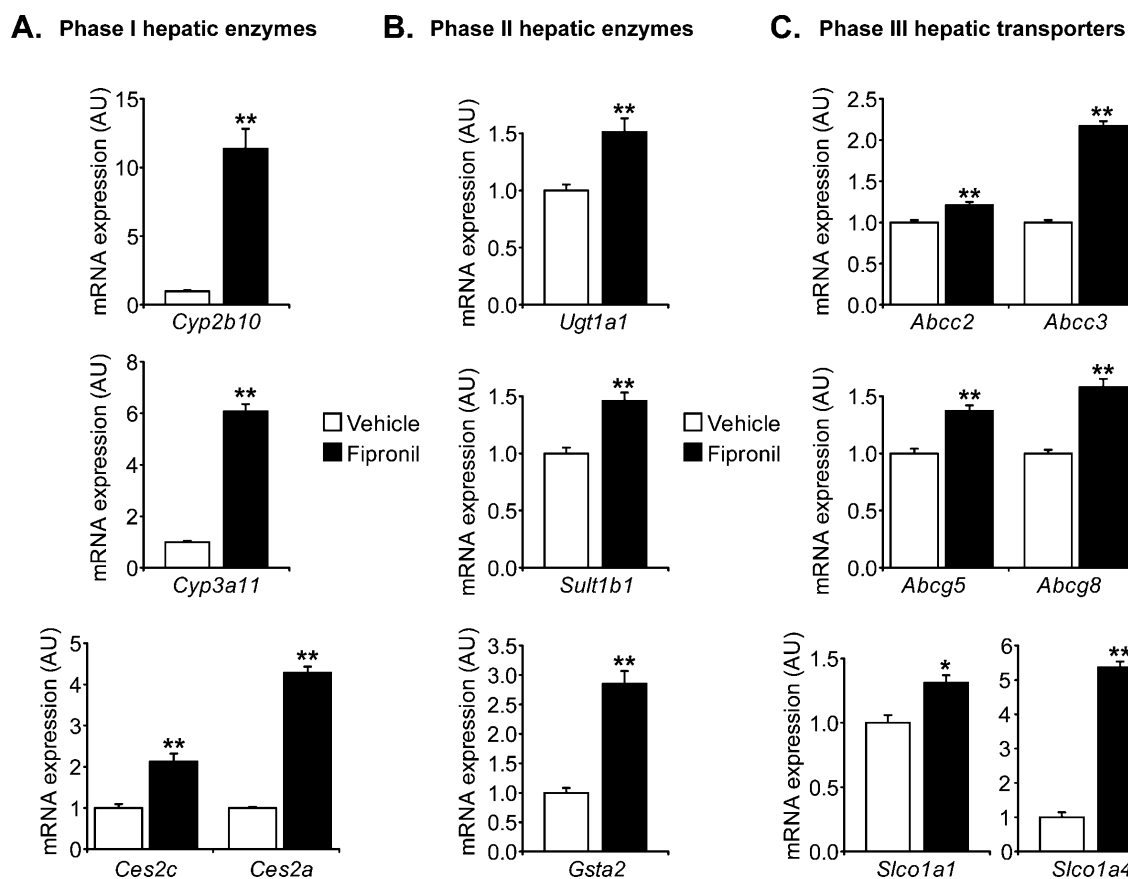


Fig. 4. Effect of fipronil on mRNA expression of orthologous genes in mouse liver. The mRNA expression of a selection of genes involved in hepatic xenobiotic metabolism, in particular phase I enzymes (A), phase II enzymes (B) and phase III transporters (C) was assayed by RT-qPCR in liver samples from male C57BL/6J mice treated with fipronil (black bars, 5 mg/kg per day for 14 days, $n = 8$) or the vehicle alone (white bars, $n = 8$). The selection included the mouse orthologs of the genes studied by RT-qPCR in rat liver (Fig. 2). Significantly different from the vehicle group: * $p < 0.05$, ** $p < 0.01$.

