Table S1. List of PCR primers for comparing RFP and GFP cells in Fig. S2

Gene Symbol	Accession ID	Forward Primer	Reverse Primer
cre	YP_006472	GCCAGCTAAACATGCTTCAT	TAACATTCTCCCACCGTCAG
xmrk	X16891	GACTGCTGCAACGAACACTG	CATTCCTTGACACAAGCGGC
ccnd1	NM_131025	TTCCTTGCCAAACTGCCTAT	GGTGAGGTTCTGGGATGAGA
ccng1	NM_199481.1	GCTCAACTGGAAGGTCAAGG	CAGGGCCAGAAGAGACAAAG
cdk1	NM_212564.2	CTCTGGGGACCCCTAACAAT	CGGATGTGTCATTGCTTGTC
cdk2	NM_213406.1	CAGCTCTTCCGGATATTTCG	CCGAGATCCTCTTGTTTGGA
pcna	NM_131404.2	GGCAACATCAAGCTCTCACA	TGCAATTTTGTCCTCAACCA
mcm2	NM_173257.2	GCTACGACCCGTCTCTAACG	CGTCGAATGTGTTGGGAAGC
pold4	NM_001256200.1	GAACCCCCACAACTGAGTGA	TGTACTCTGGGTCAGTGTCCT
tp53	NM_001271820.1	GCTTGGTGCTGAATGGACAAC	CGTTTGGTCCCAGTGGTGG
cyp1a	NM_131879.2	TGCGAAGACCGAAAACTGGA	GTGCGATCCTTCCCGATCTT
adh5	NM_131849.2	AGCTCTTCCACTTCATGGGC	ACTTGCAGCCCATTACGACA
adh8a	NM_001001946.4	AAGCGAGGTTTTCCTGTCGT	GAAGGTGCTGGTTCCCATGA
apoa1b	NM_001100144.2	AGTCTCTTCCCAGACCAGCC	GGTGAGTGAGGGACTTGTGT
apoa2	NM_001130586.1	GAGGCTTGTCAATGCTTGGG	ATTCAGGCGAGCTTTGTCCA
fabp3	NM_152961.3	GGACGGTAAAGAGACGACCC	GAAACGGTGCAAAGGAGAGC
pklr	NM_201289.1	GGACAACCGTGTCACCTTCG	CAGGAGGCTGTCAATCAAAGAC
pdhb	NM_213154.1	TGCTTGGTACGGTCACTGTC	CCATTCGGGAGTGAGACACC
aldob	NM_194367.3	GCCACTGAGAAGGTCCTAGC	CACTCTGACCCCCAGAGAGA
gapdh	NM_001115114.1	GGGCTGCCAAGGCTGTAGGC	GGACACAACCTGGTGCTCCGTG

Table S2.

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Table S3. List of PCR primers for validation of RNA-seq data in Fig. S4

Type	Gene symbol	Forward Primer	Reverse Primer
unique up_T	*ccng1*	GGTGTGCAGGGCAGAAGTAA	GTCCACAGAGTTTGGGCTGA
unique up_T	*dynll1*	AGTCGCTGTTTTCTCCGTGT	GCCAGGTGGGGTTGTACTTT
unique up_T	*cox6a1*	CGAGTTCGTACCCTACAGCC	ACAAACTGGACAGGCGTCAT
unique up_T	*b2m*	TTGTCTGCTTGGCTCTCTCG	CCTGTCCGTTCTTCAGCAGT
unique up_T	*rbp5*	ATCTGGCGGCTTTGGATGTT	CGTAGTTTGGCACTTTCGCC
unique up_RFP+R	*adh8a*	AAGCGAGGTTTTCCTGTCGT	GAAGGTGCTGGTTCCCATGA
unique up_RFP+R	*fbp1b*	AGCCATTTCCACTGCTGTCA	AGAGCCATCCAGAGGGTCAA
unique up_RFP+R	*C7*	ATGTCCAAGCGGAATGCAGA	CTGGCAGACACTCATTCGGT
unique up_RFP+R	*agt*	GAGGGAGCCAGTCTACAGGA	GCCCTCCGTCATCTCAAACA
unique up_RFP+R	*cetp*	CTGTTCCTGGTTGTCGCTCT	TGAATCTCTAAATTGTGGAATCCGT
unique up_GFP+R	*eef1g*	GCAGTGGGTCAGTTTTGCTG	GACGCAGGTCACAAACCAAC
unique up_GFP+R	*rpl39*	GTCGCACAAGACCTTCAGGA	CTGGCAGGGAACAGATGGAG
unique up_GFP+R	*tm4sf4*	GTCCTCTGCAACATCCTGCT	CGCCGCAAACAGAATAGAGC
unique up_GFP+R	*vdac1*	AGGAACCGCATCACACAGAG	CTGGTATTTGGCTGCGATGC
unique up_GFP+R	*nlk1*	CTGCAAACGTGTGTTCAGGG	GTGGAGAATGCCTGCTGAGT
unique down_T	*rpl19*	CTTTCCGCTGACCACCAGC	TGACGACCCTTCCTTCGTG
unique down_T	*hgd*	CTGATCACACCTTTCGGCCT	GACGCTGACAGGTCTCCAAA
unique down_T	*adh5*	AGCTCTTCCACTTCATGGGC	ACTTGCAGCCCATTACGACA
unique down_T	*cyp1a*	TGCGAAGACCGAAAACTGGA	GTGCGATCCTTCCCGATCTT
unique down_RFP+R	*dap*	AAGACAACGACGCGACTCTT	GACCACAACAGGCAGCTTTG
unique down_RFP+R	*sord*	CTGGTCGAGTGGTGAAGGTC	CTGACAGGGGCTCAATCAGG
unique down_RFP+R	*aco2*	CCTGGGAGTTGAAGTGTCCC	TGGCAATTTCTCCTCGACCC
unique down_RFP+R	*nipal4*	AAAAAGAAGGCACTGCTGCG	GCAGCCCAATTTTCCAAGCA
unique down_RFP+R	*psmd1*	AAAACGGCAGACGCTAAGGA	CCCAGTTTGTTGCTCTTGCC
unique down_GFP+R	*sgk1*	GCTGGGCTTCACTGATGACT	CCATAGCAGGGGCGTAAGAG
unique down_GFP+R	*cyb5b*	CACGGAGTGAAAATGGGGGA	TTGCTCCAGCAAAACCTCCT
unique down_GFP+R	*psmb4*	CGAAAGCCATCCACTCCTGG	CTCATCAGAGGCTGTGCCAA
unique down_GFP+R	*cebpa*	AGTACAGGCTGAGGAGGGAG	CAGTTGCCCATGGCTTTGAC
unique down_GFP+R	*psma5*	TGTGCCATGAGTGGCTTGAT	CGCGTCACACTGGACAAAAG
Reference 1	*mat1a*	GTCTACCATCTGCAGCCCAG	GGCGTAAGACACCTGAACCA
Reference 2	*cox7b*	TATTAGCACGCGCAGTCAGT	GACAGGTTCCATGCAATGCC

