

Null *cyp11b1* activity in zebrafish leads to variable craniofacial defects associated with altered expression of extracellular matrix and lipid metabolism genes

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Supplemental Figures

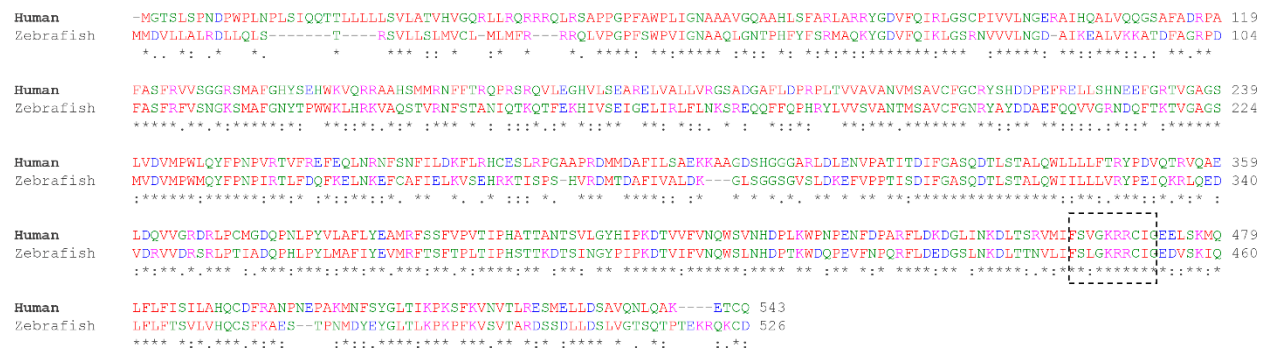


Figure S1. Amino acid sequence comparison of Human and Zebrafish cyp1b1. The alignment the human (ENSP00000478561.1 and) and zebrafish (ENSDARP00000107132.2) proteins was carried out with ClustalW (<https://embnet.vital-it.ch/software/ClustalW.html>). The asterisks indicate the positions where all the amino acids are identical, two vertical dots show amino acids with similar chemical properties and one dot denotes amino acid positions with weak chemical similarity. Dotted black square: Cytochrome P450 cysteine heme-iron ligand which is indicated according to the Prosite database (<https://prosite.expasy.org/>). The numbers correspond to amino acid positions.

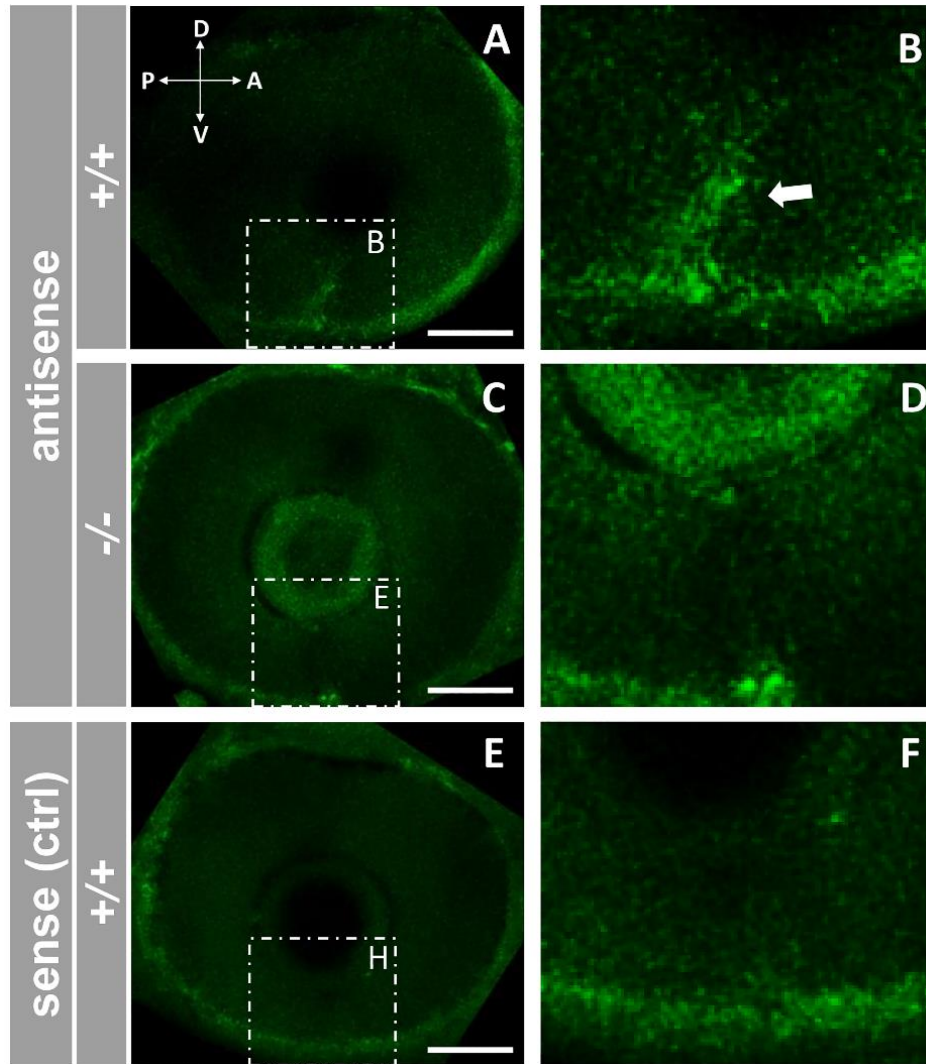


Figure S2. *Cyp1b1* expression analysis by fluorescent-whole mount *in situ* hybridization in zebrafish embryo eyes at 48 hpf. (A-D) *Cyp1b1* antisense or (E and F) sense (control) RNA probes were labelled with Alexa Fluor-488 (green). The arrow indicates specific *cyp1b1* expression in the optic fissure. The inset in (A) indicates the position of embryonic axes (D: dorsal; P: posterior; V: ventral; A: anterior). The image is representative of the result observed in 3 embryos of each genotype. Scale bar 50 μ m.

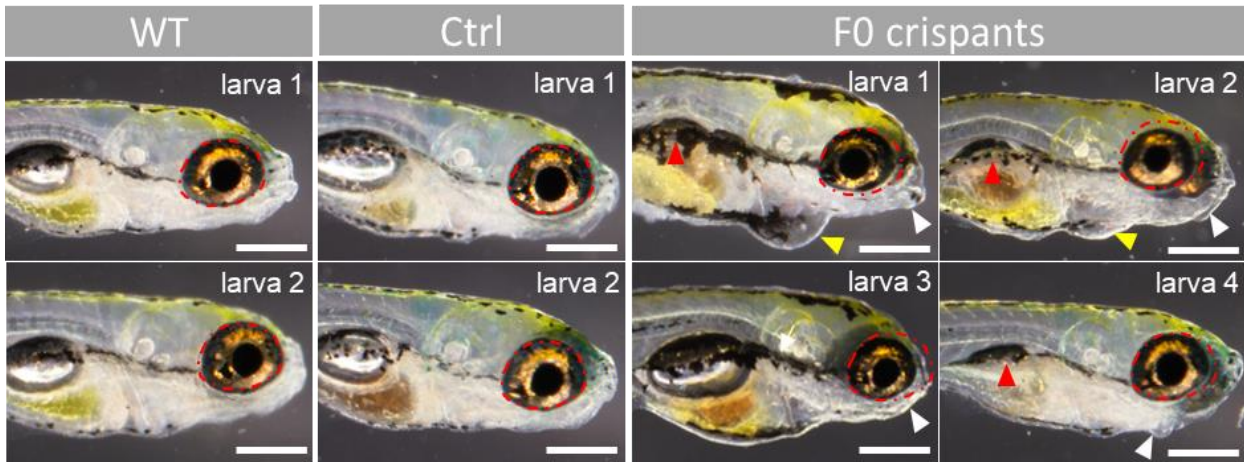


Figure S3. Phenotypic variability of *cyp1b1* F0 crispants (144 hpf) shown in Fig 3. One-cell embryos were microinjected with CRISPR/Cas9 ribonucleoprotein complexes targeting *cyp1b1* exon 1. Morphology of four crispant larvae with variable phenotypic manifestation was assessed microscopically at 144 hpf. **(WT)** Non injected wild type larvae were used as controls. **(Ctrl)** Control (no crRNA) microinjected embryos. White arrow: lower jaw underdevelopment. Red arrowhead: altered swim bladder development. Red dotted circle: wild type ocular periphery is indicated as a reference to show microphthalmia. Yellow arrowhead: pericardial edema. Scale bar = 250 μ m (A-D).