metabolism [7,16]. We also confirmed the induction by fipronil of mRNA expression of the phase II conjugation enzymes *Ugt1a1* and *Sult1b1* [5], identified as key enzymes involved in T_4 conjugation in the liver of female rats [20,21]. Furthermore, we report the induction by fipronil of hepatic transporters including *Abcc2* and *Abcc3* encoding the Multidrug Resistance-associated Proteins (MRP) MRP2 and MRP3, respectively as well as *Slco1a1* and *Slco1a4* encoding the organic anion-transporting polypeptides (OATP) OATP1 and OATP2, respectively (Fig. 2 and Table 2). Thus, our study further suggests that the induction of thyroid hormone transporters involved in both the influx of thyroid hormones into hepatocytes [OATP1 and OATP2, [23]] and the efflux of glucuronide conjugates of thyroid hormones [MRP2, [24]] may also contribute to increase hepatic thyroid hormone metabolism following fipronil treatment. Because MRPs and OATPs have a broad range of substrates, the impacts of these regulations may extend beyond the specific metabolism of thyroid hormones.

The analysis of the effect of fipronil on the hepatic transcriptome and its comparison with the effects of prototypical activators of the nuclear receptors CAR and/or PXR [19] strongly suggested that these two xenosensors mediated the effects of fipronil on liver gene expression. Consistently, fipronil was shown to activate human PXR *in vitro* [13]. CAR and PXR are closely related transcriptional regulators that share target genes, DNA response elements and activators [25]. They act in concert as major regulators of hepatic xenobiotic metabolism. Additionally, they play key roles in regulating the clearance of toxic byproducts of endogenous metabolism and can also interfere with the metabolism of endogenous hormones [25]. In wild-type but not in

CAR-deficient mice, the strong mouse CAR activators TCPOBOP and phenobarbital are able to reduce T_4 but not T_3 levels, increase plasma TSH and induce the hepatic expression of genes involved in TH metabolism [10,26]. Furthermore, CAR was shown to play a role in the physiological reduction of TH levels during fasting [10]. The role of PXR in regulating thyroid hormone metabolism has been less precisely described. However, using PXR-deficient mice, it was shown that PXR is necessary for the induction by pregnenolone-16 alpha-carbonitrile (PCN) of hepatic UDP-glucuronosyltransferase activities toward T_3 and T_4 [27]. Additionally, the role of PXR in regulating hepatic TH metabolism can be easily inferred from the well described thyroid disrupting effects of its numerous xenobiotic activators [28]. Thus, both receptors mediate the effects of several xenobiotics on TH homeostasis.

To investigate the respective roles of these transcriptional regulators in mediating the effect of fipronil on hepatic gene expression, we used CAR- and PXR-deficient mice. Overall, we observed that the panel of genes modulated by fipronil was highly similar between rats and mice, although several responses were attenuated in mice compared to rats. We selected a set of genes on which fipronil had a similar impact in both species and evaluated their regulations in wild-type, CAR-deficient and PXR-deficient mice. Because CAR and PXR deficiencies had a functional impact on the internal exposure to fipronil sulfone (Fig. 7A) which could indirectly alter the gene expression modulations, we evaluated the effects at two different doses: 3 and 10 mg/kg per day. One notable difference between rats and mice was the absence of induction of *Cyp2b10* mRNA in mice at 3 mg/kg per day (Fig. 6A). While the use of older mice in this experiment may have played a role, gender

