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Article

Potential involvement of *Drosophila* flightless-1 in carbohydrate metabolism

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Running title: role of *Drosophila* flightless-1 in gene expression

Keywords: Flightless-1, gene expression, metabolomics, RNA sequencing, metabolism

Abstract

A previous study of ours indicated that *Drosophila* flightless-1 controls lipid metabolism, and that there is an accumulation of triglycerides in *flightless-1* (*fliI*)-mutant flies, where this mutation triggers metabolic stress and an obesity phenotype. Here, with the aim of characterizing the function of FliI in metabolism, we analyzed the levels of gene expression and metabolites in *fliI*-mutant flies. The levels of enzymes related to glycolysis, lipogenesis, and the pentose phosphate pathway increased in *fliI* mutants; this result is consistent with the levels of metabolites corresponding to a metabolic pathway. Moreover, high-throughput RNA sequencing revealed that *Drosophila* FliI regulates the expression of genes related to biological processes such as chromosome organization, carbohydrate metabolism, and immune reactions. These results showed that *Drosophila* FliI regulates the expression of metabolic genes, and that dysregulation of the transcription controlled by FliI gives rise to metabolic stress and problems in the development and physiology of *Drosophila*.

Introduction

Flightless-1 was originally identified in *Drosophila* (1) and has been described as an actin-remodeling protein that belongs to the gelsolin protein superfamily (2-4). Flightless-1 contains a gelsolin-like actin-binding domain at the C terminus whereas a leucine-rich repeat (LRR) domain is located at the N terminus (1). The LRR domain is involved in both intramolecular recognition and structural organization. The gelsolin like domain mediates actin-binding and protein–protein interactions. The Flightless protein has been implicated in actin filament organization during cell migration and tissue repair (5). Beyond cytoskeletal function, flightless-1 has been shown to act as a transcriptional coregulator that can either positively or negatively affect the activity of transcription factors (6-9). Flightless-1 interacts with nuclear receptor (NR), transcription coactivators, and the SWI/SNF chromatin-remodeling complex. Flightless-1 binds to BAF53, a component of SWI/SNF complexes, as well as to estrogen receptor α (ERα), thus contributing to the recruitment of SWI/SNF complexes to the promoter of ERα targets (10). In addition, flightless-1 forms a complex with NR coactivators—glucocorticoid receptor–interacting protein 1 (GRIP1) and coactivator-associated arginine methyltransferase 1 (CARM1)—which leads to the enhancement of NR function (6). In contrast, flightless-1 inhibits β-catenin–mediated transcription through interfering with the binding of FLII leucine-rich repeat–associated protein 1 (FLAP1) to p300 and β-catenin (8).

A recent study of ours has shown that *Drosophila* flightless-1 (FliI) plays a role in lipid metabolism (11). *Drosophila fliI* mutants show increased levels of triglycerides and are resistant to starvation. In that study, the upregulation of FliI suppressed the mRNA expression of Desaturase-1, and conversely, the mRNA expression of Desaturase-1 increased in *fliI*-mutant flies, suggesting that *Drosophila* FliI downregulates Desaturase-1 at the transcriptional level, thereby contributing to the obese phenotype of *fliI* mutants. Based on

these results, our purpose here was to investigate the genes whose expression levels are regulated by flightless-1 in *Drosophila*, thereby contributing to the above phenotype. Specifically, we examined the expression levels of genes related to energy metabolism, lipogenesis, and lipolysis; these genes may contribute to the obese phenotype, specifically, the increased levels of triglycerides and insulin resistance, in *fliI*-mutant flies. The mRNA expression of most glycolytic-enzyme genes and of some lipogenic enzymes was found to be specifically higher in *fliI*-mutant flies. Accordingly, we found that the levels of stearoyl-coenzyme A (CoA) and palmitoyl-CoA specifically increased in *fliI* mutants according to metabolomic analysis. In addition, high-throughput RNA sequencing (RNAseq) analysis of *fliI*-mutant flies revealed that flightless-1 regulates the expression of genes related to chromatin organization, carbohydrate metabolic process, and proteolysis. Taken together, these results support the transcriptional role of flightless-1 in the expression of genes associated with metabolism.

Results

Metabolic reprogramming in *fliI* mutants

Our recent study indicates that *Drosophila flightless-1* mutant flies contain large amounts of triglycerides, which contribute to starvation resistance (11). In general, fat accumulation has been primarily attributed to food intake and energy expenditure (12, 13). Based on the fact that our previous results revealed that *fliI* mutant flies do not consume more food (11), we tested whether or not FliI is required for the gene expression related to energy metabolism. To that end, we compared the transcript levels of glycolytic genes between seven-day-old controls and $fliI^{3/14}$ mutants. These *fliI* mutant alleles, $fliI^{3}$ and $fliI^{14}$, have been characterized in previous studies (11, 14, 15). The $fliI^{3}$ mutant allele has a single-base substitution of Gly to Ser at amino acid position 602, which is homozygotically viable. In contrast, the $fliI^{14}$ allele is

lethal during the larval and pupal stages. The mRNA expression of most glycolytic-enzyme genes, including *HexA*, *Pgi*, *Gapdh*, *Pgk*, and *Eno,* specifically increased in *fliI*$^{3/14}$ mutants. Among them, the *Ald* transcript was upregulated more than sixfold in *fliI*$^{3/14}$ mutant flies, while the mRNA expression of *Ldh* significantly decreased (Fig. 1A). In contrast, the mRNA expression of tricarboxylic acid (TCA) cycle genes, *CG7430* and *Scsa*, did not significantly increase (Fig. 1B). These results showed that the mutation of *fliI* in *Drosophila* accelerated glucose metabolism throughout the body. 6-Phosphogluconate dehydrogenase (Pgd) in the pentose phosphate pathway, which is essential for the supply of NADPH (16), was also upregulated in *fliI*$^{3/14}$ mutant flies (Fig. 1C). The byproduct of NADPH produced by 6-Phosphogluconate dehydrogenase activity may be utilized for lipid synthesis. In addition, we found that the mRNA expression of lipogenic genes, such as sterol-regulatory element–binding protein (*SREBP*) and its downstream target genes, *fatty acid synthase (FAS)* and *acetyl-CoA carboxylase (ACC)*, was slightly higher in *fliI*$^{3/14}$ mutants (Fig. 1D). In line with these data, we found that the mRNA expression of DGAT1, which catalyzes the conversion of diacylglycerol and fatty acyl CoA to triglycerides, was significantly increased (Fig. 1D). In contrast, the mRNA expression levels of lipolytic genes, *brummer* (*Bmm*) and *hormone-sensitive lipase* (*HSL*), did not significantly change (Fig. 1E). Altogether, these results suggest that FliI is necessary for the regulation of glucose metabolism and the transcription of lipogenic genes.

Metabolomic analysis of *fliI* mutants reveals a change in precursors of long-chain fatty acids

In order to understand how changes in gene expression influence fat metabolism in *fliI* mutants, we compared the metabolic profiles of control and *fliI*$^{3/14}$ flies through mass spectrometry.

Specifically, we examined the intermediates of glycolysis, of the TCA cycle, of the pentose phosphate pathway, and the coenzymes involved in the metabolism of fatty acids. In agreement with the results of mRNA expression analysis by quantitative PCR, two important metabolic pathways, glycolysis and the TCA cycle, differed between w^{1118} flies (controls) and $fliI^{3/14}$ mutants (Fig. 2A, B). Although lactate was shown to be downregulated in $fliI^{3/14}$ mutants, the amounts of glycolysis intermediates, such as fructose-1,6-bisphosphate, 3-phosphoglycerate, and phosphoenolpyruvate, increased relative to controls. $FliI^{3/14}$ mutants also manifested slight but significant increases in the amounts of TCA cycle intermediates, namely citrate/isocitrate, succinate, and fumarate. Nevertheless, the total ATP level did not differ between the two groups. In addition, we found that a pentose phosphate pathway intermediate, 6-phosphogluconate, was significantly upregulated in $fliI^{3/14}$ mutant flies. The amount of ribulose-1,5-bisphosphate, which is formed from ribulose 5-phosphate in the cooperative pentose phosphate pathway, significantly increased in $fliI^{3/14}$ mutant flies. A previous study suggests that ribulose-1,5-bisphosphate stimulates phosphofructokinase-1 and inhibits its opposing enzyme, fructose 1,6-bisphosphatase (17); this mechanism may contribute to glycolysis and the pentose phosphate pathway. NADPH is generated by the pentose phosphate pathway and is utilized for fatty acid synthesis. $FliI^{3/14}$ mutants also manifested a significant reduction in the ratio of NADPH/NADP (Fig. 2C).

The accumulation of long-chain acyl CoAs is frequently observed in obesity or type 2 diabetes (18, 19). Given that $fliI^{3/14}$ mutants had an obesity-like phenotype, we tested whether this phenotype in $fliI^{3/14}$ mutants directly affects the amounts of long-chain acyl CoAs. Although seven-day-old $fliI^{3/14}$ mutants showed decreased levels of coenzyme A and short-chain acyl CoA compared to the wild type, long-chain acyl CoAs, such as palmitoyl-CoA, oleoyl-CoA, and stearoyl-CoA, were found to be upregulated in $fliI^{3/14}$ mutant flies (Fig. 2D).

Differences in the expression levels of metabolic genes and relevant metabolites between w^{1118} flies (control) and $fliI^{3/14}$ mutants, as well as the changes in $fliI^{3/14}$ mutants are summarized in Fig. 3. In particular, increased levels of mRNA or a metabolite in $fliI^{3/14}$ mutants are labeled in red, downregulation is indicated with blue, and unchanged ones are shown in black.

Given that *Drosophila* flightless-1 represses the expression of Desaturase-1 (11), whose preferred substrates are palmitoyl-CoA and stearoyl-CoA, we believe that the elevated amounts of long-chain acyl CoAs contributed to the obesity-like phenotype of $fliI^{3/14}$ mutant flies.