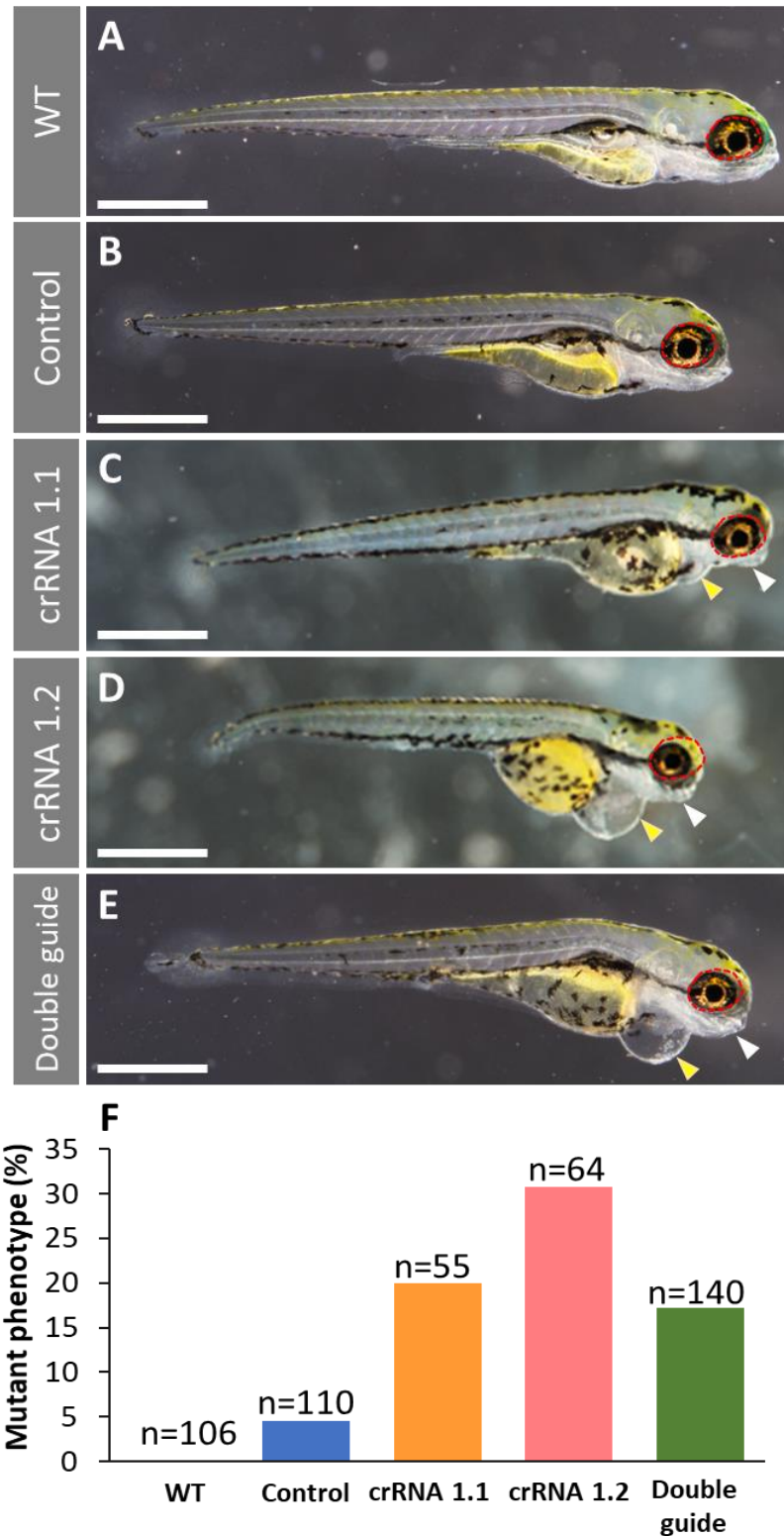


Figure S4. Phenotypic characterization of *cyp1b1* F0 crispants (96 hpf) obtained by independent or simultaneous microinjection of two single crRNA guides. One-cell embryos were microinjected with CRISPR/Cas9 ribonucleoprotein complexes with the indicated crRNAs targeting *cyp1b1* exon 1. (A) Crispants' morphology was assessed microscopically at 96 hpf. Non microinjected (WT) and control microinjected (control) larvae were used as controls. White arrow: lower jaw underdevelopment. Red dotted circle: wild type ocular periphery is indicated as a reference to show microphthalmia. Yellow arrowhead: pericardial edema. Scale bar= 500 μ m. (D) Proportion of F0 mutant phenotypes, n indicate the number of embryos analyzed.

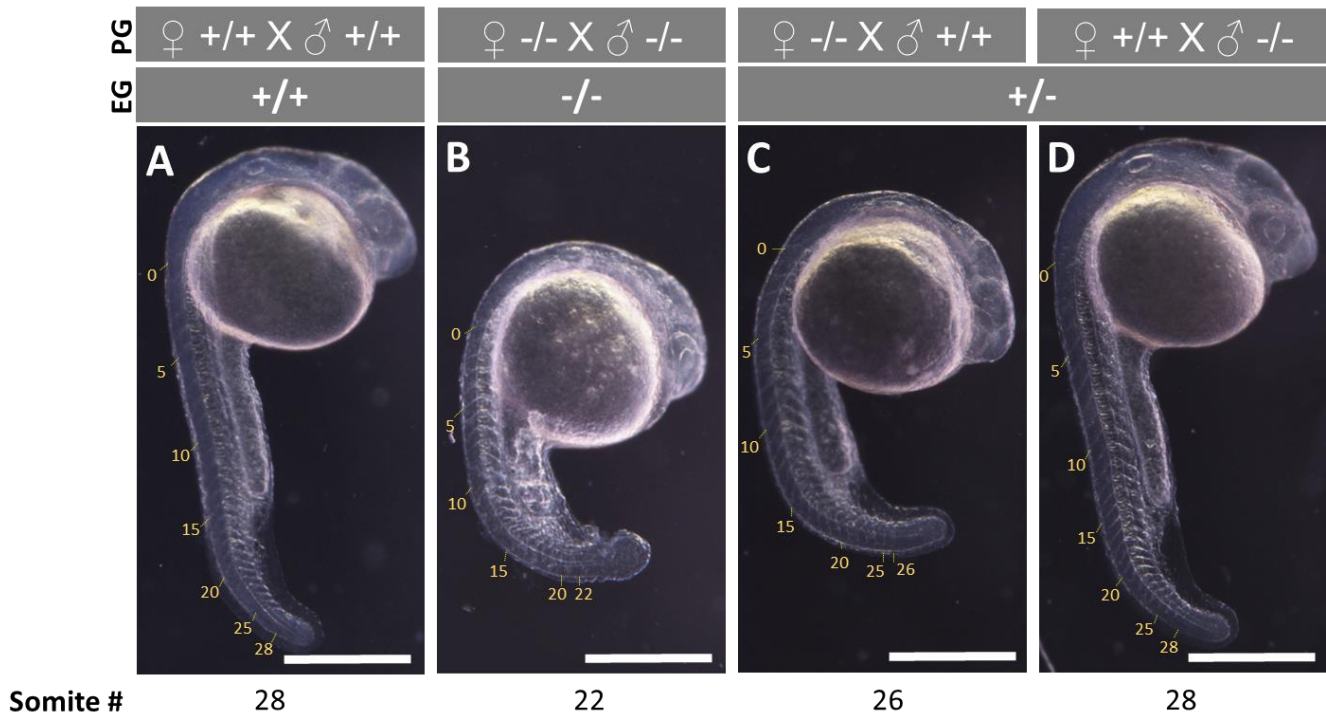


Figure S5. Somite development of *cyp1b1* $+/+$, $+/-$ and $-/-$ zebrafish larvae (24 hpf) shown in figure 4. Images in A, B, C, D correspond to panels B, F, J, N in figure 4, respectively. EG: embryo genotype. PG: parental genotype. ♀: female. ♂: male. Yellow lines indicate somite number. All images are representative of the results observed in 10 embryos of each treatment. Scale bar = 500 μ m.

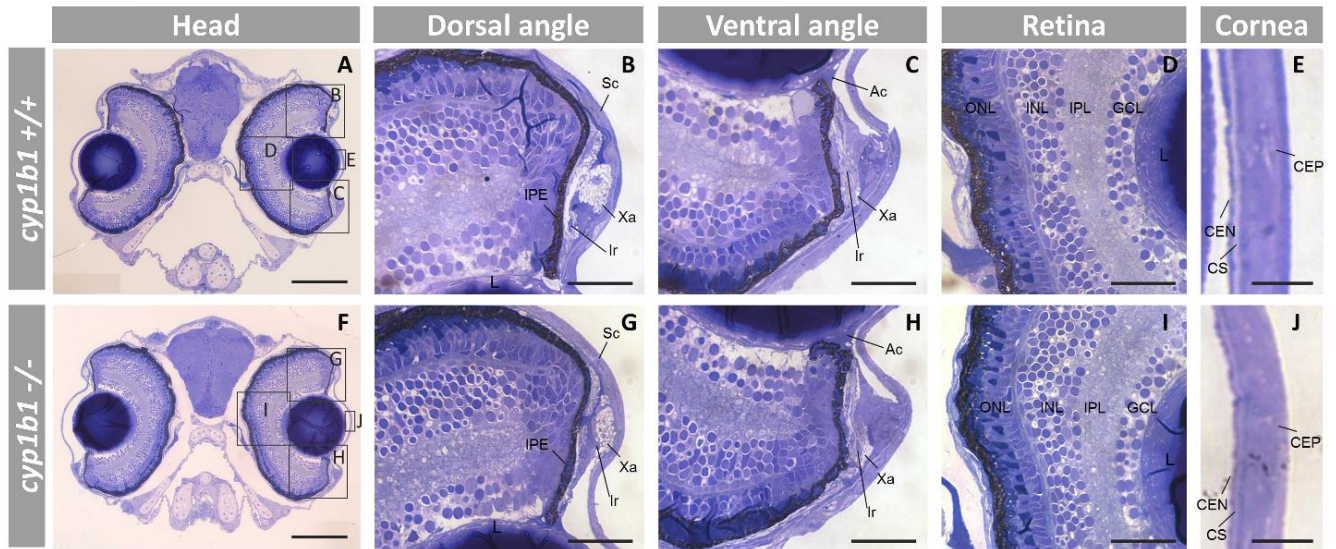


Figure S6. Histology of the established *cyp1b1*-KO zebrafish line (168hpf). The histological phenotypes were analyzed in F4 zebrafish obtained by inbreeding of young (<6 months) F3 siblings. (A-K) Semi-thin (500 nm) tissue sections were stained with Toluidine blue. The squares and rectangles indicate the areas of the images magnified in the indicated panels. No significant differences were observed between the eyes of wild type and *cyp1b1*-KO zebrafish siblings. Scale bar in A and F: 100 μ m. Scale bar in B-D and G-I: 25 μ m. Scale bar in E and J: 5 μ m. Ac: Anterior chamber. CEN: Corneal Endothelium. CEP: Corneal Epithelium. CS: Corneal Stroma. GCL: Ganglion Cell Layer. IPE: Iris Pigmented Epithelium. Sc: Sclera. INL: Inner Nuclear Layer. IPL: Inner Plexiform Layer. Ir: Iridophores. L: Lens. ONL: Outer Nuclear Layer. Xa: Xantophores. These images are representative of at least 10 histological sections of three different larvae of each genotype.