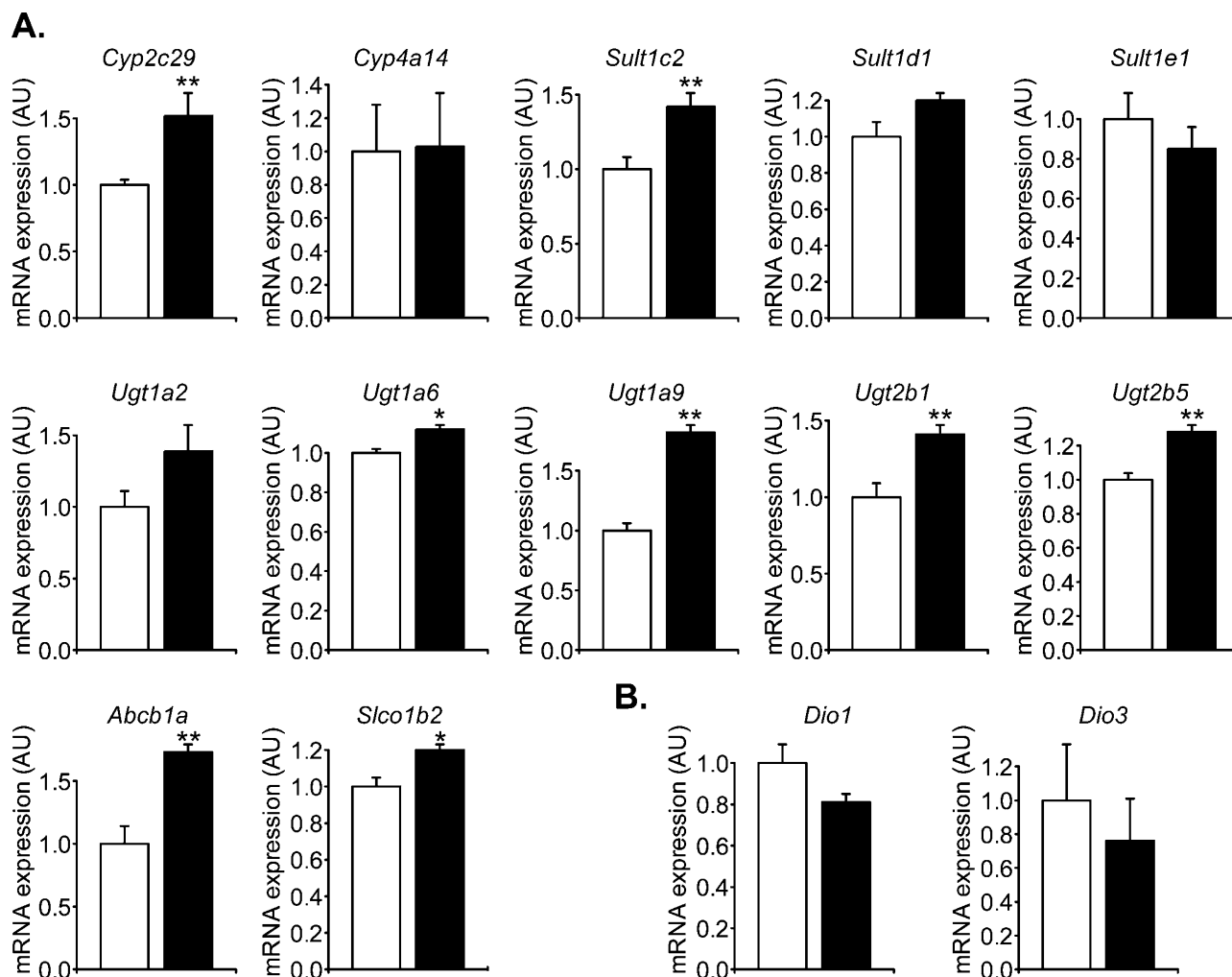


Fig. 5. Effect of fipronil on mRNA expression of genes involved in the metabolism or transport of xenobiotics and endogenous compounds in mouse liver. The mRNA expression of genes involved in the metabolism (phase I and II) and transport (phase III) of xenobiotics and endogenous compounds, including thyroid hormones (A) and the mRNA expression of the deiodinases *Dio1* and *Dio3* (B) were assayed by RT-qPCR in liver samples from mice treated with fipronil (black bars, 5 mg/kg per day for 14 days, $n = 8$) or the vehicle alone (white bars, $n = 8$). Significantly different from the vehicle group: * $p < 0.05$, ** $p < 0.01$.

differences may also underlie this difference because female rats and male mice were used in our studies. Endogenous estrogens can activate both rodent and human CAR [29,30] but only at high concentrations, reached during pregnancy or pharmacological treatment. However, it is conceivable that an inhibition of CAR by testosterone in male mice [29] and/or a synergistic activation of *Cyp2b* mRNA expression by fipronil and estradiol in female rats [as in Ref. [30]] could have contributed to the observed differences between female rats and male mice for the regulation of *Cyp2b* mRNA at 3 mg of fipronil/kg per day. Nevertheless, the induction by fipronil of *Cyp2b10* mRNA, together with other genes involved in hepatic metabolism, was observed in two independent studies using younger animals and higher fipronil doses (5 and 10 mg/kg per day, Figs. 4 and 6B). Taken together, our results show that the gene expression regulations induced by fipronil are generally abolished in PXR-deficient mice and are in most of the cases only reduced in CAR-deficient animals. Thus PXR, and to a lesser extent CAR, are both involved in mediating the effect of fipronil on liver gene expression.