Drosophila flightless-1 regulates the expression of genes related to chromatin remodeling

In order to gain a genome-wide view of the changes in gene expression specifically induced by flightless-1, we performed a differentially expressed gene (DEG) analysis of RNA-seq data from seven-day-old w^{1118} control and $fliI^{3/14}$ adult flies. Only the transcripts with adjusted *P* values (Benjamini-Hochberg correction) < 0.05 and a fold change > 2 in gene expression between the two groups were selected for subsequent Gene Ontology (GO) enrichment analysis. According to this criterion, 181 genes were downregulated in *fliI* mutants, while 160 genes were upregulated (see Table S1). The Gene Ontology (GO) terms with adjusted $P <$ 0.05 are listed in Tables 1 and 2. Specifically, GO terms enriched in the downregulated genes included those involved in chromosome organization (GO:0051276, adjusted P value of 7.44×10^{-5}), the negative regulation of histone modification (GO:0031057, adjusted P value of 8.39×10^{-5}), nucleosome assembly (GO:0006334, adjusted P value of 9.87×10^{-5}), and a carbohydrate metabolic process (GO:0005975, adjusted P value of 1.26×10^{-4}). This indicates that *Drosophila* FliI not only regulates specific gene expression related to glucose

metabolism, but also seems to regulate the gene expression in general under certain conditions by reorganizing chromatin structure. Prominent among the genes whose expression increased significantly were those encoding proteolytic enzymes (GO:0006508, adjusted P value of 7.29×10^{-7}), proteins related to a defense response to a gram-positive bacterium (GO:0050830, adjusted P value of 1.49×10^{-3}), and proteins associated with cytolysis (GO:0019835, adjusted P value of 6.45×10^{-3}). The activators of Imd signaling (PGRP-LC) and lysozymes (LysB, -D, and -E) were highly expressed in *fliI* mutant flies (Table S1). An abnormally active immune response is associated with the upregulation of stress response factors, all of which have been previously linked to immune function, including the translational repressor 4E-BP/Thor (20). These data are in agreement with those of our recent study suggesting that the mRNA level of 4E-BP is increased in $fliI^{3/14}$ mutants (11). The RNA-seq. results were further validated through quantitative real-time PCR (supplemental Fig. 2). These observations indicate that the transcriptional activity of flightless-1 controls the expression of genes related to chromatin remodeling, metabolism, and immune responses.

Discussion

Here, we reveal the transcriptional influence of *Drosophila* FliI on the expression of genes including those participating in chromatin remodeling, carbohydrate metabolic processes, and immune responses. Unexpectedly, our RNAseq analysis suggests that *Drosophila* flightless-1 regulates the expression of histones, which are basic nuclear proteins that are responsible for the nucleosome structure of the chromosomal fiber (21, 22). Histones are required for the condensation of nucleosome chains into higher-order structures. They also function as regulators of individual gene transcription through chromatin remodeling. In addition, the genes whose expression decreased in *flightless-1* mutants, *rhino* and *CREG*, are known to

control gene transcription through producing Piwi-interacting RNA (23) or inhibiting transcription factor binding (24). Thus, although *Drosophila* flightless-1, as a transcription factor, may regulate the expression of genes related to specific pathways including glucose metabolism, immune responses, or proteolysis, it seems to regulate gene expression by reorganizing the chromatin structure under certain conditions. These phenomena need to be validated through further studies.

Given that *fliI*$^{3/14}$ mutants show features of a metabolic disorder (11), we analyzed the changes in metabolites in the metabolic pathways including glycolysis, the TCA cycle, pentose phosphate pathway, and fatty acid synthesis (Fig. 2). Through this assay, we found that the NADPH/NADP ratio was clearly lower in the mutants. NADPH is an essential cofactor in *de novo* lipogenesis, which requires NADPH as a reducing agent for the conversion of acetyl-CoA into fatty acids (25-27). The amounts of NADPH in *fliI*$^{3/14}$ mutants were relatively low as compared to those in w^{1118} flies. We can explain this result as a form of supply and demand: NADPH is mainly generated by the pentose phosphate pathway. Our results indicate that the level of ribulose 1,5-phosphate, which is a product of the pentose phosphate pathway, significantly increased in *fliI*$^{3/14}$ mutant flies (Fig. 2). In addition, mRNA expression of the gene encoding one of the NADPH-producing enzymes, phosphogluconate dehydrogenase (Pgd), increased slightly but significantly in *fliI* mutants (Fig. 1C). Therefore, we can theorize that in *fliI*$^{3/14}$ mutants, NADPH and acetyl-CoA were rapidly consumed for the elongation of long-chain fatty acids, driving the increase in fat contents throughout the body. Among the intermediates of glycolysis, the amount of lactate significantly decreased in *fliI*$^{3/14}$ mutant flies; this is consistent with the observed reduction in *Ldh* mRNA expression. As shown in Fig. 3, the levels of expression of glycolytic genes and glycolysis intermediates were significantly increased in *fliI*$^{3/14}$ mutant flies compared to in control flies. However, the mRNA expression levels of tricarboxylic acid (TCA) cycle genes and the levels of TCA

cycle intermediates were only slightly changed. Thus, we believe that the increased amounts of glycolytic intermediates were not consumed for lactate production but were instead mostly converted to acetyl-CoA for the elongation of long-chain fatty acids.

Given that *fliI*$^{3/14}$ mutant flies showed increased levels of triglycerides, we expected that the amounts of lipogenic enzymes, such as SREBP, FAS, and ACC, would be greater in *fliI*$^{3/14}$ mutant flies, but there were slight and significant differences in the expression of these proteins between w^{1118} and *fliI*$^{3/14}$ flies. Emerging evidence indicates that the activity of a metabolic enzyme can be regulated post-translationally under certain conditions without changing the expression level (28-30). We assumed that an enzyme's activity can somewhat contradict its expression level because enzymes may be regulated by post-translational modifications in the mutant. Therefore, in future studies, it is necessary to test the activities of the enzymes that we examined in this study.

In summary, we analyzed the expression levels of metabolic genes and the levels of metabolites in *fliI*-mutant flies. These results support previous findings showing that *Drosophila* FliI serves as a key regulator of lipid metabolism. In addition, RNAseq analysis revealed the transcriptional targets of FliI in *Drosophila*, which include the genes related to chromosome organization, carbohydrate metabolism, proteolysis, and immune responses.

Materials and methods

Plasmids and fly strains

All *Drosophila* stocks were raised at 25 °C on a standard cornmeal medium containing 4.94% molasses, 3.8% cornmeal, 1.6% yeast, and 1.2% agar. Genes were expressed in *Drosophila* through the standard Gal4/UAS system. Fly strains w^{1118} (stock number 5905), *fliI*^{3} (stock

number 4730), and *fliI*^{14}*/FM6* (stock number 7481) were obtained from the Bloomington Stock Center.

Quantitative RT-PCR

Total RNA was isolated from five female flies using the TRIzol Reagent (Invitrogen, USA), and 200 ng of RNA was transcribed using the ReverTra Ace qPCR RT Kit (Toyobo Co., Japan). Quantitative PCR amplification was run for 40 cycles by means of the TOPreal™ qPCR 2X PreMIX (SYBR Green with high ROX) and a LightCycler® 480 Real-Time PCR System. *Rp49* served as a reference for normalization. Relative quantification of mRNA was performed through the comparative C_T method. The primers are listed in Supplemental Table 2.

Detailed information is included in the Supplemental Material.

Conflicts of interest

The authors have declared that no conflicts of interest exist.

Acknowledgements

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Figure Legends

Fig. 1. The changes in expression of metabolic genes in *fliI* mutants. Quantitative RT-PCR analysis of each gene in seven-day-old w^{1118} flies (controls) and $fliI^{3/14}$ mutants. The values were normalized to *Rp49* data. (A) Relative mRNA abundance of glycolytic-enzyme genes. (B) Relative mRNA expression of TCA cycle genes. (C) Relative expression of *Pgd* mRNA. (D) Relative expression levels of lipogenic genes. (E) Relative mRNA expression of lipolytic genes. Data are presented as mean ± SE from at least five independent experiments; *p < 0.05, **p < 0.01, and ***p < 0.001.

Fig. 2. *FliI* mutants show increased levels of precursors of long-chain fatty acids. The metabolites from seven-day-old w^{1118} flies (controls) and $fliI^{3/14}$ mutants were monitored by LC-MS/MS. (A) The amounts of intermediates of glycolysis. The values of each metabolite amount were normalized to the total protein level. (B) The relative levels of intermediates of the TCA cycle. These amounts significantly increased in $fliI^{3/14}$ mutants compared to w^{1118} flies, the controls. (C) The levels of intermediates of the pentose phosphate pathway (PPP). The ratio of NADPH/NADP involving a byproduct of the PPP, which was strongly diminished in $fliI^{3/14}$ mutant flies. The relative levels of fatty acyl CoAs are illustrated in (D). The amounts of precursors of long-chain fatty acyl-CoAs, such as palmitoyl-CoA, stearoyl-CoA, and oleoyl-CoA, were considerably larger in $fliI^{3/14}$ mutants relative to w^{1118} flies (controls). Data are presented as mean ± SE from at least three independent experiments; *p < 0.05, **p < 0.01, and ***p < 0.001.

Fig. 3. A schematic diagram of glucose metabolism and lipid metabolism according to the data from Figs. 1 and 2. The red color indicates that mRNA or metabolite levels were

significantly upregulated in terms of statistics in *fliI*$^{3/14}$ mutants, the blue color denotes downregulation in *fliI*$^{3/14}$ mutants, and black indicates no change.

Table 1. GO terms of genes regulated in *flightless-1* mutant flies.