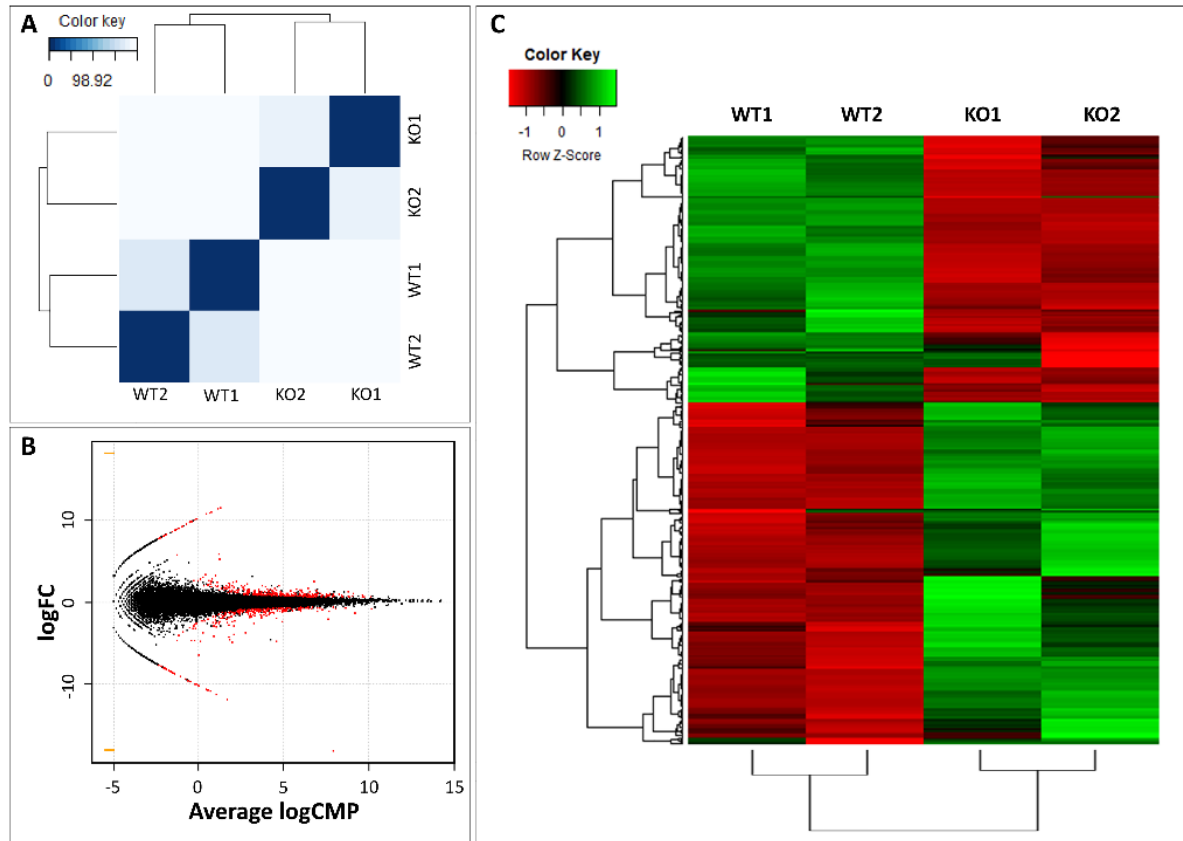


Figure S7. Differential expression analyses of RNA-seq data obtained from *cyp1b1* knockout and wild type zebrafish larvae (168 hpf). (A) Correlation matrix of all samples, showing the similarity between samples. Pearson's coefficient of sample's normalized value ($-1 \leq r \leq 1$) is used to evaluate similarity between samples. The closer to zero the greater the similarity. (B) MA plot of logFC and LogCPM of all tested genes (wild type vs. *cyp1b1* knockout). Dots above zero denote upregulated genes whereas red dots below zero indicate downregulated genes. Red dots correspond to significantly differentially expressed genes ($|\log_2(\text{FC})| > 1$, p-value < 0.05). FC: fold change. CPM: counts per million. (C) Heatmap of hierarchical clustering showing significantly DEGs which are represented by red dots in B. Clustering was done using z-score for normalized values (log10 based, wild type vs. *cyp1b1* knockout). The color key indicates the intensity associated with normalized expression values: Red, green and black represent the highest, the lowest and no different expression levels, respectively.

Table S1. List of 451 DEGs of the *cyp1b1*-KO with an absolute fold change (FC) of at least 2, and a p-value <0.05 (185 up- and 266 down-regulated). Upper case gene names correspond to human orthologues of zebrafish unnamed genes.

Gene name	FC	P-Value	Function
<i>ackr4a</i>	2.1	5.2E-03	Atypical chemokine receptor 4
<i>aco1</i>	-2.9	1.6E-11	Aconitase 1
<i>acot12</i>	-2.9	2.0E-03	Acyl-CoA thioesterase 12
<i>acta1b</i>	-2.6	7.2E-17	Actin alpha 1, skeletal muscle
<i>ADAMTS20 (LOC101886654)</i>	-2.6	1.6E-02	A disintegrin and metalloproteinase with thrombospondin motifs 20-like
<i>adcy1a</i>	-2.1	4.1E-04	adenylate cyclase 1
<i>ADGRL2 (LOC100535070)</i>	2.8	4.6E-05	Adhesion G protein-coupled receptor L2-like
<i>adra2b</i>	2.3	2.4E-02	Alpha-2B adrenergic receptor-like
<i>ADTRP (LOC100537455)</i>	-2.5	7.3E-04	Androgen-dependent TFPI-regulating protein-like
<i>aep1</i>	-2.1	2.5E-03	Aerolysin-like protein
<i>AGL (LOC101886684)</i>	-2.6	1.6E-09	Glycogen debranching enzyme-like
<i>ahrra</i>	2.2	1.2E-02	Aryl-hydrocarbon receptor repressor
<i>ak7a</i>	2.6	2.2E-09	Adenylate kinase 7
<i>ak8</i>	2.8	1.6E-02	Adenylate kinase 8
<i>alp3</i>	-2.7	1.5E-02	Alkaline phosphatase
<i>alpk3a</i>	2	4.0E-08	Alpha kinase 3
<i>amotl1</i>	-2	1.3E-02	Angiomotin like 1
<i>ampd3b</i>	2.1	2.8E-07	Adenosine monophosphate deaminase 3
<i>apoa4b.3</i>	-2.9	1.6E-06	Apolipoprotein A4
<i>apoea</i>	-2.2	4.1E-05	Apolipoprotein E
<i>aqp7</i>	-2.1	3.3E-02	Aquaporin 7
<i>aqp8a.2</i>	-2.1	8.0E-03	Aquaporin 8
<i>arf3b</i>	-2.1	2.1E-03	ADP ribosylation factor 3
<i>arsh</i>	-2.2	4.0E-03	Arylsulfatase
<i>asb2a.2</i>	2.3	1.8E-02	Ankyrin repeat and SOCS box containing 2
<i>asf1ba</i>	-2.1	1.2E-03	Anti-silencing function 1B histone chaperone
<i>BCAM (LOC100536698)</i>	-2.3	3.5E-02	Basal cell adhesion molecule-like
<i>BDP1 (LOC553492)</i>	-2.2	1.6E-02	Transcription factor TFIIB component B" homolog
<i>bsk146</i>	-2.9	1.7E-12	Brain specific kinase 146
<i>bub1bb</i>	-2	1.1E-02	BUB1 mitotic checkpoint serine/threonine kinase B
<i>C1QDC1L (si:dkeyp-110c7.4)</i>	3.3	8.2E-11	C1q domain tumour necrosis factor-like domain superfamily
<i>c6ast3</i>	2.5	3.7E-05	Six-cysteine containing astacin protease 3
<i>c6ast4</i>	2.1	9.7E-04	Six-cysteine containing astacin protease 4
<i>ca4c</i>	2.2	3.8E-02	Carbonic anhydrase 4
<i>calhm2</i>	-2.2	8.0E-03	Calcium homeostasis modulator family member 2
<i>calr3b</i>	-2	5.6E-06	Calreticulin 3
<i>CAPN1 (si:dkeyp-50d11.2)</i>	-2.1	3.8E-05	Calpain 1
<i>CARD8 (si:ch211-195h23.3)</i>	2.4	3.9E-11	Caspase recruitment domain family member 8
<i>casp7</i>	3.2	2.1E-17	Caspase 7
<i>casp8l2</i>	-3.1	3.3E-02	Caspase 10
<i>ccdc149a</i>	3.1	1.5E-02	Coiled-coil domain containing 149
<i>ccl19a.1</i>	-2.3	2.0E-04	C-C motif chemokine ligand 19