However, the activation of CAR and PXR by fipronil in mouse liver was not associated with a marked increase in thyroid hormone clearance (Fig. 7B), contrary to the observation made previously in rats [4]. In rats, the induction of phase II enzymes

such as UDP-glucuronosyltransferases is thought to largely contribute to the increase in thyroid hormone clearance upon fipronil treatment [5,20]. Of importance, we observed that fipronil treatment had a reduced effect in mouse compared to rat on the expression of phase II enzymes, including Ugts (Table 2, Figs. 2, 4 and 5). Other liver enzyme inducers activating CAR and PXR were previously shown to have a reduced effect on T_4 - and bilirubin-UDP-glucuronosyltransferase activities in mouse compared to rat [31]. Thus, a differential regulation of phase II glucuronidation enzymes may well contribute to the different sensitivities of mice and rats to the induction of thyroid hormone clearance by liver enzyme inducers, including fipronil. On the other hand, it has been shown that thyroid disruption by PXR activators does not fully rely on TH glucuronidation [32]. Thus, differences between rats and mice in the regulation of genes other than Ugts may also contribute to the lack of fipronil effect on TH clearance in mice, as reported in our study. Overall, while CAR and PXR activation by fipronil is not associated with increased thyroid hormone clearance in mouse, it is still unclear whether the activation of these nuclear receptors in rat have functional consequences on thyroid hormone metabolism and elimination. The development of PXR- and CAR-deficient rats could represent valuable models to evaluate such a link.