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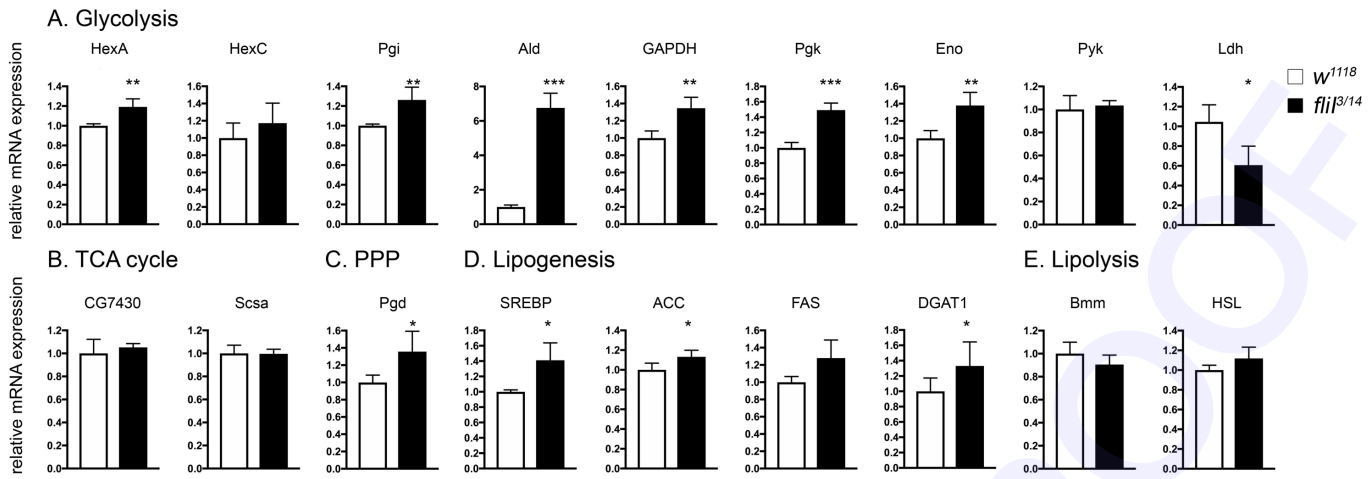

Fig. 1

Fig. 1. Figure 1

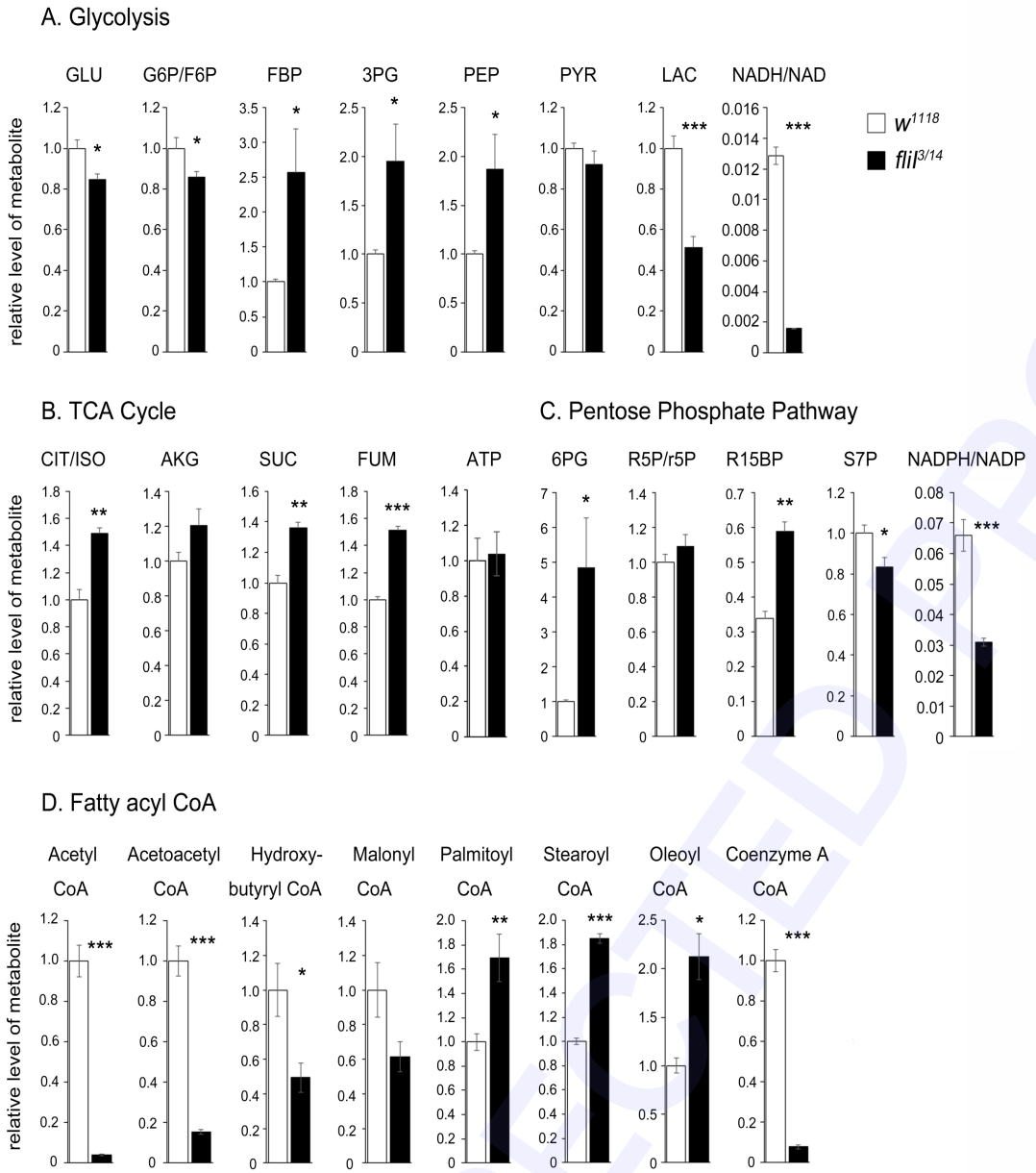

Fig. 2. Figure 2

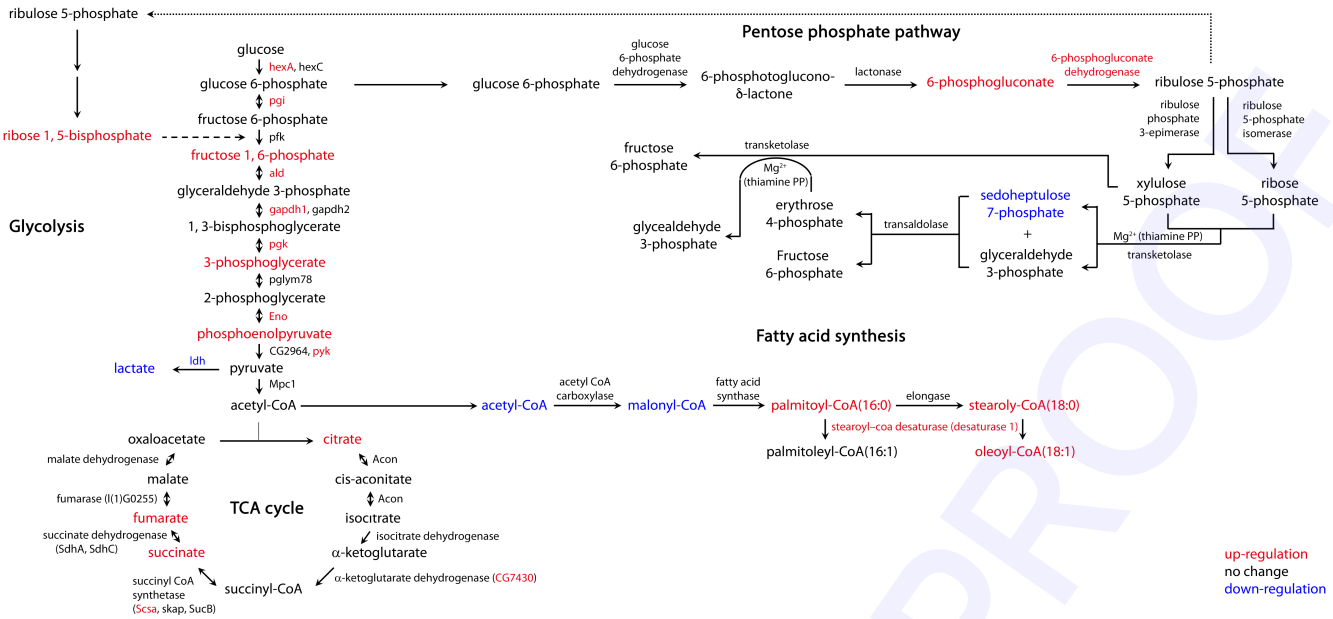

Fig. 3. Figure 3

Table 1. GO terms of genes regulated in *flightless-1* mutant flies

downregulated

GO term	P value	Benjamini	Genes
GO:0051276 - chromosome organization	3.98×10^{-7}	7.44×10^{-5}	CG33822, CG33810, CG33825, RHI, CG33816, CG33828, CG33861, CG33831, CG33858
GO:0031057 - negative regulation of histone modification	8.97×10^{-7}	8.39×10^{-5}	CG33822, CG33810, CG33825, CG33816, CG33828, CG33831
GO:0006334 - nucleosome assembly	1.58×10^{-6}	9.87×10^{-5}	CG33822, CG33810, CG33850, CG33825, CG33816, CG33828, CG33861, CG33844, CG33831, CG33858, CG33847
GO:0005975 - carbohydrate metabolic process	2.70×10^{-6}	1.26×10^{-4}	MAL-A7, MAL-A6, TOBI, MAL-A8, AMY-P, MAL-A1, AMY-D, AMYREL, CHT8, MAL-B1
GO:0006342 - chromatin silencing	1.39×10^{-4}	5.19×10^{-3}	CG33822, CG33810, CG33850, CG33825, CG33816, CG33828, CG33844, CG33831, CG33847

upregulated

GO term	P value	Benjamini	Genes
GO:0006508 - proteolysis	3.74×10^{-9}	7.29×10^{-7}	CG9897, CG32523, ANCE-4, SPH93, CG42694, CG8539, CG1304, CG17239, SER6, CG15254, CG11842, GAMMATRY, CG9676, CG31267, CG7829, CG31681, CG3088, CG14529, ZETATRY, CG17475, CG8329, CG11911
GO:0050830 - defense response to Gram-positive bacterium	1.53×10^{-5}	1.49×10^{-3}	LYSP, LYSE, LYSD, SPH93, LYSB, GNBP1, IM23
GO:0019835 - cytolysis	9.95×10^{-5}	6.45×10^{-3}	LYSP, LYSE, LYSD, LYSB
GO:0016998 - cell wall macromolecule catabolic process	2.32×10^{-4}	1.13×10^{-2}	LYSP, LYSE, LYSD, LYSB