Gene name	FC	P-Value	Function
<i>ccn1l1</i>	-5.6	8.0E-10	Cellular communication network factor 1, like 1
<i>ccnd2b</i>	-2.2	1.5E-02	Cyclin D2
<i>CD58 (si:dkey-11f4.14)</i>	-2.6	9.6E-06	CD58 molecule. Member of the immunoglobulin superfamily
<i>cdc45</i>	-2.1	4.1E-03	Cell division cycle 45
<i>cdca8</i>	-2.1	1.5E-03	Cell division cycle associated 8
<i>cdk6</i>	-2	5.9E-03	Cyclin dependent kinase 6
<i>cel.2</i>	2.5	2.8E-04	Carboxyl ester lipase
<i>cep135</i>	-3.3	5.7E-14	Centrosomal protein 135
<i>cfh</i>	2.4	7.3E-10	Complement factor D
<i>ch25h</i>	-3.1	1.3E-03	Cholesterol 25-hydroxylase
<i>chia.3</i>	-2.3	3.4E-03	Chitinase
<i>CLDN23 (si:ch211-95j8.2)</i>	2.3	1.1E-07	Claudin 23
<i>clcc19a</i>	-2.5	4.3E-02	C-type lectin domain containing 19A
<i>clip2</i>	-2.1	2.9E-07	CAP-Gly domain containing linker protein 2.
<i>cln8</i>	-2.2	2.6E-02	CLN8 transmembrane ER and ERGIC protein
<i>col8a1a</i>	-2	3.6E-05	Collagen type VIII alpha 1 chain
<i>cpeb4a</i>	-2.3	7.4E-11	Cytoplasmic polyadenylation element binding protein 4
<i>cpt2</i>	-2.1	3.9E-06	Carnitine palmitoyltransferase 2
<i>crb1</i>	-2.2	7.6E-04	Crumbs cell polarity complex component 1
<i>crybb1l3</i>	-2.1	6.8E-03	Crystallin, beta B1, like 3
<i>CSPG4 (si:dkey-193c22.2)</i>	4.2	1.6E-02	Chondroitin sulfate proteoglycan 4-like
<i>cspg4b</i>	-2.1	1.6E-02	Chondroitin sulfate proteoglycan 4b
<i>cspg4bb</i>	2.9	6.3E-09	Chondroitin sulfate proteoglycan 4bb
<i>cthl</i>	-2.4	3.1E-06	Cystathionine gamma-lyase.
<i>ctsd</i>	2.2	1.2E-04	Cathepsin D
<i>ctsl</i>	4.9	4.5E-08	Cathepsin L
<i>ctss1</i>	2.1	4.4E-04	Cathepsin K
<i>CXCL1 (LOC101883994)</i>	-3.2	1.7E-02	Growth-regulated alpha protein-like
<i>cxcl18b</i>	-2.2	1.4E-03	Chemokine (C-X-C motif) ligand 18b
<i>cyp11c1</i>	-2.8	1.1E-04	cytochrome P450, family 11, subfamily C, polypeptide 1
<i>cyp1b1</i>	-2.3	2.7E-03	Cytochrome P450 family 1 subfamily B member 1
<i>cyp24a1</i>	2.7	3.3E-13	Cytochrome P450 family 24 subfamily A member 1
<i>cyp4v8</i>	-2.3	6.9E-04	Cytochrome P450 family 4 subfamily V member 2
<i>cyp7a1</i>	-2.5	9.5E-07	Cytochrome P450 family 7 subfamily A member 1
<i>cyp8b1</i>	-3.1	4.1E-05	Cytochrome P450 family 8 subfamily B member 1
<i>dcac2b</i>	-3.1	9.1E-12	Doublecortin domain containing 2B
<i>dcun1d4</i>	-2.3	9.8E-11	Defective in cullin neddylation 1 domain containing 4
<i>dhrrs13l1</i>	-2.1	1.9E-06	Dehydrogenase/reductase 13
<i>dolk</i>	-2.2	1.7E-02	Dolichol kinase
<i>dsc2l</i>	2.3	1.1E-09	Desmocollin 1-3
<i>dsg2.1</i>	2.1	3.1E-07	Desmoglein 2
<i>duox</i>	2.4	2.4E-02	Dual oxidases
<i>dusp3b</i>	2.4	3.6E-02	Dual specificity phosphatase 3
<i>e2f7</i>	-2	6.0E-04	E2F transcription factor 7
<i>eepe1</i>	2.1	4.4E-06	Endonuclease/exonuclease/phosphatase family domain containing 1
<i>egr2a</i>	-2	5.9E-06	Early growth response 2

Gene name	FC	P-Value	Function
<i>elf3</i>	-2.4	8.9E-08	E74 like ETS transcription factor 3
<i>elovl8b</i>	-3.8	4.0E-04	ELOVL fatty acid elongase 8b
<i>enpp7.1</i>	-3.1	3.3E-09	Ectonucleotide pyrophosphatase/phosphodiesterase 7
<i>epgn</i>	-2.4	4.4E-07	Epithelial mitogen
<i>epsti1</i>	2	3.5E-02	Epithelial stromal interaction 1
<i>esr2b</i>	2.2	1.3E-03	Estrogen receptor 2
<i>f3b</i>	-2.3	1.3E-07	Coagulation factor III, tissue factor
<i>fabp11b</i>	-2.1	3.0E-03	Fatty acid binding protein X
<i>fam126a</i>	2.7	9.4E-14	Family with sequence similarity 126 member A
<i>FAM126B (LOC100536464)</i>	2.1	1.9E-02	Family with sequence similarity 126 member B
<i>fam159a</i>	-3.6	3.4E-02	Family with sequence similarity 159 member A
<i>fam167aa</i>	-2.6	1.3E-02	Family with sequence similarity 167 member A
<i>far1</i>	-2	1.5E-07	Fatty acyl-CoA reductase 1
<i>fbxo32</i>	2	4.7E-10	F-box protein 32
<i>FCRL5 (LOC570739)</i>	2.5	5.0E-02	Fc receptor-like protein 5
<i>fgf18a</i>	-2.5	1.1E-02	Fibroblast growth factor 18
<i>fgf4</i>	-2	1.1E-03	Fibroblast growth factor 4
<i>fhl3a</i>	-2	7.5E-06	Four and a half LIM domains 3
<i>FILIP1L (LOC101884302)</i>	-2.2	2.9E-02	Filamin-A-interacting protein 1-like
<i>fkbp5</i>	2.1	6.9E-11	FKBP prolyl isomerase 5
<i>FMO1 (LOC793236)</i>	-3.8	1.5E-03	Flavin-containing monooxygenase
<i>fosab</i>	-2.2	4.9E-10	Fos proto-oncogene, AP-1 transcription factor subunit
<i>fosl1a</i>	-3.4	1.2E-08	FOS like 1, AP-1 transcription factor subunit
<i>foxj2</i>	2.3	2.4E-06	Forkhead box J2
<i>fsta</i>	2	1.1E-07	Follistatin
<i>fthl29</i>	3.4	2.3E-06	Ferritin, heavy polypeptide-like 29
<i>fthl31</i>	2.3	3.2E-09	Ferritin, heavy polypeptide-like 31
<i>ftr02</i>	2.2	3.1E-02	FinTRIM family member 2
<i>ftr14l</i>	6.5	4.9E-06	FinTRIM family member 14-like
<i>furina</i>	3.9	5.6E-19	Furin
<i>fxyd7</i>	-2	3.4E-08	FXYP Domain Containing Ion Transport Regulator 7
<i>g2e3</i>	-2.1	1.6E-03	G2/M-phase specific E3 ubiquitin protein ligase
<i>gabpb2b</i>	-2.4	1.5E-02	GA binding protein transcription factor subunit beta 2
<i>gal3st2</i>	-2.1	5.0E-03	Galactose-3-O-sulfotransferase 2
<i>gbe1a</i>	2.8	2.1E-03	1,4-alpha-glucan branching enzyme 1
<i>gc2</i>	-2.2	3.5E-02	Guanylate cyclase 2F, retinal
<i>gcga</i>	-2.1	4.5E-03	Glucagon
<i>gdf2</i>	2.5	1.1E-02	Growth differentiation factor 2
<i>GIMAP4 (LOC101884484)</i>	2.5	4.1E-02	GTPase IMAF family member 4-like
<i>gkup</i>	2.8	3.8E-02	Glucuronokinase
<i>gng10</i>	2	3.3E-02	G protein subunit gamma 10
<i>gnrh3</i>	-2	3.6E-02	Gonadotropin releasing hormone 1
<i>gnrhr2</i>	3.2	3.9E-02	Gonadotropin releasing hormone receptor 2
<i>GOLGA6L22 (LOC103909796)</i>	-2.8	3.3E-03	Golgin subfamily A member 6-like protein 2
<i>grb2a</i>	-2.2	2.6E-05	Growth factor receptor bound protein 2
<i>grhl3</i>	3.2	7.3E-07	Grainyhead like transcription factor 3
<i>grm1b</i>	-2.1	2.3E-02	Glutamate metabotropic receptor 1
<i>grxcr1</i>	2.4	2.7E-05	Glutaredoxin And Cysteine Rich Domain Containing 1

Gene name	FC	P-Value	Function
<i>gstt2</i>	-2.5	1.6E-04	Glutathione S-transferase theta 2
<i>hephl1b</i>	3.8	1.7E-02	Hephaestin like 1
<i>heyl</i>	-2.3	3.2E-03	Hes related family bHLH transcription factor with YRPW motif like
<i>hhla2a.2</i>	3.1	3.5E-05	HERV-H LTR-associating 2
<i>hmf4a</i>	-3.3	3.6E-02	Hepatocyte nuclear factor 4 alpha
<i>hsd11b2</i>	2.1	8.2E-08	Hydroxysteroid 11-beta dehydrogenase 2
<i>ido1</i>	-4.5	1.5E-03	Indoleamine 2,3-dioxygenase 1
<i>igfbp1b</i>	4	2.6E-11	Insulin like growth factor binding protein 1
<i>igfbp2b</i>	-2.3	1.8E-02	Insulin like growth factor binding protein 2
<i>il12bb</i>	3.3	2.6E-02	Interleukin 12B
<i>il1b</i>	-2.8	1.8E-02	Interleukin 1 beta
<i>INHBB (LOC103909000)</i>	-2.6	3.9E-02	Inhibin beta B chain-like
<i>insc</i>	2.7	1.9E-03	Inscuteable Spindle Orientation Adaptor Protein
<i>insl3</i>	2.1	1.1E-02	Insulin like 3
<i>iqcc</i>	-3.1	1.2E-05	IQ motif containing C
<i>itgae.1</i>	3.8	1.3E-04	Integrin subunit alpha E
<i>itgae.2</i>	-2.6	1.9E-02	Integrin subunit alpha E
<i>itgb4</i>	2	6.9E-08	Integrin subunit beta 4
<i>jac1</i>	-4.1	1.6E-02	Jacalin 1 (lectin)
<i>jac8</i>	2.8	2.8E-02	Jacalin 8 (lectin)
<i>jdp2b</i>	-3.1	1.8E-15	Jun dimerization protein 2
<i>jmjd8</i>	-2.4	3.7E-02	Jumonji domain containing 8
<i>junba</i>	-2.1	2.4E-10	JunB proto-oncogene, AP-1 transcription factor subunit
<i>junbb</i>	-2.2	5.9E-10	JunB proto-oncogene, AP-1 transcription factor subunit
<i>KBTBD13 (LOC101886608)</i>	-2.1	2.6E-02	Kelch repeat and BTB domain-containing protein 13-like
<i>kbtbd7</i>	-2.3	1.4E-03	Kelch repeat and BTB domain containing 7
<i>kdelc1</i>	-2.6	3.0E-05	protein O-glucosyltransferase 2
<i>khnyln</i>	-2	9.0E-04	KH and NYN domain containing
<i>KIAA0753 (si:dkey/243i1.1)</i>	-2.6	1.6E-11	Protein moonraker. Involved in centriole duplication
<i>klf10</i>	-4.8	5.7E-03	Kruppel like factor 10
<i>KLHL33 (si:ch211-63p21.8)</i>	2.3	7.9E-04	Kelch like family member 33
<i>lamc2</i>	2.8	3.8E-05	Laminin subunit gamma 2
<i>lmln</i>	-2.2	1.7E-02	Leishmanolysin like peptidase
<i>lnx1</i>	2.3	3.6E-13	Ligand of numb-protein X 1
<i>LOC100005008</i>	2.6	3.0E-04	ARAP1-arf-GAP with Rho-GAP domain, ANK repeat and PH domain-containing protein 1-like
<i>LOC100005923</i>	-2.4	1.3E-02	Gastrula zinc finger protein XICGF49.1-like
<i>LOC100006428</i>	2.2	9.7E-07	Ferritin
<i>LOC100007488</i>	-2	3.9E-02	MFAP4 -microfibril-associated glycoprotein 4-like
<i>LOC100147849</i>	2.8	4.6E-02	Mucin
<i>LOC100149234</i>	3.8	3.7E-03	GVIN1-interferon-induced very large GTPase 1-like
<i>LOC100330257</i>	-2.5	7.5E-04	RAB39B-ras-related protein Rab-39A-like
<i>LOC100334202</i>	-3.1	3.5E-08	NLRP3-NACHT, LRR and PYD domains-containing protein 3-like.
<i>LOC100535428</i>	-4.4	2.7E-10	NACHT, LRR and PYD domains-containing protein 3-like
<i>LOC101882592</i>	3.1	2.7E-02	Predicted to have G protein-coupled receptor activity