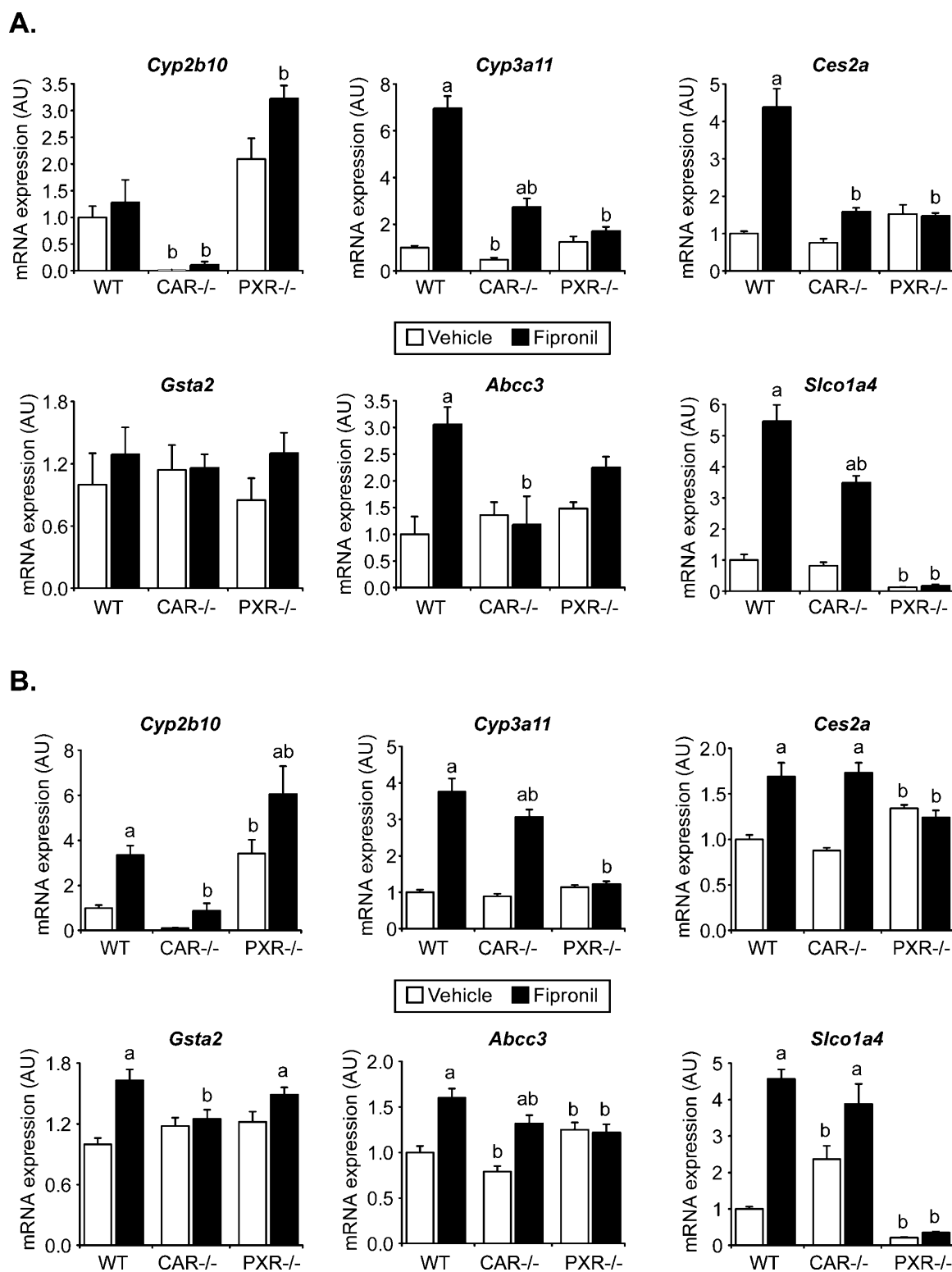


Fig. 6. Effect of fipronil on liver mRNA expression of a selection of genes in wild-type, CAR^{-/-} and PXR^{-/-} mice. The mRNA expression of *Cyp2b10*, *Cyp3a11*, *Ces2a*, *Gsta2*, *Abcc3* and *Slco1a4* was assayed by RT-qPCR in liver samples from wild-type C57BL/6J (WT), CAR^{-/-} and PXR^{-/-} male mice treated with fipronil (black bars) or the vehicle alone (white bars). Fifteen to 22-week-old mice (A) or 9-week-old mice (B) were treated for 14 days with 3 mg/kg per day (A) or 10 mg/kg per day (B) of fipronil or the vehicle alone ($n = 5$ mice/group for panel A and $n = 8$ mice/group for panel B). Significantly different from the vehicle group: a, $p < 0.05$. Significantly different from wild-type mice: b, $p < 0.05$.

The analysis of our microarray data clearly indicates that CAR and PXR are the major transcription factors involved in modulating the hepatic gene expression profile upon fipronil treatment but other pathways may also be involved. Because the corresponding

regulations were less robust, we did not further evaluate the involvement of peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs) in regulating gene expression related to hepatic lipid metabolism in response to fipronil. The aryl