Supplemental material and methods

Metabolic profiling

Fruit flies were homogenized using TissueLyzer (Qiagen) with MeOH. Internal standard solutions (malonyl-$^{13}C_3$ CoA, 5 μM Gln-d_4) were added to the samples. Then, the samples were centrifuged at 13 000 rpm for 10 min (Eppendorf Centrifuge 5415R). The precipitate was stored for measurement of protein amounts later by the Bradford assay. For the supernatant, the aqueous phase after liquid-liquid extraction was collected, and used for analysis. Metabolites were analyzed on LC-MS/MS (1290 HPLC (Agilent)-Qtrap 5500 (ABSciex)). For metabolites related to energy metabolism, Synergi Fusion RP 50 × 2 mm was employed. Here, 5 mM CH_3COONH_4 in H_2O and in MeOH served as mobile phases A and B, respectively. The separation gradient was as follows: hold at 0% B for 5 min, 0% to 90% B for 2 min, hold at 90% for 8 min, 90% to 0% B for 1 min, and then hold at 0% B for 9 min. LC flow was 70 μl/min, except for 140 μl/min between 7-15 min, at 23 °C. For fatty acyl CoAs, a Zorbax 300 Extend-C18 column (2.1 × 150 mm) was used. Mobile phase A was ACN–H_2O (10:90) with 15 mM NH_4OH, and mobile phase B was ACN containing 15 mM NH_4OH. The separation gradient was the following: hold at 0% B for 3 min, 0% to 50% B for 2 min, 50% to 80% B for 5 min, 80% to 0% B for 0.1 min, and then hold at 0% B for 4.9 min. LC flow was 200 μl/min, and column was kept at 25 °C. Multiple reaction monitoring (MRM) was employed for analysis. The quantitative value of each metabolite was normalized to the total protein amount.

Transcriptome sequencing

Total RNA from the flies was isolated using the Trizol reagent (Invitrogen, USA). A library was prepared with 1ug of total RNA for each sample by Illumina TruSeq mRNA Sample

Prep kit (Illumina, Inc., San Diego, CA, USA). The libraries were quantified using qPCR according to the qPCR Quantification Protocol Guide (KAPA Library Quantificatoin kits for Illumina Sequecing platforms) and qualified using the 2100 Bioanalyzer (Agilent Technologies, Waldbronn, Germany). Indexed libraries were then sequenced using the HiSeq4000 platform (Illumina,San Diego, USA by the Macrogen Incorporated).

Read mapping and differential gene expression analysis

Reads were filtered with NGS QC Toolkit (1) (v.2.3.3) and mapped to the *D. melanogaster* reference transcriptome assembly (dm6) with Bowtie (2) and RSEM (3). Differential gene expression analysis was carried out with expected counts data from RSEM results using DEseq2 (4). We adjusted all p-values using multiple testing with a Benjamini-Hochberg correction with a false discovery rate (FDR) of 5%. Differentially expressed genes were identified with following thresholds: a fold change > 2, a p-value < 0.05 and an adjusted p-value < 0.05.

Enrichment analysis

Identification of GO biological processes related to genes characterized with significant expression change was conducted using Database for Annotation, Visualization and Integrated Discovery (DAVID) (5). Significant GO biological processes were defined by p-value < 0.05 and FDR < 0.05.

Statistical analysis

Each experiment was repeated at least three times, and the data are presented as mean ± SE. Significance testing was based on Student's *t* test.

References

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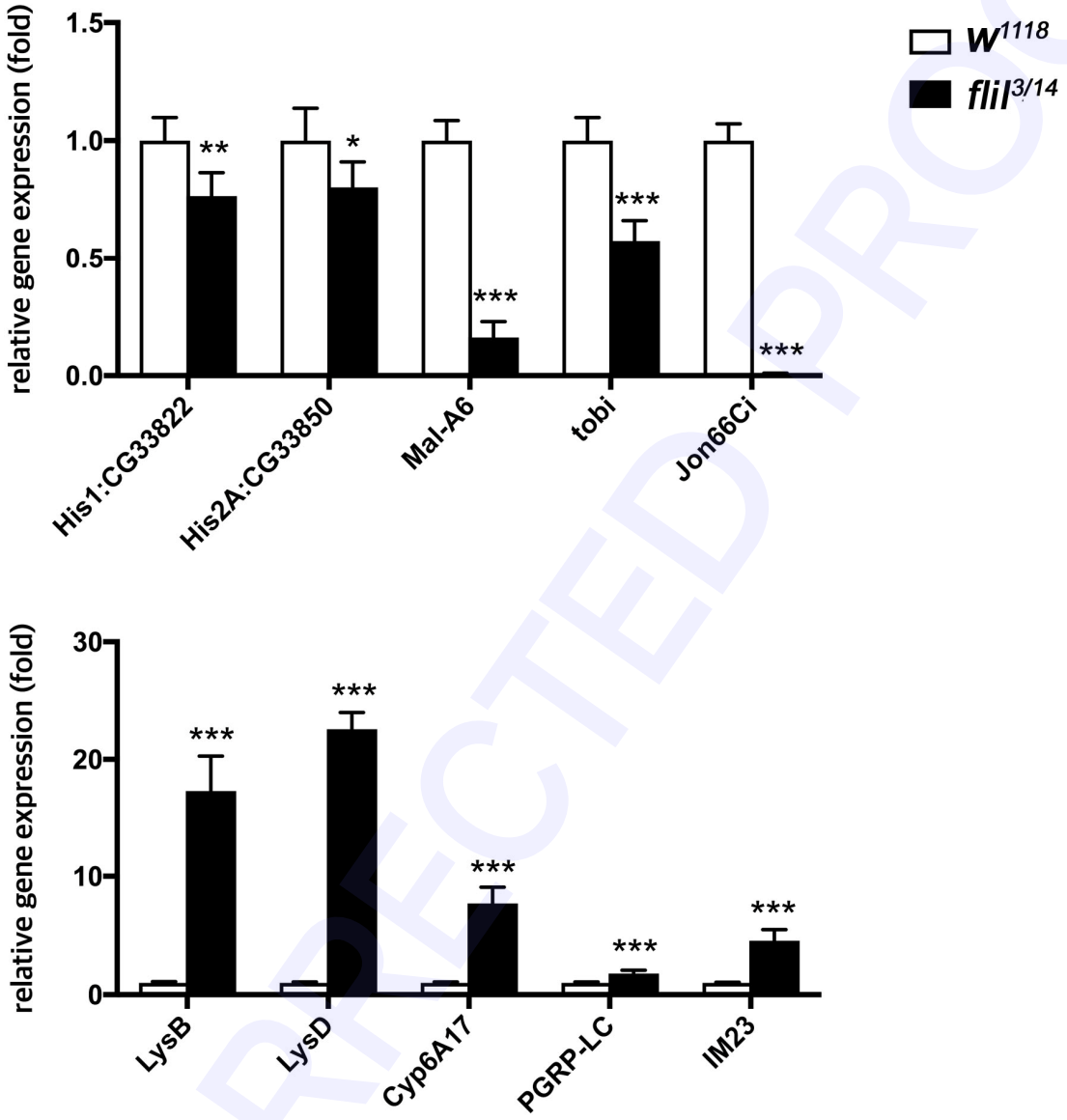
4. Love, M. I., Huber, W. and Anders, S. (2014) Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biol* **15,** 550.
5. Huang da, W., Sherman, B. T. and Lempicki, R. A. (2009) Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc* **4,** 44-57.



Supplemental Figure 1. Quantitative real-time PCR analysis for representative gene expression changes in *w*^{1118} and *flil*$^{3/14}$ mutants. The values were normalized to rp49 levels. Data are presented as mean ± SE from at least three independent experiments; *p < 0.05, **p < 0.01, and ***p < 0.001.