Gene name	FC	P-Value	Function
<i>LOC101885212</i>	-3.1	1.8E-02	NLRP3-NACHT, LRR and PYD domains-containing protein 3-like
<i>LOC558816</i>	5.7	3.1E-07	Ferritin, middle subunit-like
<i>LOC559107</i>	-2.4	7.8E-04	Lactase-phlorizin hydrolase
<i>lox14</i>	5.2	2.0E-14	Lysyl oxidase like 4
<i>lox15b</i>	-2.1	7.3E-03	Lysyl oxidase like 5
<i>lratb.2</i>	-2.2	4.1E-06	Lecithin retinol acyltransferase b, tandem duplicate 2
<i>lrch2</i>	-2.3	2.8E-05	Leucine rich repeats and calponin homology domain containing 2
<i>lrrc10b</i>	-2.1	4.4E-02	Leucine rich repeat containing 10
<i>ltb4r2b</i>	2.7	4.2E-02	Leukotriene B4 receptor
<i>lyz</i>	-2.7	3.6E-06	Lysozyme like 1
<i>maff</i>	2	2.3E-08	MAF bZIP transcription factor F
<i>mbtps1</i>	2	1.2E-06	Membrane-bound transcription factor peptidase, site 1
<i>me1</i>	-4.7	1.8E-03	NADP-dependent malic enzyme-like
<i>megf6b</i>	-2.2	1.4E-03	Multiple EGF like domains 6
<i>mfsd2aa</i>	-5.4	2.3E-12	Major facilitator superfamily domain containing 2A
<i>mgat3a</i>	-2.9	8.9E-03	β -1,4-mannosyl-glycoprotein 4- β -N-acetylglucosaminyltransferase
<i>mhc1ula</i>	-2.9	8.2E-04	Major histocompatibility complex, class I-related
<i>mkks</i>	-2.2	4.5E-03	McKusick-Kaufman syndrome
<i>mlphb</i>	-2.4	3.5E-05	Melanophilin
<i>mmp11b</i>	-2.9	5.6E-03	Matrix metalloproteinase 11
<i>mmp28</i>	2.1	1.8E-02	Matrix metalloproteinase 28
<i>mns1</i>	2.2	6.9E-04	Meiosis specific nuclear structural 1
<i>mtmr12</i>	3	1.9E-13	Myotubularin related protein 12
<i>MUL1 (LOC402879)</i>	2.6	1.5E-06	Mitochondrial ubiquitin ligase activator of nfkb 1-A
<i>mybpha</i>	-2.3	1.5E-05	Myosin binding protein H
<i>ncam2</i>	-2.1	3.5E-08	Neural cell adhesion molecule 2
<i>ncapg2</i>	-2.2	7.2E-03	Non-SMC condensin II complex subunit G2
<i>ndrg4</i>	-4.2	7.9E-27	NDRG family member 4
<i>nfr</i>	3.2	3.2E-02	Notochord formation related gene
<i>nipsnap1</i>	-2.3	2.9E-02	nipsnap homolog 1
<i>nkx6.3</i>	2.4	3.5E-02	NK6 homeobox 3
<i>nlrp5</i>	2.7	3.7E-02	NOD-like receptor family B, member 5
<i>nlrp12</i>	-7.6	1.4E-19	NACHT, LRR and PYD domains-containing protein 12-like
<i>notum2</i>	-2.1	1.8E-02	Notum pectinacetylase 2
<i>npffl</i>	-2.6	2.9E-04	Neuropeptide FF-amide peptide precursor
<i>npsn</i>	-2.2	2.2E-05	Astacin like metalloendopeptidase
<i>npy2r</i>	2.6	5.0E-02	Neuropeptide Y receptor Y2
<i>nr0b2a</i>	-2.4	1.7E-02	Nuclear receptor subfamily 0 group B member 2.
<i>nr4a3</i>	2.5	2.7E-14	Nuclear receptor subfamily 4 group A member 3
<i>nsl1</i>	-2.3	3.2E-02	NSL1 component of MIS12 kinetochore complex
<i>nudt3b</i>	-2.1	8.1E-04	Nudix (nucleoside diphosphate linked moiety X) hydrolase 3
<i>numa1</i>	-2.1	2.7E-05	Nuclear mitotic apparatus protein 1
<i>olfml2ba</i>	-3.5	2.6E-12	Olfactomedin like 2B
<i>omph</i>	-3.2	1.6E-02	Olfactory marker protein
<i>opn4xa</i>	-2.5	4.8E-02	Opsin 4xa

Gene name	FC	P-Value	Function
<i>or111-11</i>	-4.1	8.3E-03	Odorant receptor, family D, subfamily 111, member 11
<i>or115-11</i>	-3.3	2.0E-03	Odorant receptor, family D, subfamily 115, member 11
<i>osbpl3a</i>	2.4	4.1E-05	Oxysterol binding protein like 3
<i>paqr3b</i>	4.1	5.5E-05	Progesterin and adipoQ receptor family member 3
<i>PCBP3 (zgc:162999)</i>	-2.6	2.9E-02	Poly(rC)-binding protein 3-like
<i>pcdh1g2</i>	2.1	5.0E-07	Protocadherin 1 gamma 2
<i>pcdh1g26</i>	3	3.6E-12	Protocadherin 1 gamma 26
<i>pcdh1g3</i>	-2.1	1.1E-03	Protocadherin 1 gamma 3
<i>pcdh1g30</i>	-4	5.0E-11	Protocadherin 1 gamma 30
<i>pcdh1gb9</i>	-5.9	7.2E-13	Protocadherin 1 gamma b 9
<i>pcyt1bb</i>	-2.3	4.4E-02	Phosphate cytidylyltransferase 1, choline, beta
<i>pde9a</i>	2.4	2.2E-02	Phosphodiesterase 9A
<i>pdxka</i>	-2.4	2.7E-07	Pyridoxal kinase
<i>pdzd3b</i>	-2.9	4.8E-03	PDZ domain containing 3
<i>pgpep1</i>	-2.2	9.8E-03	Pyroglutamyl-peptidase I
<i>pigr</i>	-2.6	2.2E-04	Polymeric immunoglobulin receptor
<i>pik3ap1</i>	-2	3.6E-02	Phosphoinositide-3-kinase adaptor protein 1
<i>PIM2 (LOC103909000)</i>	4	3.3E-03	Serine/threonine-protein kinase pim-2-like
<i>pimr130</i>	-3.2	4.2E-02	Pim proto-oncogene, serine/threonine kinase, related 130
<i>pimr197</i>	2.6	2.8E-02	Pim proto-oncogene, serine/threonine kinase, related 197
<i>pkd1l1</i>	3.4	2.0E-02	Polycystin 1 like 1
<i>pkhd1l1</i>	2.2	8.3E-07	PKHD1 like 1
<i>pld2</i>	-6	1.6E-25	Phospholipase D2
<i>plekhs1</i>	-3.3	2.8E-02	Pleckstrin homology domain containing S1
<i>plin2</i>	2.8	8.6E-09	Perilipin 2
<i>plpp4</i>	-3.1	2.2E-03	Phospholipid phosphatase 4
<i>pltp</i>	2	1.0E-06	phospholipid transfer protein
<i>pnpla1</i>	-2.3	5.0E-02	Patatin like phospholipase domain containing 1
<i>ponzr6</i>	2.3	1.4E-02	Plac8 onzin-related protein 6
<i>postna</i>	-2.4	3.5E-08	Periostin
<i>ppifa</i>	-2.2	1.7E-08	Peptidylprolyl isomerase F
<i>ppm1f</i>	-3.2	4.1E-02	Protein phosphatase, Mg ²⁺ /Mn ²⁺ dependent 1F
<i>ppp1r27b</i>	2	6.8E-04	Protein phosphatase 1 regulatory subunit 27
<i>ppp1r3b</i>	-3.1	2.0E-02	Protein phosphatase 1 regulatory subunit 3B
<i>prg4b</i>	2.1	4.6E-06	Proteoglycan 4
<i>prp</i>	-2.1	5.1E-05	Prion protein. Glycosylphosphatidylinositol-anchored glycoprotein
<i>pskh1</i>	-4.2	3.1E-05	Protein serine kinase H1
<i>psmb7</i>	2.1	4.5E-10	Proteasome 20S subunit beta 7
<i>psmc1b</i>	2	3.6E-09	Proteasome 26S subunit, ATPase 1
<i>psme1</i>	2.1	4.3E-04	Proteasome activator subunit 1
<i>ptpn20</i>	-2.3	1.8E-10	Protein tyrosine phosphatase non-receptor type 20
<i>ptrh2</i>	2.3	3.9E-07	Peptidyl-tRNA hydrolase 2
<i>pycr1a</i>	2.1	1.0E-03	Pyrroline-5-carboxylate reductase 1
<i>qkia</i>	2.2	4.7E-11	QKI, KH domain containing RNA binding
<i>rab42b</i>	2.4	1.5E-02	Member RAS oncogene family
<i>rab43</i>	3.8	2.9E-09	Member RAS oncogene family