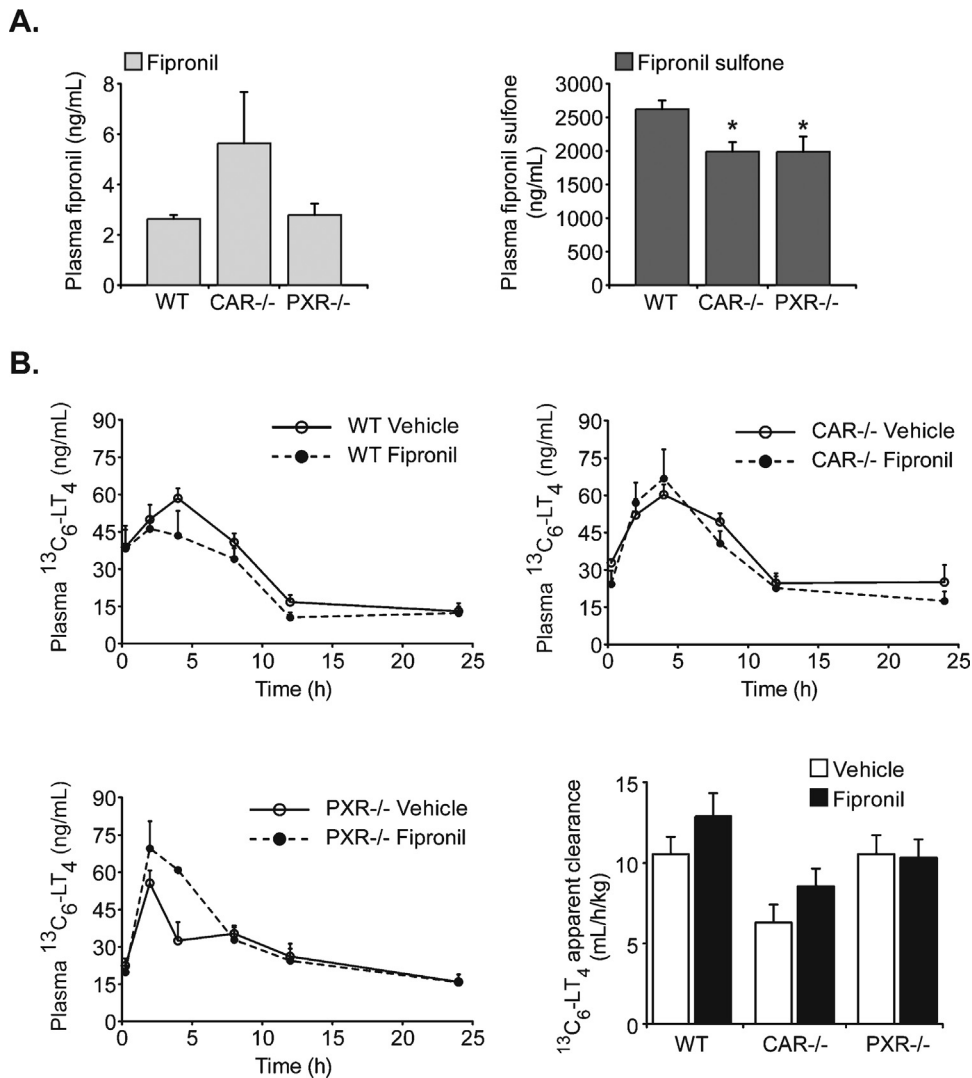


Fig. 7. Functional consequences of CAR or PXR deficiency on internal exposure to fipronil and fipronil sulfone and on time-course disposition of ¹³C₆-LT₄. (A) Fipronil (light gray) and fipronil sulfone (dark gray) concentrations were assayed in plasma samples from wild-type C57BL/6J (WT, *n* = 11), CAR^{-/-} (*n* = 10) and PXR^{-/-} male mice (*n* = 8) treated with fipronil (3 mg/kg per day for 14 days). Significantly different from wild-type mice: **p* < 0.05. (B) ¹³C₆-LT₄ concentrations were assayed in plasma samples collected 0.25, 2, 4, 8, 12 or 24 h after the administration of an ip bolus of ¹³C₆-LT₄ (10.2 μg/kg) to wild-type C57BL/6J, CAR^{-/-} and PXR^{-/-} mice (*n* = 5–10 mice/genotype/time point) treated with fipronil (dashed lines and black bars, 3 mg/kg per day for 14 days) or the vehicle alone (solid lines and white bars). ¹³C₆-LT₄ apparent clearance was determined by pharmacokinetic analysis.

hydrocarbon receptor (AhR) and the nuclear factor erythroid 2-related factor 2 (Nrf2) pathways are other important regulators of hepatic metabolism, notably phase II conjugation [33]. As reported previously [5] we did not observe any induction by fipronil of the typical AhR target gene *Cyp1a1* in rat liver (data not shown). Additionally, the intersections between the changes in liver gene expression induced by fipronil (our microarray data) and the changes induced by the AhR agonist TCDD [34] or by Nrf2 activators [35] were limited to a few target genes (data not shown). Thus, these other pathways are unlikely to play a major role, like CAR and PXR, in mediating the effects of fipronil but may still contribute to some specific regulations.

Overall, this study represents a step further toward a better understanding of the respective roles of the xenosensors CAR and PXR in regulating liver gene expression, notably related to hepatic TH metabolism. Because these receptors are modulated by numerous species-specific ligands, including drugs and environmental contaminants which could act synergically, further studies

are needed to assess their precise roles in inducing thyroid disruption *via* increased TH clearance, including in humans.

Conflict of interest

None.

Acknowledgments

The authors thank Sylvie Puel for performing the HPLC assays, Colette Bétoulières and Caroline Sommer for animal breeding, Nabila Moussaoui for her help during *in vivo* experiments and Didier Concordet for his advices on statistical analysis. We are grateful to Pr David D. Moore and Pr Steven A. Kliewer for the CAR- and PXR-deficient mice. We thank Pr Urs A. Meyer for the mouse lines and for constructive discussions. This work was supported by grants from the Région Midi-Pyrénées and from the French Ministry of Ecology and Sustainable Development (Programme

National de Recherche sur les Perturbateurs Endocriniens, PNRPE 000442). Béatrice Roques was funded by a grant from the Ministère de l'Enseignement Supérieur et de la Recherche.