Supplementary Table 1

DEG_list_high

gene_id	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
CG43090|12798122	385.7350469	12.17355009	1.495046108	8.142591737	3.87E-16	7.23E-14
p24-2|318890	354.9852182	12.05286769	1.475049448	8.171161796	3.05E-16	5.91E-14
CG1304|33074	68.31774398	9.674951082	1.570668563	6.159766171	7.29E-10	6.64E-08
CR40469|5740321	36.78760781	8.783916674	1.644660137	5.340870418	9.25E-08	5.97E-06
LysD|38127	1633.068465	8.635257928	0.878140805	9.833568694	8.07E-23	2.87E-20
CG32581|318098	571.7986249	7.96403544	1.955580493	4.07246619	4.65E-05	0.001541326
CR46123|26067439	15.02179023	7.491178964	1.807571948	4.144332387	3.41E-05	0.001174287
CG13032|39863	30.47718627	7.049831905	1.592032778	4.428195198	9.50E-06	0.000380122
CG4570|41306	1406.394415	6.779828363	0.248792211	27.25096711	1.62E-163	1.78E-159
CG44142|14462464	8.234063377	6.623349329	2.068456756	3.202072902	0.001364425	0.025455408
CG15534|43613	782.7497285	6.600244692	1.532013037	4.308217055	1.65E-05	0.000617215
CR43426|12798470	7.683276003	6.523486519	2.108159429	3.094399043	0.00197212	0.033922197
nsr|37577	17.60427986	6.283834203	2.041647844	3.07782472	0.002085175	0.035465384
Cyp4p2|35946	47.70624482	6.095091485	1.20129024	5.073787567	3.90E-07	2.22E-05
CG14456|40481	15.44482987	6.088590278	1.850818521	3.289674385	0.001003034	0.02029257
LysB|38125	374.1279326	5.60840238	1.505983972	3.7240784	0.00019603	0.005403567
Cyp6d2|37594	140.3247031	5.443756137	0.89003933	6.116309642	9.58E-10	8.45E-08
Cyp6a17|45556	207.7939681	5.318287221	0.509717624	10.43379112	1.74E-25	7.67E-23
Cyp309a2|33439	116.0927709	5.282468044	0.937878294	5.632359846	1.78E-08	1.29E-06
SPH93|35049	47.43717378	5.278225958	1.716963417	3.074163319	0.002110938	0.035569279
Obp99b|43497	321.819425	5.264764956	1.263525075	4.16672772	3.09E-05	0.001074785
CG33337|2768678	26.56681867	5.23699243	1.100727508	4.757755569	1.96E-06	9.22E-05
CG32212|317917	120.4036977	5.201175637	0.524145724	9.923148093	3.30E-23	1.21E-20
CG32523|318071	62.3675854	5.005508249	0.843609337	5.933443394	2.97E-09	2.44E-07
CG30382|246582	793.0894746	4.906646706	0.377010906	13.01460152	1.01E-38	9.29E-36
CG14715|41403	549.574085	4.883335197	0.294277003	16.5943487	7.66E-62	2.11E-58
GstE1|37106	591.7204962	4.676472047	0.290906549	16.07551313	3.79E-58	5.97E-55
CG34195|37018	309.957321	4.475154517	0.286172009	15.63798825	4.01E-55	4.92E-52
CG15711|36834	14.86883953	4.457889284	1.455651741	3.062469654	0.002195187	0.036506992
CG33509|3346225	15.16901876	4.331014639	1.449232609	2.988488261	0.002803613	0.043538921
Hesr|32800	80.51000781	4.233321809	0.527082761	8.031607407	9.62E-16	1.74E-13
gammaTry|36221	687.5566106	4.095240571	1.204177667	3.400860758	0.00067174	0.014466033
dpr21|8674044	38.50697147	3.997650475	0.757891133	5.274702792	1.33E-07	8.33E-06
IM23|37099	38.17373541	3.959791435	1.300123261	3.045704629	0.002321358	0.038031632
CG32641|318136	111.7956183	3.928411629	0.473857584	8.290279103	1.13E-16	2.35E-14
LysE|38128	268.0427113	3.778601592	0.613920655	6.154869626	7.51E-10	6.79E-08
Ssl2|43424	18.99749814	3.753735389	1.089683355	3.444794649	0.000571493	0.012898042
CG12655|33004	66.14360973	3.751018809	1.013731332	3.700209995	0.000215421	0.005835954
CG17470|35321	97.5859958	3.747874038	0.477464185	7.84953962	4.18E-15	7.19E-13
Unc-115b|41178	600.6922525	3.720074578	0.859869549	4.326324363	1.52E-05	0.000572514
vis|36372	105.8914909	3.680582968	0.559422607	6.579253188	4.73E-11	4.87E-09
CG3259|41739	72.27370258	3.62379465	0.612474106	5.916649563	3.29E-09	2.68E-07
CG8768|36400	204.9775998	3.605685493	0.307704214	11.7180244	1.03E-31	6.31E-29
CG11893|43056	48.97910361	3.561276636	0.70066686	5.082695985	3.72E-07	2.13E-05
sosie|42961	600.9655065	3.423107041	0.208692914	16.40260315	1.83E-60	4.04E-57
CG10182|42780	63.71533278	3.405772905	0.761725121	4.471131136	7.78E-06	0.000318922
Cyp6a14|35835	57.29817113	3.398101639	0.758986329	4.477157902	7.56E-06	0.000312376
CG15254|34915	156.4513099	3.313522797	0.420683283	7.876525947	3.37E-15	5.99E-13
CG34423|5740313	135.7448029	3.219752827	0.453937777	7.092938696	1.31E-12	1.77E-10
CG2064|35708	234.4982602	3.138966094	0.489405651	6.413832962	1.42E-10	1.37E-08
TpnC4|35498	129.1000562	3.070136436	0.903086465	3.399604087	0.000674835	0.014504346
CG5961|41541	467.8178785	2.976941687	0.21823237	13.64115548	2.28E-42	2.28E-39
Act88F|41885	256.7003012	2.972416658	0.438816865	6.773706509	1.26E-11	1.40E-09
Ipod|31954	27.62673407	2.970495903	0.77011448	3.857213415	0.000114687	0.003417673
Hsp70Bbb|50022	136.3041967	2.954080208	0.97769703	3.021467916	0.002515523	0.040314181
Cyp6a2|35587	391.8760965	2.910802197	0.450095932	6.467070662	9.99E-11	9.93E-09
Tep4|35248	1084.25104	2.895487398	0.302518898	9.571261228	1.06E-21	3.53E-19
Map205|43765	3556.397689	2.886395425	0.156968838	18.38833398	1.63E-75	5.99E-72
Uro|34060	474.2833766	2.878713551	0.406359985	7.084146219	1.40E-12	1.86E-10
phr6-4|35322	316.0475746	2.828328133	0.252999034	11.17920527	5.15E-29	2.99E-26
CG3819|40069	225.2015691	2.725827882	0.474284392	5.747243487	9.07E-09	6.95E-07
CG34141|4379870	173.1971676	2.723474382	0.312521414	8.714520871	2.92E-18	6.85E-16
Uhg5|8673975	145.0524102	2.720028781	0.412142787	6.599724332	4.12E-11	4.28E-09
CG5568|38658	555.5949254	2.64524801	0.346356978	7.63734579	2.22E-14	3.70E-12
CG33282|2768939	55.4983788	2.565777058	0.68763189	3.731323542	0.000190476	0.005291101
CG14692|41298	61.19092474	2.549219275	0.547747814	4.65400173	3.26E-06	0.000145326
Ilp7|31328	36.86704764	2.543225088	0.814324223	3.123111184	0.001789501	0.031243189
CR43973|14462864	37.59819688	2.369092174	0.630379349	3.758200798	0.00017114	0.004863362
Cyp4p3|35948	67.97941115	2.246636409	0.674821999	3.329228169	0.00087087	0.017914582
CG18343|36297	310.2222071	2.20170765	0.2310391	9.529588934	1.58E-21	4.84E-19
CG15126|50202	26.35439874	2.193754046	0.724129947	3.029503277	0.002449562	0.03958573
CG45071|19834908	515.0380108	2.191164379	0.287535437	7.620502031	2.53E-14	4.16E-12
w|31271	93.15242074	2.180097842	0.417848586	5.217435016	1.81E-07	1.12E-05
pncr014:3L|10178937	147.0957588	2.172110689	0.34977889	6.209953642	5.30E-10	4.87E-08
CG31681|318882	460.4414762	2.163306573	0.448613324	4.822207578	1.42E-06	6.93E-05
CG8539|38842	74.94327451	2.160377242	0.454194641	4.756500951	1.97E-06	9.24E-05
CG9676|32647	759.5410725	2.1603192	0.335798118	6.433386861	1.25E-10	1.22E-08
CG32243|317935	699.193622	2.117025193	0.171078956	12.37455057	3.59E-35	3.04E-32
tipE|38504	300.0508728	2.106237566	0.257440204	8.181463257	2.80E-16	5.52E-14
CG14879|41982	215.2392536	2.088565175	0.306177433	6.821421011	9.01E-12	1.01E-09
CG7408|39991	176.77322	2.074113438	0.360269735	5.757112617	8.56E-09	6.64E-07
CG13091|34188	564.1296426	2.044239746	0.302261395	6.763151961	1.35E-11	1.47E-09
CG7829|43522	91.89343023	2.043630502	0.553486317	3.692287307	0.000222246	0.005976796
Cyp12d1-p|246648	176.9877362	1.995869142	0.416913881	4.7872456	1.69E-06	8.07E-05
CG13397|46386	3442.816471	1.94617562	0.105670796	18.41734616	9.54E-76	5.26E-72
Ser6|33073	140.260446	1.886357901	0.51579974	3.657151711	0.000255033	0.006743402
PGRP-LC|39063	680.1529209	1.878143693	0.227623119	8.251111323	1.57E-16	3.15E-14
CG11211|35545	92.98517366	1.844055911	0.473714748	3.892755961	9.91E-05	0.003027167
CG30440|35496	1387.796765	1.836199908	0.165673024	11.08327637	1.51E-28	8.34E-26
CG8329|39123	827.9202743	1.797989854	0.259753633	6.921904551	4.46E-12	5.52E-10
CG11842|43431	106.2704535	1.783848364	0.423075459	4.216383454	2.48E-05	0.000885832
CG33774|3772288	50.15411296	1.7343085	0.531961302	3.260215534	0.001113276	0.021958817
CG43255|12797953	66.26322975	1.732498878	0.490729872	3.530453266	0.000414848	0.010053005
CG15529|43584	205.7281732	1.728795793	0.389243507	4.441424874	8.94E-06	0.00036093
CG14529|43408	86.19729379	1.718759614	0.576906252	2.979270217	0.002889359	0.044247315
CG32708|318161	237.6263576	1.705806575	0.266574105	6.39899578	1.56E-10	1.49E-08
CG3104|33486	58.68888752	1.70565964	0.5462608	3.122427309	0.001793664	0.031243189
CG17239|59224	254.3356147	1.693401406	0.425490115	3.979884247	6.89E-05	0.002190864
CG12105|38190	78.75418978	1.680580676	0.454732602	3.69575585	0.000219234	0.005910194
CR45873|26067201	59.92574281	1.670849902	0.556110874	3.004526577	0.002659945	0.042017988
Uhg1|3772106	426.3881344	1.662404701	0.330484381	5.030206561	4.90E-07	2.71E-05
CG4302|37420	382.9207183	1.643917114	0.32833994	5.006753417	5.54E-07	2.95E-05
simj|39212	1889.376435	1.639149933	0.176873136	9.26737646	1.91E-20	5.01E-18
Ance-4|35909	385.5436808	1.615410197	0.535576658	3.016207245	0.002559583	0.040855643
CG5621|42476	232.85462	1.60702193	0.355099625	4.525552316	6.02E-06	0.000257436
SmydA-4|32034	91.17622216	1.571792603	0.452908659	3.470440608	0.000519605	0.012138066
Axud1|33419	1110.869247	1.556425833	0.15667834	9.933892764	2.96E-23	1.13E-20
hng3|38090	220.0936124	1.544686832	0.253659815	6.089600082	1.13E-09	9.91E-08
CR31781|12798248	1508.970537	1.543195836	0.178852937	8.62829465	6.23E-18	1.43E-15
CG3088|39115	768.3987474	1.539714434	0.300677428	5.12081817	3.04E-07	1.78E-05
E(spl)m3-HLH|43156	160.1553993	1.535835108	0.440750728	3.484588928	0.000492894	0.01161249
CG17180|38068	329.0403395	1.525143271	0.24226123	6.29544923	3.07E-10	2.86E-08
CG10062|37224	115.6519887	1.504992643	0.408447575	3.684665393	0.000229003	0.006128617
CG8343|35544	994.1600677	1.490351715	0.213056048	6.995115734	2.65E-12	3.44E-10
Cht10|3355116	86.31070544	1.465846459	0.489863227	2.992358638	0.002768308	0.043112102
CG34109|4379890	98.54906172	1.44915017	0.421063076	3.441646279	0.000578186	0.012983862
Dhc93AB|42485	103.33132	1.421704627	0.440341299	3.228642484	0.001243793	0.023850538
CG2641|40921	93.54387761	1.410987332	0.378700854	3.725862556	0.000194648	0.005378932
CG9897|37651	377.0808477	1.408169752	0.380337178	3.702424673	0.000213549	0.00579948
CG11911|33206	1403.669372	1.387594269	0.149376963	9.289211961	1.55E-20	4.18E-18
Alp2|37539	498.1820254	1.351576234	0.390703596	3.459339123	0.000541503	0.012516998
CG12428|43332	1258.953716	1.350359128	0.16078944	8.398307303	4.53E-17	9.79E-15
metro|36176	570.7722868	1.328966813	0.339486069	3.914643146	9.05E-05	0.002819978
CG14022|33763	187.6521198	1.302099014	0.306476454	4.248610288	2.15E-05	0.00078274
CG3552|39097	582.4201908	1.298807254	0.212228745	6.119846088	9.37E-10	8.33E-08
CG12116|31782	2699.831413	1.298702524	0.274432402	4.732322119	2.22E-06	0.000102832
CG17475|42069	434.497097	1.298145831	0.183294155	7.082308943	1.42E-12	1.86E-10
Pxn|38326	719.7876691	1.293683709	0.34329746	3.768404542	0.000164294	0.004705218
GNBP1|40034	194.1366041	1.28730747	0.296747293	4.338059685	1.44E-05	0.000544655
CG15628|33681	1189.498691	1.284491589	0.188087791	6.829213016	8.54E-12	1.00E-09
LysP|38129	700.4402037	1.270529346	0.190786891	6.659416383	2.75E-11	2.91E-09
Rh4|39887	745.8461655	1.255018619	0.150838249	8.320294279	8.77E-17	1.86E-14
CG9451|40118	348.4987994	1.240888007	0.361373849	3.433806876	0.000595168	0.013150948
CG43103|12798325	116.0001657	1.235606681	0.406085939	3.042722153	0.002344487	0.03829676
Sema2a|36846	3108.01803	1.218181505	0.150266329	8.106816171	5.20E-16	9.55E-14
fog|33148	1609.435307	1.202363464	0.129089948	9.314152524	1.23E-20	3.48E-18
alpha-Est10|40896	374.9631609	1.199690671	0.211352699	5.676249594	1.38E-08	1.03E-06
CR44179|14462519	161.4636559	1.197091728	0.286311092	4.181087504	2.90E-05	0.001015506
CG40178|3354941	604.5342173	1.190105559	0.159478775	7.462469882	8.49E-14	1.32E-11
CG31517|251711	230.2640472	1.174060386	0.276135782	4.251750266	2.12E-05	0.000774399
nolo|35424	532.3866407	1.168588128	0.234085858	4.992134667	5.97E-07	3.15E-05
CG42694|10178792	128.5013306	1.1599633	0.332523019	3.488369924	0.000485975	0.011523361
CG40472|8673970	131.7174886	1.159686257	0.35916371	3.228851424	0.001242884	0.023850538
CG6401|37020	220.4534637	1.158410787	0.365695105	3.167695634	0.001536523	0.027818886
CG42259|7354475	294.6549933	1.146242991	0.238398894	4.808088541	1.52E-06	7.40E-05
CG33301|2768917	302.3973785	1.14568887	0.347676088	3.295276577	0.000983249	0.019928858
CG42319|36473	408.896028	1.143634486	0.319344005	3.581199172	0.000342021	0.008551295
CG33978|3885646	262.3893438	1.134431471	0.281182885	4.034496871	5.47E-05	0.001774519
CG11241|40492	357.0562755	1.130400769	0.223476582	5.058251545	4.23E-07	2.39E-05
CG30503|246656	259.7868463	1.125783758	0.262980882	4.280857787	1.86E-05	0.000688845
CG4461|39074	860.6571228	1.124268269	0.154734806	7.265774877	3.71E-13	5.32E-11
CG31267|318651	220.8885891	1.124089665	0.339813235	3.30796317	0.000939772	0.019188745
Mlc1|43323	1853.654806	1.11914166	0.124012466	9.024428714	1.81E-19	4.53E-17
IMPPP|36486	803.2227218	1.106711324	0.297935047	3.714606038	0.000203521	0.005582132
CG15822|38273	309.9742066	1.098837833	0.239828784	4.581759603	4.61E-06	0.000199367
CG42806|10178814	492.8529956	1.098111265	0.207789786	5.284722048	1.26E-07	7.93E-06
Tsp42Eg|35616	252.3455711	1.078721184	0.254941079	4.231256847	2.32E-05	0.000840106
zetaTry|36216	253.9773297	1.028829452	0.252640552	4.07230527	4.66E-05	0.001541326
Hsc70-1|39542	388.8567165	1.027861034	0.232526232	4.420408934	9.85E-06	0.000392137
CG13315|50300	824.7010272	1.016559694	0.284990132	3.566999622	0.000361092	0.008887054