Gene name	FC	P-Value	Function
<i>rac1</i>	-3.2	6.9E-04	ras-related C3 botulinum toxin substrate 1-like
<i>racgap1</i>	-2.3	5.1E-03	Rac GTPase activating protein 1
<i>rbm25a</i>	2.5	1.4E-12	RNA binding motif protein 25
<i>rbp1</i>	-3.4	8.4E-03	Retinol binding protein 1
<i>rbp2b</i>	-2.2	3.8E-06	Retinol binding protein 2
<i>rdh12l</i>	2.3	2.3E-04	Retinol dehydrogenase 12 like
<i>rdh20</i>	-2.4	6.1E-04	Retinol dehydrogenase 20
<i>relb</i>	-2.3	7.6E-06	RELB proto-oncogene, NF-kB subunit
<i>RFTN1 (LOC101885083)</i>	-3.1	1.9E-02	Raftlin, Lipid Raft Linker 1
<i>rgs13</i>	-2.1	3.4E-03	Regulator of G protein signaling 13
<i>rh50</i>	-2.7	4.2E-03	Rh50-like protein
<i>RNF14 (LOC100537178)</i>	-2.1	3.3E-02	The protein encoded by this gene contains a RING zinc finger
<i>rnf150</i>	-2.2	4.9E-02	Ring finger protein 150
<i>RNF39 (si:dkey/219e21.2)</i>	-2.7	2.3E-06	Ring finger protein 39
<i>rps6kb1a</i>	2	3.4E-04	Ribosomal protein S6 kinase B1
<i>rrh</i>	-3.1	5.4E-06	Retinal pigment epithelium-derived rhodopsin homolog
<i>sb:cb288</i>	-2.2	9.0E-04	Uncharacterized zebrafish gene
<i>sc5d</i>	-2.2	4.0E-02	Sterol-C5-desaturase
<i>scarf2</i>	-2.8	9.1E-04	Scavenger receptor class F member 2
<i>scn4bb</i>	-2.1	3.2E-02	Sodium voltage-gated channel beta subunit 4
<i>sele</i>	-3.2	1.6E-06	Selectin E
<i>sell</i>	-2.7	7.1E-03	Selenoprotein L
<i>shpk</i>	2.1	3.3E-02	Sedoheptulokinase
<i>si:busm1-105l16.2</i>	3.8	1.3E-09	Predicted to have microtubule binding activity
<i>si:cabz01036006.1</i>	5.1	1.3E-08	Predicted to have transmembrane signaling receptor activity
<i>si:ch1073-13h15.3</i>	-3	1.2E-04	Predicted to have GDP-dissociation inhibitor, GTPase activator and oxidoreductase activity
<i>si:ch1073-143l10.2</i>	-2.7	1.7E-02	Predicted to be involved in autophagosome
<i>si:ch1073-147h9.1</i>	2.1	1.6E-04	Uncharacterized zebrafish gene
<i>si:ch211-207e14.4</i>	-2.9	2.7E-07	Predicted to have interleukin-17 receptor activity
<i>si:ch211-217g15.3</i>	-3.6	5.2E-07	Uncharacterized zebrafish gene
<i>si:ch211-220d9.3</i>	-2.4	7.8E-06	Enkurin domain containing 1
<i>si:ch211-220i18.4</i>	2.4	3.0E-04	Predicted to have MAP kinase activity
<i>si:ch211-241d24.1</i>	2.9	1.4E-02	Solo transcritos no codificantes descritos
<i>si:ch211-241e1.3</i>	2.8	2.1E-08	Predicted to have signaling receptor binding activity
<i>si:ch211-243p7.3</i>	2.1	3.4E-04	Uncharacterized zebrafish gene
<i>si:ch211-25d12.7</i>	3.5	8.9E-03	Src like adaptor 2
<i>si:ch211-261n11.8</i>	3	1.2E-09	TNF receptor superfamily member 14
<i>si:ch211-107n13.1</i>	-3.5	4.0E-05	Family with sequence similarity 110 member D
<i>si:ch211-133h13.1</i>	-2.8	2.2E-02	Predicted to be involved in intracellular signal transduction
<i>si:ch211-133l11.10</i>	-2.6	4.4E-02	Ras homolog family member U
<i>si:ch211-14c7.2</i>	5.6	3.0E-32	Uncharacterized zebrafish gene
<i>si:ch211-156l18.8</i>	-2	1.1E-02	G-protein coupled receptor 158
<i>si:ch211-157c3.4</i>	2.5	4.2E-07	Predicted to have metal ion binding activity
<i>si:ch211-176g13.8</i>	-6.1	3.9E-05	Predicted to have lipid binding activity
<i>si:ch211-178n15.1</i>	-2.6	1.3E-02	Domains Protein Largen/Inhibitory synaptic factor 1

Gene name	FC	P-Value	Function
<i>si:ch211-199m9.3</i>	-3.2	3.0E-03	Unmapped lincRNA
<i>si:ch211-66i8.3</i>	-3.4	6.3E-04	Unmapped lincRNA
<i>si:ch211-69l10.2</i>	2.3	7.6E-03	Encodes a long, intervening non-coding RNA
<i>si:ch73-226l13.2</i>	-2.1	2.4E-02	Predicted to have cytokine activity
<i>si:ch73-263o4.4</i>	-2.3	3.0E-02	Serine racemase
<i>si:ch73-334d15.1</i>	-2.1	2.1E-02	Predicted to have UDP-glycosyltransferase activity
<i>si:ch73-335l21.4</i>	-2.7	2.8E-12	Predicted to have metal ion binding and transferase activity
<i>si:ch73-18b11.2</i>	-2.5	1.1E-02	Uncharacterized zebrafish gene
<i>si:dkey-208k4.3</i>	-3	8.4E-03	Uncharacterized zebrafish gene
<i>si:dkey-22i16.9</i>	-3.9	1.4E-07	Predicted to be involved in cell surface receptor signaling
<i>si:dkey-23n7.10</i>	2.3	2.4E-06	Predicted to be involved in proteasome-mediated ubiquitin-dependent protein catabolic process
<i>si:dkey-266f7.9</i>	2.1	5.3E-03	Predicted to have phosphoric diester hydrolase activity
<i>si:dkey-10h3.1</i>	7.2	6.7E-10	Sialoadhesin-like
<i>si:dkey-111e8.5</i>	3	4.2E-02	Metal ion binding and ubiquitin-protein transferase activity
<i>si:dkey-190g11.3</i>	2.4	4.5E-02	Predicted to have protein-lysine N-methyltransferase activity
<i>si:dkey-192d15.2</i>	3	1.6E-02	Apolipoprotein
<i>si:dkey-1k23.3</i>	3	1.9E-02	Alpha crystallin/Hsp20 domain
<i>si:dkey-56d12.4</i>	6	5.3E-05	Uncharacterized zebrafish gene
<i>si:dkey-58f10.6</i>	3.1	8.1E-03	Predicted to have GTP binding activity
<i>si:dkey-61o18.2</i>	-2.7	2.2E-02	Unmapped lincRNA
<i>si:dkey-74i1.3</i>	2.1	4.1E-02	Unmapped lincRNA
<i>si:dkey-76k16.6</i>	-3.6	5.1E-06	Predicted to have N-acyltransferase activity
<i>si:dkey-7c18.24</i>	-2.5	3.4E-07	Translation initiation factor IL-2
<i>si:dkey-9c18.3</i>	2.1	7.8E-03	B cell receptor CD22 / sialoadhesin
<i>si:dkey-9i23.15</i>	-2	2.6E-04	Transmembrane protein 109
<i>si:dkeyp-34c12.1</i>	2.3	2.1E-04	Proteoglycan
<i>si:rp71-45g20.11</i>	-2.4	2.4E-02	Predicted to have ubiquitin protein ligase activity and zinc ion binding activity
<i>si:rp71-77l1.1</i>	2.1	5.2E-03	Dispanin subfamily A member 2b-like
<i>si:zfos-2326c3.2</i>	-2.2	2.6E-06	Misshapen-like kinase 1
<i>sipa1l3</i>	-2.2	1.4E-06	Signal induced proliferation associated 1 like 3
<i>slc13a5b</i>	-2.8	4.4E-02	Solute carrier family 13 member 5
<i>slc15a1a</i>	-2	5.6E-03	Solute carrier family 15 member 1
<i>slc15a1b</i>	-2	8.5E-05	Solute carrier family 15 member 1
<i>slc25a15b</i>	2	1.0E-05	Solute carrier family 25 member 15
<i>slc25a47a</i>	2.5	9.3E-10	Solute carrier family 25 member 47
<i>slc30a1b</i>	-3	2.1E-02	Solute carrier family 30 member 1
<i>slc34a2a</i>	-2.7	2.3E-04	Solute carrier family 34 member 2
<i>slc43a1a</i>	2.1	1.8E-04	Solute carrier family 43 member 1
<i>slc47a3</i>	-2.7	2.5E-04	Solute carrier family 47 member 3
<i>slx4ip</i>	-3.8	1.9E-07	SLX4 interacting protein
<i>smcr8b</i>	2	9.2E-04	SMCR8-C9orf72 complex subunit
<i>SMIM18 (si:dkey-92j12.6)</i>	2.3	2.9E-08	Small integral membrane protein 18
<i>smpd5</i>	2	1.4E-06	Sphingomyelin phosphodiesterase 5 (pseudogene)
<i>socs3b</i>	-2.1	1.3E-08	Suppressor of cytokine signaling 3