References

- [1] Cole LM, Nicholson RA, Casida JE. Action of phenylpyrazole insecticides at the GABA-gated chloride channel. *Pest Biochem Physiol* 1993;46:47–54.
- [2] Hainzl D, Cole LM, Casida JE. Mechanisms for selective toxicity of fipronil insecticide and its sulfone metabolite and desulfinyl photoproduct. *Chem Res Toxicol* 1998;11:1529–35.
- [3] Agence Française de Sécurité Sanitaire des Aliments (AFSSA), Agence Française de Sécurité Sanitaire Environnementale (AFSSE). Evaluation des risques pour la santé humaine liés à une exposition au fipronil; 2005, 173.
- [4] Leghait J, Gayraud V, Picard-Hagen N, Camp M, Perdu E, Toutain PL, et al. Fipronil-induced disruption of thyroid function in rats is mediated by increased total and free thyroxine clearances concomitantly to increased activity of hepatic enzymes. *Toxicology* 2009;255:38–44.
- [5] Roques BB, Lacroix MZ, Puel S, Gayraud V, Picard-Hagen N, Jouanin I, et al. CYP450-dependent biotransformation of the insecticide fipronil into fipronil sulfone can mediate fipronil-induced thyroid disruption in rats. *Toxicol Sci* 2012;127:29–41.
- [6] Yen PM. Physiological and molecular basis of thyroid hormone action. *Physiol Rev* 2001;81:1097–142.
- [7] Tang J, Amin Usmani K, Hodgson E, Rose RL. In vitro metabolism of fipronil by human and rat cytochrome P450 and its interactions with testosterone and diazepam. *Chem Biol Interact* 2004;147:319–29.
- [8] Wei P, Zhang J, Dowhan DH, Han Y, Moore DD. Specific and overlapping functions of the nuclear hormone receptors CAR and PXR in xenobiotic response. *Pharmacogenomics J* 2002;2:117–26.
- [9] Xie W, Yeuh MF, Radominska-Pandya A, Saini SP, Negishi Y, Botttroff BS, et al. Control of steroid, heme, and carcinogen metabolism by nuclear pregnane X receptor and constitutive androstane receptor. *Proc Natl Acad Sci U S A* 2003;100:4150–5.
- [10] Maglich JM, Watson J, McMillen PJ, Goodwin B, Willson TM, Moore JT. The nuclear receptor CAR is a regulator of thyroid hormone metabolism during caloric restriction. *J Biol Chem* 2004;279:19832–38.
- [11] Staudinger JL, Goodwin B, Jones SA, Hawkins-Brown D, MacKenzie KI, LaTour A, et al. The nuclear receptor PXR is a lithocholic acid sensor that protects against liver toxicity. *Proc Natl Acad Sci U S A* 2001;98:3369–74.
- [12] Cherrington NJ, Slitt AL, Maher JM, Zhang XX, Zhang J, Huang W, et al. Induction of multidrug resistance protein 3 (mrp3) in vivo is independent of constitutive androstane receptor. *Drug Metab Dispos* 2003;31:1315–9.
- [13] Lemaire G, Mnif W, Pascussi JM, Pillon A, Rabenoelina F, Fenet H, et al. Identification of new human pregnane X receptor ligands among pesticides using a stable reporter cell system. *Toxicol Sci* 2006;91:501–9.
- [14] Wei P, Zhang J, Egan-Hafley M, Liang S, Moore DD. The nuclear receptor CAR mediates specific xenobiotic induction of drug metabolism. *Nature* 2000;407:920–3.
- [15] Lacroix MZ, Puel S, Toutain PL, Viguie C. Quantification of fipronil and its metabolite fipronil sulfone in rat plasma over a wide range of concentrations by LC/UV/MS. *J Chromatogr B Analyt Technol Biomed Life Sci* 2010;878:1934–8.
- [16] Das PC, Cao Y, Cherrington N, Hodgson E, Rose RL. Fipronil induces CYP isoforms and cytotoxicity in human hepatocytes. *Chem Biol Interact* 2006;164:200–14.
- [17] Klachko DM, Johnson ER. The liver and circulating thyroid hormones. *J Clin Gastroenterol* 1983;5:465–71.