DEG_list_low

gene_id	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
CG4009|42054	155.145622	-23.95975365	4.785065876	-5.007194106	5.52E-07	2.95E-05
His2A:CG33850|3772148	173.6759445	-10.74463342	1.478839263	-7.265585716	3.71E-13	5.32E-11
Jon66Ci|38952	164.9028499	-10.67143234	1.501899432	-7.105290879	1.20E-12	1.63E-10
His2A:CG33847|3771774	134.1833653	-10.37319363	2.165365244	-4.790505277	1.66E-06	8.01E-05
mthl8|38013	123.7640112	-10.256398	1.487618092	-6.894510128	5.41E-12	6.47E-10
His2A:CG33844|3772565	55.84768017	-9.10992067	1.58188275	-5.75891018	8.47E-09	6.63E-07
His1:CG33861|3771736	50.79705422	-8.97064898	1.559527843	-5.752156987	8.81E-09	6.79E-07
Cp19|39000	2373.955789	-8.61142104	2.111478613	-4.078384212	4.53E-05	0.001515232
Cp16|39001	1143.302214	-8.254052493	1.523549745	-5.41764555	6.04E-08	4.08E-06
Ada1-1|318991	138.5667272	-7.977137138	1.079233531	-7.39148378	1.45E-13	2.18E-11
CG46275|26067074	20.73336926	-7.681368609	1.87680525	-4.092789388	4.26E-05	0.001432757
CG18107|37101	40.84054007	-7.200278204	1.559764376	-4.616260196	3.91E-06	0.000170278
CG7017|40213	13.66713982	-7.078194737	1.833927174	-3.859583324	0.000113581	0.003393872
CG43680|14462862	12.07133825	-6.897821645	1.882133982	-3.664894056	0.000247441	0.006590059
CG30083|246444	10.61026856	-6.712364971	1.934540802	-3.469745877	0.000520951	0.012143775
CG12970|36744	10.56743877	-6.704023516	2.012771818	-3.330741943	0.000866149	0.017884184
CG5770|37054	56.5001673	-6.667216183	1.329888015	-5.013366619	5.35E-07	2.92E-05
Cp18|38998	1438.888783	-6.39718311	1.444741465	-4.427908568	9.52E-06	0.000380122
CG15263|34898	46.14072479	-6.362839493	1.198708512	-5.30807901	1.11E-07	7.06E-06
CR45151|19835439	8.009786504	-6.305738501	2.08612939	-3.022697697	0.002505324	0.040267784
CG31926|326174	49.63606424	-5.923530691	1.396548519	-4.241550228	2.22E-05	0.00080512
CR43309|12798456	32.96950305	-5.896916923	1.237900318	-4.763644403	1.90E-06	9.00E-05
tut|317996	387.2796431	-5.856418758	0.367528294	-15.93460655	3.64E-57	5.02E-54
LysX|38122	176.7666708	-5.814851057	0.843563299	-6.893200624	5.46E-12	6.47E-10
Femcoat|31367	127.1795966	-5.702293019	1.57455524	-3.621526176	0.00029287	0.007513285
CG7567|43479	72.07958788	-5.655422886	0.946662573	-5.974064093	2.31E-09	1.92E-07
Jon66Cii|38953	12.97626278	-5.519599833	1.767287198	-3.123204784	0.001788932	0.031243189
CG42825|39179	1612.825948	-5.415088868	1.207319965	-4.485214381	7.28E-06	0.000305377
Mur11Da|318139	73.41872208	-5.252918399	1.299783383	-4.041379869	5.31E-05	0.001733418
Muc4B|31368	73.74296531	-4.867151916	1.334412651	-3.647411399	0.000264896	0.006970737
CG30090|246448	32.48223374	-4.832378919	1.018469213	-4.744747171	2.09E-06	9.75E-05
l(2)03659|47905	419.2491808	-4.816225377	0.391988488	-12.28665007	1.07E-34	8.41E-32
Dhc98D|43379	215.9288105	-4.748225488	0.429472463	-11.05594862	2.05E-28	1.08E-25
Cnx14D|32620	29.41590889	-4.698168702	1.010571875	-4.649019844	3.34E-06	0.000148146
dsx-c73A|39831	67.19350492	-4.555179591	0.667370491	-6.825563394	8.76E-12	1.01E-09
m|44835	18.77396532	-4.435446382	1.177712327	-3.766154331	0.000165781	0.004735505
CR46256|26067566	17.15032669	-4.344221566	1.475849171	-2.943540336	0.003244815	0.048023267
Amyrel|36863	57.56927915	-4.319046442	0.816068317	-5.292505972	1.21E-07	7.65E-06
CG6277|43251	390.7986037	-4.306545944	0.486426372	-8.853438452	8.49E-19	2.08E-16
Spn85F|41221	27.91923811	-4.289481554	0.979996635	-4.377037023	1.20E-05	0.000470378
lectin-37Da|3346222	649.3055551	-4.073347243	0.391098902	-10.41513342	2.12E-25	8.97E-23
Lsp2|45326	877.8279413	-3.864569935	1.047579673	-3.689046316	0.000225096	0.006038713
CG33346|2768690	296.9454269	-3.670719026	0.50809674	-7.224449077	5.03E-13	7.11E-11
CG15199|32051	173.6576373	-3.455115249	0.646923275	-5.340842387	9.25E-08	5.97E-06
CG34040|3885655	117.9231491	-3.431743254	0.496688941	-6.909240307	4.87E-12	5.90E-10
CG6839|40067	445.307232	-3.396802175	0.524218485	-6.479745136	9.19E-11	9.22E-09
CR43857|14462718	65.98378211	-3.255506793	0.66686654	-4.881796575	1.05E-06	5.27E-05
CG33926|39092	907.4293571	-3.122090585	0.368827995	-8.4648959	2.56E-17	5.65E-15
CR45923|26067251	49.25227116	-3.08163093	0.597295844	-5.159304155	2.48E-07	1.49E-05
Mal-A6|246565	2457.045077	-3.05023673	0.291965207	-10.44726103	1.51E-25	6.93E-23
Mal-A7|35829	1103.336646	-3.038464144	0.328206367	-9.257785483	2.09E-20	5.35E-18
CR45822|26067150	87.25077778	-3.012563808	0.445567466	-6.761184423	1.37E-11	1.48E-09
Ir25a|33683	49.13110032	-2.991850369	0.588211496	-5.0863514	3.65E-07	2.10E-05
Sox21a|39567	37.92141759	-2.948321762	0.878945699	-3.354384423	0.000795418	0.016705288
CG32368|317997	333.2375215	-2.923299735	0.590467548	-4.950822013	7.39E-07	3.79E-05
CR44357|19836209	57.32012813	-2.811707083	0.650248881	-4.324047557	1.53E-05	0.000576484
CG4927|36852	19.53487411	-2.787545007	0.92944741	-2.99914226	0.002707409	0.042504739
His1:CG33828|3771910	240.7922969	-2.737091322	0.417024563	-6.563381546	5.26E-11	5.37E-09
Mur29B|319014	1740.812508	-2.666680888	0.625874074	-4.260730712	2.04E-05	0.000748885
CG42807|36511	1054.612929	-2.542006076	0.179432735	-14.16690254	1.47E-45	1.62E-42
CG14567|40420	79.0622841	-2.540419593	0.618062185	-4.110297724	3.95E-05	0.00134059
CG9826|37625	33.59637874	-2.526907048	0.696002584	-3.630600098	0.000282763	0.007301511
His1:CG33858|3772581	211.5412904	-2.505457416	0.284149787	-8.817382713	1.17E-18	2.81E-16
CR32773|19835374	88.63196866	-2.470768488	0.479668337	-5.15099351	2.59E-07	1.54E-05
CG13947|33250	37.9868947	-2.457152314	0.715368513	-3.434806354	0.000592977	0.013150948
His1:CG33822|3772665	304.7072222	-2.444590534	0.334309124	-7.312365585	2.62E-13	3.86E-11
Amy-d|36932	9884.111641	-2.433932843	0.206380548	-11.79342175	4.22E-32	2.74E-29
pre-mod(mdg4)-X|10178	35.78650085	-2.433379985	0.767279917	-3.171437087	0.001516867	0.027555563
Cpr72Ec|39816	334.488894	-2.43007338	0.257727483	-9.428848443	4.15E-21	1.20E-18
Mal-A8|35830	819.9984325	-2.417251733	0.14981281	-16.13514719	1.44E-58	2.65E-55
CG10943|39462	112.6712278	-2.401353463	0.516600519	-4.648376014	3.35E-06	0.000148146
Mal-B1|34597	99.9183978	-2.358867242	0.467337865	-5.047455853	4.48E-07	2.51E-05
CG6300|42351	57.02380719	-2.347286586	0.646352538	-3.631588717	0.000281682	0.007290665
His1:CG33831|3772075	93.5532905	-2.342786911	0.438051977	-5.348193903	8.88E-08	5.80E-06
tobi|43072	2994.823369	-2.273200044	0.520081155	-4.370856397	1.24E-05	0.000482184
CG14500|37087	118.7950827	-2.26839655	0.607243846	-3.735561202	0.000187297	0.005241464
CG12200|32932	323.5913908	-2.263373273	0.227241818	-9.960196997	2.28E-23	8.96E-21
CG2233|31721	8252.240406	-2.228132769	0.20372239	-10.93710301	7.66E-28	3.84E-25
AstC-R1|40020	28.4817909	-2.170654354	0.73523694	-2.952319499	0.003153964	0.047057656
PGRP-SD|38858	112.1262195	-2.153273276	0.372790752	-5.776090917	7.65E-09	6.06E-07
CG4562|42362	1770.815514	-2.140984265	0.298908129	-7.162683309	7.91E-13	1.09E-10