Gene name	FC	P-Value	Function
<i>soul5l</i>	-3.1	2.1E-02	Heme-binding protein soul5, like
<i>SPACA5 (LOC100536671)</i>	2.1	2.0E-02	Sperm acrosome-associated protein 5-like
<i>spata6l</i>	2.6	6.2E-07	Spermatogenesis associated 6 like
<i>sptssb</i>	3.9	3.4E-08	Serine palmitoyltransferase small subunit B
<i>src</i>	-2.4	3.7E-06	SRC proto-oncogene, non-receptor tyrosine kinase
<i>srd5a2b</i>	-4.2	3.3E-03	Steroid 5 alpha-reductase 2
<i>SSC4D (LOC100331436)</i>	2.4	8.8E-03	Scavenger Receptor Cysteine Rich Family Member With 4 Domains
<i>st3gal7</i>	-2.6	2.0E-04	ST3 beta-galactoside alpha-2,3-sialyltransferase 7
<i>stoml3b</i>	-2.2	2.6E-05	Stomatin like 3
<i>stx11a</i>	2.5	2.4E-02	Syntaxin 11
<i>swap70b</i>	2.1	2.0E-04	Switching B cell complex subunit SWAP70
<i>syf18b</i>	-2	5.4E-04	Synaptotagmin XVIIIb
<i>tas1r1</i>	3.1	4.2E-02	Taste 1 receptor member 1
<i>tcaf1</i>	-2	1.5E-02	TRPM8 channel associated factor 1
<i>tekt1</i>	2	4.2E-05	Tektin 1
<i>tekt3</i>	2.3	9.2E-03	Tektin 3
<i>thap1</i>	2.5	4.2E-08	THAP domain containing 1
<i>THBS1 (LOC100535166)</i>	-2.3	6.6E-04	Thrombospondin-1-like
<i>thfp5</i>	-5	1.2E-13	Three-finger protein 5
<i>tk1</i>	-2	6.5E-04	Thymidine kinase 1
<i>tmc1</i>	2.8	3.2E-04	Transmembrane channel like 1
<i>tmc2a</i>	4.7	4.3E-03	Transmembrane channel like 2
<i>tmem150ab</i>	-2.5	1.3E-05	Transmembrane protein 150A
<i>tmem163a</i>	-3.7	5.2E-13	Transmembrane protein 163
<i>tmem205</i>	-2.1	2.6E-04	Transmembrane protein 205
<i>tmem37</i>	-2.5	1.5E-03	Transmembrane protein 37
<i>tmem86b</i>	-2.2	7.4E-04	Transmembrane protein 86B
<i>tmprss13b</i>	2.2	3.0E-05	Transmembrane serine protease 13
<i>tmtops3b</i>	-2.1	2.5E-02	Teleost multiple tissue opsin 3b
<i>TNFRSF14 (si:ch211/261n11.8)</i>	3.8	1.2E-09	TNF receptor superfamily member 14
<i>tnfsf13b</i>	-23.8	4.2E-30	TNF superfamily member 13b
<i>tnni4b.1</i>	2.8	2.3E-02	Troponin I4b, tandem duplicate 1
<i>tprg1</i>	-2	5.1E-04	Tumor protein p63 regulated 1
<i>trim109</i>	2.3	9.2E-07	Tripartite motif containing
<i>trim63a</i>	2.4	8.8E-15	Tripartite motif containing 63
<i>tspan14</i>	2.6	5.9E-10	Tetraspanin 14
<i>ttc23</i>	2.4	1.3E-02	Tetratricopeptide repeat domain 23
<i>ttc7a</i>	-2.2	1.8E-05	Tetratricopeptide repeat domain 7A
<i>ttpal</i>	-3	9.9E-12	Alpha tocopherol transfer protein like
<i>txnipb</i>	-2	3.9E-08	Thioredoxin interacting protein
<i>txnl1</i>	3.1	2.6E-15	Thioredoxin like 1
<i>txnrd2.2</i>	-3.5	1.8E-08	Thioredoxin reductase 2
<i>tym5</i>	-2	9.1E-04	Thymidylate synthetase
<i>tyr</i>	-2.6	2.2E-03	Tyrosinase.
<i>tyro3</i>	-2.3	4.5E-04	TYRO3 protein tyrosine kinase
<i>ubb</i>	2	1.8E-09	Ubiquitin C
<i>ubl7b</i>	2.2	1.0E-10	Ubiquitin like 7

Gene name	FC	P-Value	Function
<i>ubxn10</i>	2.2	4.1E-02	UBX domain protein 10
<i>ugp2b</i>	2.1	1.0E-08	UDP-glucose pyrophosphorylase 2
<i>ugt1ab</i>	-4.5	3.6E-06	UDP glucuronosyltransferase family 1 member A1
<i>ugt2a2</i>	6.3	5.2E-05	UDP glucuronosyltransferase 2 family, polypeptide A2
<i>ugt5b3</i>	-2.1	1.3E-02	UDP glucuronosyltransferase 5 family, polypeptide B3
<i>utp23</i>	2.1	4.9E-08	UTP23 small subunit processome component
<i>vti1b</i>	-2.1	1.1E-05	Vesicle transport through interaction with t-SNAREs 1B
<i>vwa10.1</i>	-3	1.1E-02	Von Willebrand factor A domain containing 7
<i>wasf3b</i>	-5.3	6.9E-36	WASP family member 3
<i>wdr35</i>	2.1	3.0E-08	WD repeat domain 35
<i>wdr66</i>	-4	1.1E-02	Cilia and flagella associated protein 251
<i>wnt9b</i>	-2.5	3.6E-05	Wnt family member 9B
<i>wu:fd06e11</i>	-2.1	3.5E-02	gastrula zinc finger protein XICGF49
<i>xirp1</i>	2.5	2.4E-10	xin actin binding repeat containing 1
<i>ydjC</i>	-2.3	9.5E-05	YdjC chitoooligosaccharide deacetylase homolog
<i>ythdf3</i>	2	1.1E-05	YTH N6-methyladenosine RNA binding protein 3
<i>zbtb5</i>	-2.3	9.7E-06	zinc finger and BTB domain containing 5
<i>zgc:100868</i>	2.9	1.7E-08	Serine protease 27
<i>zgc:100920</i>	2.7	5.2E-05	Sodium/potassium transporting ATPase interacting 4
<i>zgc:101785</i>	-5.4	3.7E-08	Annexin
<i>zgc:103601</i>	-3.1	4.9E-02	Arylamine N-acetyltransferase
<i>zgc:109982</i>	-2.1	4.8E-02	Retinol dehydrogenase 8
<i>zgc:112160</i>	2.1	5.5E-06	Chymotrypsinogen B2
<i>zgc:114046</i>	4.2	6.0E-04	Histone H2B
<i>zgc:152945</i>	-2.8	1.9E-03	Hemopexin
<i>zgc:153431</i>	-3	1.5E-03	CSC1-like protein 2
<i>zgc:153759</i>	3	3.6E-05	TNF receptor superfamily member 14
<i>zgc:154142</i>	-2.1	2.0E-05	Predicted to have serine-type endopeptidase activity
<i>zgc:162999</i>	2	8.1E-03	PCBP3 Poly(rC)-binding protein 3
<i>zgc:172122</i>	3.5	8.2E-06	CD200 molecule
<i>zgc:174379</i>	2.5	7.0E-03	Saccharopine dehydrogenase
<i>zgc:174653</i>	2.1	4.1E-02	Predicted to have DNA-binding transcription factor activity
<i>zgc:198329</i>	-8	1.0E-05	Carcinoembryonic antigen-related cell adhesion molecule 8
<i>zgc:64201</i>	2.1	4.6E-03	Prolyl-tRNA synthetase associated domain containing 1
<i>zgc:86764</i>	-2.3	6.5E-04	Predicted to have microtubule binding activity
<i>zgc:92137</i>	-2.9	1.1E-05	Predicted to have alpha-amylase activity
<i>zgc:92745</i>	3.4	3.7E-05	Chymotrypsin like elastase 1
<i>znf750</i>	4.1	4.3E-07	Zinc finger protein 750
<i>znhit3</i>	2.1	1.4E-04	Zinc finger HIT-type containing 3
<i>Zp3</i>	2.6	1.9E-03	Zona pellucida glycoprotein 3

Table S2. Biological process analysis of 451 DEGs in the *cyp1b1*-KO using the DAVID bioinformatic tool. Count indicates the number of genes included in each pathway.