- [18] Kelly GS. Peripheral metabolism of thyroid hormones: a review. *Altern Med Rev* 2000;5:306–33.
- [19] Ren H, Vallanat B, Nelson DM, Yeung LW, Guruge KS, Lam PK, et al. Evidence for the involvement of xenobiotic-responsive nuclear receptors in transcriptional effects upon perfluoroalkyl acid exposure in diverse species. *Reprod Toxicol* 2009;27:266–77.
- [20] Wu SY, Green WL, Huang WS, Hays MT, Chopra IJ. Alternate pathways of thyroid hormone metabolism. *Thyroid* 2005;15:943–58.
- [21] Kester MH, Kaptein E, Roest TJ, van Dijk CH, Tibboel D, Meinel W, et al. Characterization of rat iodothyronine sulfotransferases. *Am J Physiol Endocrinol Metab* 2003;285:E592–8.
- [22] Hurley PM, Hill RN, Whiting RJ. Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. *Environ Health Perspect* 1998;106:437–45.
- [23] Hagenbuch B. Cellular entry of thyroid hormones by organic anion transporting polypeptides. *Best Pract Res Clin Endocrinol Metab* 2007;21:209–21.
- [24] Lecureux L, Dieter MZ, Nelson DM, Watson L, Wong H, Gemzik B, et al. Hepatobiliary disposition of thyroid hormone in Mrp2-deficient TR-rats: reduced biliary excretion of thyroxine glucuronide does not prevent xenobiotic-induced hypothyroidism. *Toxicol Sci* 2009;108:482–91.
- [25] di Masi A, De Marinis E, Ascenzi P, Marino M. Nuclear receptors CAR and PXR: molecular, functional, and biomedical aspects. *Mol Aspects Med* 2009;30:297–343.
- [26] Qatanani M, Zhang J, Moore DD. Role of the constitutive androstane receptor in xenobiotic-induced thyroid hormone metabolism. *Endocrinology* 2005;146:995–1002.
- [27] Chen C, Staudinger JL, Klaassen CD. Nuclear receptor, pregnane X receptor, is required for induction of UDP-glucuronosyltransferases in mouse liver by pregnenolone-16 alpha-carbonitrile. *Drug Metab Dispos* 2003;31:908–15.
- [28] Curran PG, DeGroot LJ. The effect of hepatic enzyme-inducing drugs on thyroid hormones and the thyroid gland. *Endocr Rev* 1991;12:135–50.
- [29] Kawamoto T, Kakizaki S, Yoshinari K, Negishi M. Estrogen activation of the nuclear orphan receptor CAR (constitutive active receptor) in induction of the mouse Cyp2b10 gene. *Mol Endocrinol* 2000;14:1897–905.
- [30] Koh KH, Jurkovic S, Yang K, Choi SY, Jung JW, Kim KP, et al. Estradiol induces cytochrome P450 2B6 expression at high concentrations: implication in estrogen-mediated gene regulation in pregnancy. *Biochem Pharmacol* 2012;84:93–103.
- [31] Viollon-Abadie C, Lassere D, Debruyne E, Nicod L, Carmichael N, Richert L. Phenobarbital, beta-naphthoflavone, clofibrate, and pregnenolone-16alpha-carbonitrile do not affect hepatic thyroid hormone UDP-glucuronosyl transferase activity, and thyroid gland function in mice. *Toxicol Appl Pharmacol* 1999;155:1–12.
- [32] Richardson TA, Klaassen CD. Disruption of thyroid hormone homeostasis in Ugt1a-deficient Gunn rats by microsomal enzyme inducers is not due to enhanced thyroxine glucuronidation. *Toxicol Appl Pharmacol* 2010;248:38–44.
- [33] Kohle C, Bock KW. Coordinate regulation of Phase I and II xenobiotic metabolisms by the Ah receptor and Nrf2. *Biochem Pharmacol* 2007;73:1853–62.
- [34] Boutros PC, Yao CQ, Watson JD, Wu AH, Moffat ID, Prokopec SD, et al. Hepatic transcriptomic responses to TCDD in dioxin-sensitive and dioxin-resistant rats during the onset of toxicity. *Toxicol Appl Pharmacol* 2011;251:119–29.
- [35] Tran QT, Xu L, Phan V, Goodwin SB, Rahman M, Jin VX, et al. Chemical genomics of cancer chemopreventive dithiolethiones. *Carcinogenesis* 2009;30:480–6.