CG32640|318135	135.3807307	-2.112969336	0.352148088	-6.000229477	1.97E-09	1.66E-07
CG34291|5740331	134.0431733	-2.068407625	0.642403756	-3.219793793	0.001282828	0.024513805
Takl1|318725	143.7423198	-2.047637717	0.548058216	-3.736168268	0.000186846	0.005241464
Vago|32040	198.4315434	-2.015025341	0.657335172	-3.065445797	0.002173458	0.0364021
CG3085|37663	263.1293442	-1.990109732	0.244148601	-8.151223149	3.60E-16	6.85E-14
CG12290|43182	948.8844334	-1.97108604	0.20668705	-9.536572508	1.48E-21	4.65E-19
CG15422|33615	161.8223488	-1.958630366	0.439982213	-4.451612604	8.52E-06	0.000345486
corolla|32739	122.0321768	-1.951711296	0.466542568	-4.183350957	2.87E-05	0.001008645
Cyp6a8|36666	240.6980177	-1.935860835	0.339904528	-5.695307577	1.23E-08	9.24E-07
CG9903|32621	59.9512765	-1.928161812	0.5611166	-3.436294367	0.00058973	0.013109599
spirit|31797	197.047761	-1.924891642	0.443416124	-4.341050174	1.42E-05	0.000542014
CG3323|31439	145.737081	-1.919375005	0.573674389	-3.345756828	0.000820583	0.017103499
CG11671|40976	226.7580793	-1.91499015	0.516652426	-3.70653471	0.000210114	0.005720301
Amy-p|47764	7622.189333	-1.884394931	0.54802954	-3.43849153	0.000584965	0.013029944
CG43064|12798207	125.5793672	-1.884389822	0.499971563	-3.768994002	0.000163907	0.004705218
CG2812|37801	93.68514446	-1.870737295	0.400871357	-4.666677384	3.06E-06	0.000137762
CG3699|31046	244.7150338	-1.858680189	0.347146756	-5.354162626	8.60E-08	5.67E-06
kirre|31292	242.9265345	-1.855509027	0.327361907	-5.668066399	1.44E-08	1.07E-06
CG4757|41330	405.2592162	-1.808321346	0.523366509	-3.455172071	0.000549942	0.012657024
otk2|36284	125.0101635	-1.793600518	0.462891417	-3.874775923	0.000106723	0.003223907
Ser8|36489	170.1231827	-1.767418489	0.600412692	-2.943672765	0.003243427	0.048023267
Obp56e|37267	236.5570077	-1.766913926	0.316100436	-5.589723152	2.27E-08	1.62E-06
Spn47C|36163	80.73531998	-1.755527175	0.516068146	-3.401735193	0.000669595	0.014448049
CG4377|37489	522.448496	-1.747692742	0.276473656	-6.321371692	2.59E-10	2.44E-08
PGRP-SC2|35862	1048.290779	-1.737713386	0.233146535	-7.453309927	9.10E-14	1.39E-11
CG16986|38325	540.631765	-1.71524343	0.259230157	-6.616681682	3.67E-11	3.86E-09
dpr6|50296	488.7771517	-1.709004603	0.250536734	-6.821373361	9.02E-12	1.01E-09
nub|34669	209.132576	-1.706658785	0.579238168	-2.946385231	0.003215117	0.047711818
CG8628|38783	454.9047725	-1.663038614	0.219179829	-7.587553201	3.26E-14	5.29E-12
gas|37572	87.30282292	-1.659713215	0.464039194	-3.576666016	0.000348004	0.008661616
CG3987|41822	847.8832426	-1.628340659	0.362425438	-4.492898362	7.03E-06	0.000295683
fit|42578	332.4832695	-1.617705374	0.515351813	-3.139031111	0.001695075	0.030096444
CG44251|36429	227.1710476	-1.610730795	0.459294264	-3.506969104	0.000453242	0.010838564
Ser12|33406	157.9136488	-1.590081383	0.395199618	-4.023489166	5.73E-05	0.0018487
CREG|42092	457.4111148	-1.587490949	0.202102936	-7.854863383	4.00E-15	7.00E-13
CG13704|38588	276.9897849	-1.582558838	0.417233012	-3.792985678	0.000148847	0.004318906
CG14696|41317	101.2313918	-1.575908488	0.437692853	-3.600489422	0.000317619	0.008013877
Phae2|34638	308.2906825	-1.551861593	0.440849101	-3.52016504	0.000431278	0.010405416
CG30054|246420	107.1596858	-1.536522785	0.430954627	-3.565393404	0.000363311	0.008921748
CG33470|2768831	490.7898851	-1.518780384	0.373528046	-4.066041095	4.78E-05	0.001578583
CG9664|33540	149.1518335	-1.511176315	0.327252259	-4.617771984	3.88E-06	0.000169935
His1:CG33825|3772715	636.3538286	-1.50515761	0.161814595	-9.301741958	1.38E-20	3.81E-18
CG31087|43062	221.8804516	-1.489590072	0.423496442	-3.517361482	0.00043586	0.01047013
lectin-37Db|3346221	398.9391355	-1.465356805	0.298150645	-4.914820181	8.89E-07	4.47E-05
Ugt86Dd|53507	424.4891625	-1.457871146	0.240907041	-6.051592104	1.43E-09	1.23E-07
Mal-A1|35824	8340.166364	-1.449415348	0.170964965	-8.477850098	2.29E-17	5.16E-15
rst|31290	502.8914373	-1.446528504	0.208237787	-6.946522658	3.74E-12	4.69E-10
Hr4|31162	344.9274342	-1.410841845	0.25323677	-5.571236147	2.53E-08	1.78E-06
His1:CG33810|3771879	681.168371	-1.407077189	0.347780615	-4.045875847	5.21E-05	0.001705524
His1:CG33816|3771816	335.1458024	-1.388364583	0.246452782	-5.633389783	1.77E-08	1.29E-06
Oatp58Db|37544	249.9240746	-1.387633115	0.272216736	-5.097530497	3.44E-07	2.01E-05
Cyp12a4|42294	935.8748755	-1.371322977	0.278718692	-4.920096915	8.65E-07	4.40E-05
CG18278|36487	969.4418761	-1.351945836	0.142031632	-9.518624965	1.75E-21	5.23E-19
CG3397|41454	211.6008787	-1.345485517	0.308186359	-4.365817877	1.27E-05	0.000491697
mex1|39677	171.436614	-1.341208048	0.373561065	-3.590331475	0.000330258	0.008275958
CG10621|35152	355.2759074	-1.335106842	0.222427293	-6.002441621	1.94E-09	1.65E-07
CG10916|37081	177.7482009	-1.331964342	0.373120687	-3.569794942	0.000357261	0.008812432
achi|36373	355.6061636	-1.319144125	0.204964578	-6.435961455	1.23E-10	1.21E-08
CG5888|34980	158.2392646	-1.284092027	0.305623817	-4.20154437	2.65E-05	0.00093987
rhi|44879	1018.227498	-1.282717455	0.134226204	-9.556386281	1.22E-21	3.95E-19
CG45080|19834892	244.0541258	-1.282081374	0.255831422	-5.011430427	5.40E-07	2.93E-05
CG1208|40727	227.8408105	-1.255712812	0.319409295	-3.931359644	8.45E-05	0.002653365
Tsf1|32821	7273.117658	-1.238167565	0.385374614	-3.212893428	0.00131405	0.024809451
CG32444|40406	823.631274	-1.237986557	0.281374273	-4.399785889	1.08E-05	0.000428227
CG15408|33548	128.5240154	-1.23543365	0.337515347	-3.660377705	0.000251844	0.00667507
CG30160|246490	264.4210465	-1.228384794	0.253800779	-4.839956745	1.30E-06	6.42E-05
MRE16|12798102	465.8619215	-1.222367381	0.246533024	-4.958229772	7.11E-07	3.67E-05
CG13795|34049	155.4362775	-1.207550919	0.392359468	-3.07766479	0.002086295	0.035465384
CG5245|41530	150.7198437	-1.18677367	0.310645597	-3.820346015	0.000133265	0.003918334
CG32485|38363	462.1917128	-1.177013003	0.249004706	-4.726870515	2.28E-06	0.00010475
CG17233|40220	4467.357321	-1.174257056	0.096843403	-12.125318	7.76E-34	5.34E-31
CG7953|34801	848.6412319	-1.174037807	0.250842183	-4.680384275	2.86E-06	0.000129924
Prosalpha1|45780	4359.207669	-1.163356306	0.121175003	-9.600629445	7.95E-22	2.74E-19
CG17752|42337	261.3183077	-1.133322721	0.328185162	-3.453302749	0.000553767	0.012694046
CG10912|37059	2050.402711	-1.132752602	0.26940723	-4.204610996	2.62E-05	0.000930209
CG31106|318594	217.250246	-1.132716779	0.269884475	-4.197043129	2.70E-05	0.000955666
CG16985|38323	293.4543473	-1.130703654	0.252239305	-4.482662429	7.37E-06	0.00030672
CG34043|3885606	154.7606794	-1.118604202	0.308886888	-3.621403968	0.000293009	0.007513285
MtnC|42416	161.0190349	-1.11444041	0.325737927	-3.421279249	0.000623273	0.013581439
Kebab|48440	282.1640037	-1.114361767	0.248657725	-4.481508734	7.41E-06	0.000307224
Hsp23|39077	615.4038358	-1.097054796	0.269904316	-4.064606347	4.81E-05	0.001583584
CG8093|36686	287.7097497	-1.094868392	0.350209863	-3.126320834	0.001770083	0.031127493
Sodh-1|40836	682.9721807	-1.094177594	0.292469795	-3.74116443	0.00018317	0.00516529