Biological Process Term	Count	P-Value	Genes
Response to lipopolysaccharide	8	<0.0001	<i>cxcl18b</i> , <i>zgc:153759</i> , <i>il1b</i> , <i>junba</i> , <i>junbb</i> , <i>loc101883994</i> , <i>si:ch211-261n11.7</i> , <i>si:ch211-261n11.8</i>
Cell adhesion	17	<0.0001	<i>pcdh1g3</i> , <i>lmln</i> , <i>cyr61l1</i> , <i>dsg2.1</i> , <i>itgae.2</i> , <i>pcdh1g2</i> , <i>itgb4</i> , <i>src</i> , <i>pcdh1g26</i> , <i>dsc2l</i> , <i>sele</i> , <i>postna</i> , <i>pcdh1gb9</i> , <i>si:ch211-241e1.3</i> , <i>tyro3</i> , <i>ncam2</i> , <i>pcdh1g30</i>
Proteolysis	22	<0.0001	<i>lmln</i> , <i>cfh</i> , <i>casp8l2</i> , <i>mbtps1</i> , <i>tmprss13b</i> , <i>zgc:154142</i> , <i>c6ast3</i> , <i>c6ast4</i> , <i>zgc:92745</i> , <i>si:dkeyp-50d11.2</i> , <i>zgc:100868</i> , <i>psmb7</i> , <i>zgc:112160</i> , <i>casp7</i> , <i>ctsl</i> , <i>mmp11b</i> , <i>ctss1</i> , <i>mmp28</i> , <i>npsn</i> , <i>pgpep1</i> , <i>ctsd</i> , <i>furina</i>
Inflammatory response	10	0.001	<i>cxcl18b</i> , <i>ltb4r2b</i> , <i>elf3</i> , <i>zgc:153759</i> , <i>il1b</i> , <i>loc101883994</i> , <i>ccl19a.1</i> , <i>si:ch211-261n11.7</i> , <i>relb</i> , <i>si:ch211-261n11.8</i>
Regulation of cell proliferation	9	0.002	<i>cxcl18b</i> , <i>cdk6</i> , <i>zgc:153759</i> , <i>src</i> , <i>junba</i> , <i>junbb</i> , <i>loc101883994</i> , <i>si:ch211-261n11.7</i> , <i>si:ch211-261n11.8</i>
Neutrophil chemotaxis	5	0.004	<i>cxcl18b</i> , <i>il1b</i> , <i>duox</i> , <i>loc101883994</i> , <i>ccl19a.1</i>
Neutrophil activation	3	0.005	<i>cxcl18b</i> , <i>il1b</i> , <i>loc101883994</i>
Oxidation-reduction process	22	0.006	<i>heph1b</i> , <i>pycr1a</i> , <i>loc793236</i> , <i>txnl1</i> , <i>srd5a2b</i> , <i>si:ch1073-179p4.3</i> , <i>lox14</i> , <i>zgc:174379</i> , <i>si:ch1073-13h15.3</i> , <i>tyr</i> , <i>cyp7a1</i> , <i>cyp8b1</i> , <i>ch25h</i> , <i>cyp24a1</i> , <i>lox15b</i> , <i>cyp11c1</i> , <i>sc5d</i> , <i>cyp1b1</i> , <i>duox</i> , <i>cyp4v8</i> , <i>zgc:109982</i> , <i>ido1</i>
Lipid metabolic process	10	0.009	<i>mbtps1</i> , <i>ch25h</i> , <i>smpd5</i> , <i>si:dkey-266f7.9</i> , <i>cpt2</i> , <i>elovl8b</i> , <i>srd5a2b</i> , <i>sptssb</i> , <i>pltp</i> , <i>cel.2</i>
Response to cytokine	3	0.014	<i>junba</i> , <i>junbb</i> , <i>relb</i>
Intracellular sequestering of iron ion	3	0.017	<i>loc558816</i> , <i>zgc:194125</i> , <i>zgc:109934</i>
Response to bacterium	4	0.020	<i>il1b</i> , <i>duox</i> , <i>ctsd</i> , <i>furina</i>
Iron ion transport	3	0.027	<i>loc558816</i> , <i>zgc:194125</i> , <i>zgc:109934</i>
Regulation of transcription from RNA polymerase II promoter	11	0.028	<i>fosl1a</i> , <i>nkx6.3</i> , <i>fosab</i> , <i>jdp2b</i> , <i>elf3</i> , <i>maff</i> , <i>junba</i> , <i>junbb</i> , <i>grhl3</i> , <i>ahrha</i> , <i>relb</i>
Lipid transport	5	0.042	<i>apoea</i> , <i>mfsd2aa</i> , <i>si:dkey-192d15.2</i> , <i>osbpl3a</i> , <i>apoa4b.3</i>
Homophilic cell adhesion via plasma membrane adhesion molecules	8	0.042	<i>pcdh1g3</i> , <i>dsg2.1</i> , <i>pcdh1g2</i> , <i>pcdh1gb9</i> , <i>pcdh1g26</i> , <i>zgc:172122</i> , <i>dsc2l</i> , <i>pcdh1g30</i>
Immune response	11	0.048	<i>cxcl18b</i> , <i>zgc:153759</i> , <i>il1b</i> , <i>ctss1</i> , <i>si:dkey-11f4.14</i> , <i>loc101883994</i> , <i>ccl19a.1</i> , <i>si:ch211-261n11.7</i> , <i>prg4b</i> , <i>tnfsf13b</i> , <i>si:ch211-261n11.8</i>

Table S3. Molecular Function analysis of 451 DEGs in the *cyp1b1*-KO using the DAVID bioinformatic tool. Count indicates the number of genes included in each pathway.

Molecular Function Term	Count	P-Value	Genes
Peptidase activity	21	<0.0001	<i>cfid</i> , <i>casp8l2</i> , <i>mbtps1</i> , <i>tmprss13b</i> , <i>zgc:154142</i> , <i>c6ast3</i> , <i>c6ast4</i> , <i>zgc:92745</i> , <i>si:dkeyp-50d11.2</i> , <i>zgc:100868</i> , <i>psmb7</i> , <i>zgc:112160</i> , <i>casp7</i> , <i>ctsl</i> , <i>mmp11b</i> , <i>ctss1</i> , <i>mmp28</i> , <i>npsn</i> , <i>pgpep1</i> , <i>ctsd</i> , <i>furina</i>
Iron ion binding	11	0.002	<i>loc558816</i> , <i>zgc:194125</i> , <i>ch25h</i> , <i>cyp24a1</i> , <i>zgc:109934</i> , <i>cyp11c1</i> , <i>sc5d</i> , <i>cyp1b1</i> , <i>cyp4v8</i> , <i>cyp7a1</i> , <i>cyp8b1</i>
Lipid binding	8	0.003	<i>rbp2b</i> , <i>apoea</i> , <i>rbp1</i> , <i>acot12</i> , <i>pltp</i> , <i>si:dkeyp-192d15.2</i> , <i>apoa4b.3</i> , <i>fabp11b</i>
Oxidoreductase activity	20	0.004	<i>hephl1b</i> , <i>pycr1a</i> , <i>si:ch1073-179p4.3</i> , <i>dhps13l1</i> , <i>zgc:174379</i> , <i>si:ch1073-13h15.3</i> , <i>tyr</i> , <i>cyp7a1</i> , <i>cyp8b1</i> , <i>hsd11b2</i> , <i>ch25h</i> , <i>cyp24a1</i> , <i>rdh20</i> , <i>cyp11c1</i> , <i>sc5d</i> , <i>cyp1b1</i> , <i>duox</i> , <i>cyp4v8</i> , <i>zgc:109982</i> , <i>ido1</i>
Hydrolase activity	30	0.005	<i>cfid</i> , <i>c6ast3</i> , <i>c6ast4</i> , <i>ugt1ab</i> , <i>zgc:92745</i> , <i>ppm1f</i> , <i>alp3</i> , <i>zgc:100868</i> , <i>psmb7</i> , <i>zgc:112160</i> , <i>smpd5</i> , <i>casp7</i> , <i>ctsl</i> , <i>mmp28</i> , <i>ctss1</i> , <i>ctsd</i> , <i>notum2</i> , <i>casp8l2</i> , <i>nudt3b</i> , <i>mbtps1</i> , <i>tmprss13b</i> , <i>zgc:154142</i> , <i>zgc:92137</i> , <i>si:dkeyp-50d11.2</i> , <i>psmc1b</i> , <i>mmp11b</i> , <i>ptrh2</i> , <i>npsn</i> , <i>furina</i> , <i>cel.2</i>
Monoxygenase activity	8	0.006	<i>loc793236</i> , <i>ch25h</i> , <i>cyp24a1</i> , <i>cyp11c1</i> , <i>cyp1b1</i> , <i>cyp4v8</i> , <i>cyp7a1</i> , <i>cyp8b1</i>
Serine-type peptidase activity	7	0.018	<i>zgc:100868</i> , <i>cfid</i> , <i>zgc:112160</i> , <i>tmprss13b</i> , <i>zgc:154142</i> , <i>zgc:92745</i> , <i>furina</i>
Heme binding	8	0.018	<i>cyp24a1</i> , <i>cyp11c1</i> , <i>cyp1b1</i> , <i>duox</i> , <i>cyp4v8</i> , <i>cyp7a1</i> , <i>cyp8b1</i> , <i>ido1</i>
Serine-type endopeptidase activity	9	0.020	<i>zgc:100868</i> , <i>cfid</i> , <i>mbtps1</i> , <i>zgc:112160</i> , <i>tmprss13b</i> , <i>zgc:154142</i> , <i>loc100149563</i> , <i>zgc:92745</i> , <i>furina</i>
Ferric iron binding	3	0.024	<i>loc558816</i> , <i>zgc:194125</i> , <i>zgc:109934</i>
Transporter activity	9	0.038	<i>aqp8a.2</i> , <i>rbp2b</i> , <i>rbp1</i> , <i>slc15a1a</i> , <i>slc13a5b</i> , <i>aqp7</i> , <i>ttpal</i> , <i>fabp11b</i> , <i>slc15a1b</i>
Transcription factor activity, RNA polymerase II core promoter proximal region sequence-specific binding	3	0.038	<i>fosl1a</i> , <i>fosab</i> , <i>jdp2b</i>
Metalloendopeptidase activity	6	0.048	<i>lmln</i> , <i>mmp11b</i> , <i>mmp28</i> , <i>c6ast3</i> , <i>npsn</i> , <i>c6ast4</i>
Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	6	0.049	<i>cyp24a1</i> , <i>cyp11c1</i> , <i>cyp1b1</i> , <i>cyp4v8</i> , <i>cyp7a1</i> , <i>cyp8b1</i>

Table S4: Primer sequences and conditions used in RT-qPCR.

Gene	Sequence 5'→3' (F: forward; R: reverse)	Cycles	Annealing temperature (°C)	Amplicon length (pb)
<i>cyp1b1</i>	F: ACAGCTCTCCAGTGGATCAT R: GTCTGCGATGGTTGGAAGAC	40	60	114
<i>ef1α</i>	F: CTGGAGGCCAGCTCAAACAT R: ATCAAGAAGAGTAGTACCGCTAGCATTAC	40	60	87
<i>igfbp1b</i>	F: GGCACAGGAGAGCATCAAGT R: GGTGAACTTCTCTCCCAACG	40	60	130
<i>junbb</i>	F: AAAATGGAGCAGCCGTTTTA R: CTCGGTCACGTTCAAGTTCA	40	60	117
<i>ubl7b</i>	F: TTCGTACGGCATCAAGTCTG R: GCCTGAAGCATCCTGAACTC	40	60	123
<i>wdr35</i>	F: TGCCGGAAAACCATAAACTG R: CTGCTTTGGGCTGGTTACAT	40	60	108
<i>rbp1</i>	F: CCATCACTTGGGATGGAGAC R: ATCTGTTTGCCCACTCC	40	60	133
<i>acta1b</i>	F: ATCTGGCTGGTCGTGATCTT R: TCCTTGATGTCACGCACAAT	40	60	106
<i>cyp24a1</i>	F: CAGCCGGACCCTGGACAAAGATAC R: CCAGCGCTCGGGTCTGAAC	40	60	139