AOX3|41896	2216.845689	-1.090930283	0.107074883	-10.18847979	2.23E-24	9.12E-22
CG10170|42774	137.8484501	-1.09034477	0.351675857	-3.100425431	0.001932429	0.033448914
CG14102|40156	426.8384604	-1.083164177	0.196222855	-5.52007143	3.39E-08	2.35E-06
Cht8|37390	436.2128371	-1.041567481	0.210627684	-4.945064497	7.61E-07	3.89E-05
GLaz|36447	408.7136762	-1.04039084	0.197280021	-5.273675627	1.34E-07	8.33E-06
CR43837|14462385	533.5606538	-1.037115447	0.251407467	-4.125237254	3.70E-05	0.001260342
CG7565|38893	858.9272342	-1.036249054	0.176620293	-5.867100751	4.43E-09	3.57E-07
CG11961|37221	1214.955439	-1.035427226	0.275762275	-3.754782003	0.000173492	0.004904942
CG14036|33735	778.0974105	-1.02076211	0.178385279	-5.7222329	1.05E-08	7.99E-07
Cyp9f2|41520	1277.844993	-1.01873118	0.185202228	-5.50064214	3.78E-08	2.59E-06
Oatp58Dc|37545	542.3278022	-1.018041126	0.244963006	-4.155897425	3.24E-05	0.001119928
CR45835|26067163	201.9671134	-1.017252548	0.301658081	-3.372203869	0.000745692	0.015750964
CG4842|39817	464.9455976	-1.016533148	0.180979456	-5.616842753	1.94E-08	1.40E-06
Mco1|34258	186.5853803	-1.01589402	0.310187224	-3.275099497	0.001056248	0.021136455
Ir76a|40157	178.3480049	-1.015236821	0.319103254	-3.181530769	0.00146499	0.026921626
CG5096|34410	705.5381285	-1.010657036	0.267373074	-3.779950692	0.000156859	0.004527571
Gli|34927	420.5673888	-1.003827696	0.326183979	-3.077489275	0.002087524	0.035465384

Suppelmental Table 1. PCR primers used in this studies

gene name	forward sequences	Reverse sequences
HexA	ATATCGGGCATGTATATGGG	CAATTTCGCTCACATACTTGG
HexC	GGCTATACTCAACGATACCAC	CGCAATAGGTCCACATTCTC
Pgi	ACTGTCAATCTGTCTGTCCA	GATAACAGGAGCATTCTTCTCG
Ald	GGCAAGAAGGAGAACATTGC	CAACCAAACGCCTTAGTAGG
Gapdh	CTCGCATATAATCACGCGTC	CACCTTGCCATACTTCTTGTC
Pgk	CTGATTGAGAACCTTCTGGAC	CTTCTCCACCAGTTTCTCGA
Eno	CAACATCCAGTCCAACAAGG	GTTCTTGAAGTCCAGATCGT
Pyk	GTGCCACTCATCTACAAGGA	ATGAAGCCGTTCTTCTTTCC
Ldh	ACAAAACAGAGCGGAATGCT	CTACGATCCGTGGCATCTTT
CG7430	AGAGCGAGGAGCAACTGAAG	GTTGGTCTTGGCACGAGAGT
Scsα	CGTCATCTATGTGCCACCAC	ACACCCTCCGTAATGCAAAC
Pgd	TCGCCAATGAGGCTAAGGAC	CCAGCAGCATGACCTTCCG
SREBP	CGCAGTTTGTCGCCTGATG	CAGACTCCTGTCCAAGAGCTGTT
ACC	GTGCAACTGTTGGCAGATCAGTA	TTTCTGATGACGACGCTGGAT
FAS	GACTTGACCGATCCGATCAAC	CCCCAGGAGGTGAACTCTATCA
DGAT1	AGTCTGCGAAACCGCAAGTC	ATCCGTTGGTTCCATTACCATTT
Bmm	GTCCCTTCAGTCCCTCCTTC	TATGAAGCACGCACACAACA
HSL	GTTCGCATGCGGAAATCACACTGC	GAGAACTCCGCGTATCGAGTCG
CG33822	CCCAAAAAGACGGTGAAGAA	TTTTTGGCAGCCGTAGTCTT
CG33850	TTCTGTTGCCCAAGAAGACC	AAAGGACGGTTTGATTGACG
Mal-A6	GACCTTGAGAGAGCGACCAC	TTGTAGGAGCGCGGATAGAT
tobi	GATGCAGCCATTTTGGACTT	ATGCCATCCTCATCCTGAAG
Jon66Ci	GCTTGTGGGAGTCACCAACT	GTCACGGATCCAGTCCAAGT
LysB	ACTACAACGGCTCCAACGAC	CTCAACCCGCACTCATTGTA
LysD	CTGGTCCACCTGGCACTACT	GGTGCGCAATCGTTTTAATC
Cyp6A17	TGCAACAGCTTGTACGATCC	AGCATATTCCCGTAGCGATG
PGRP-LC	TTTGTCCTTTTCTGCCCAAC	TACGATACCCAGCAGGAAGG
IM23	GCACGCAGATTGAGAATGAA	CTCCGCCGATAATCACATTT
rp49	AGATCGTGAAGAAGGCACCAAG	CACCAGGAACTTCTTGAATCCGG