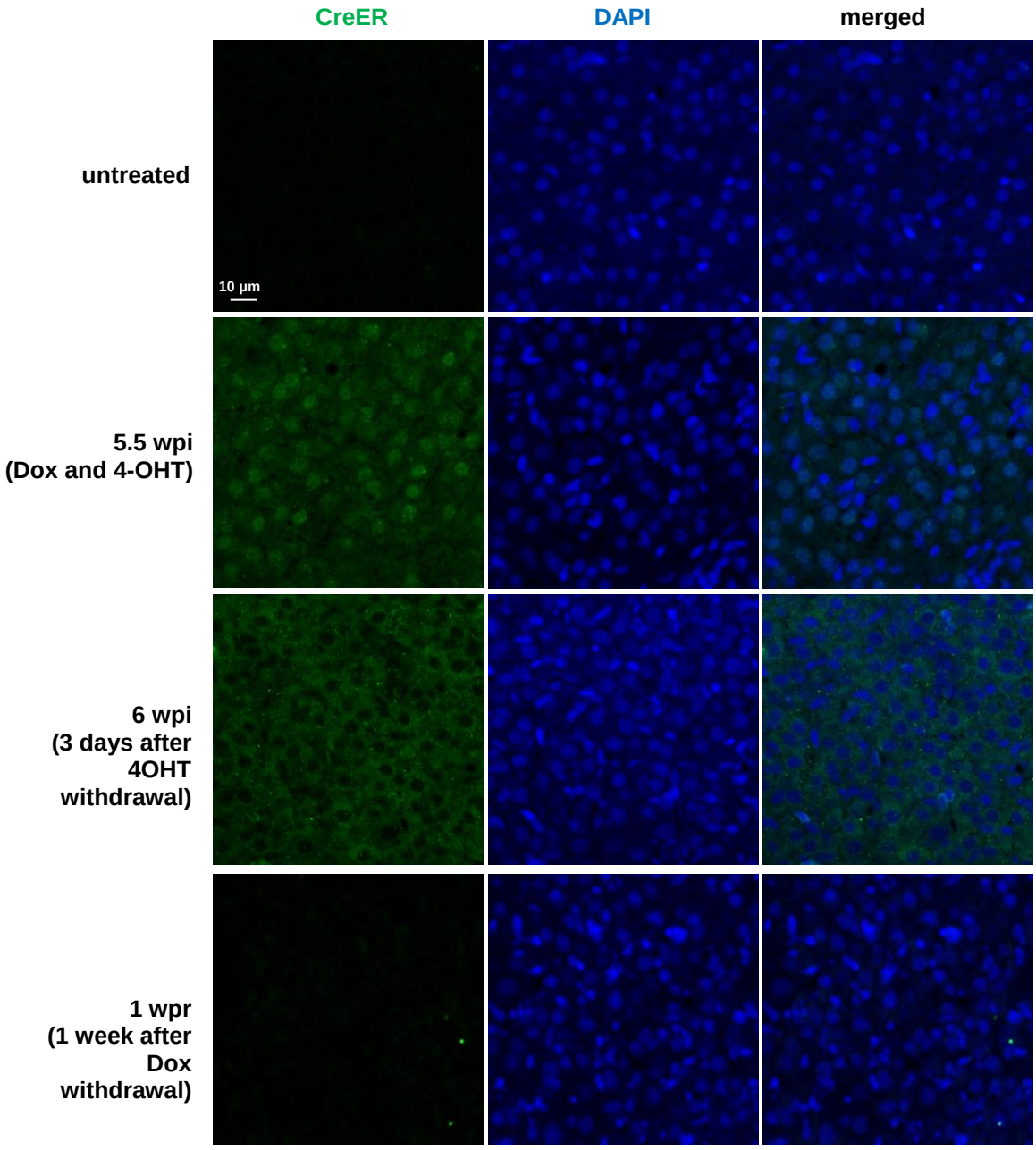

Fig. S1. Immunofluorescent staining of liver sections to validate the expression, cellular localization and stability of CreER. In untreated *CreER/xmrk* fish, no expression of CreER was detected. After Dox and 4-OHT induction at 5.5 wpi, CreER was expressed and was localized into nucleus. After 4-OHT withdrawal at 6 wpi, CreER was localized in the cytoplasm while not in the nucleus anymore. After Dox withdrawal at 1 wpr, CreER was basically undetectable.

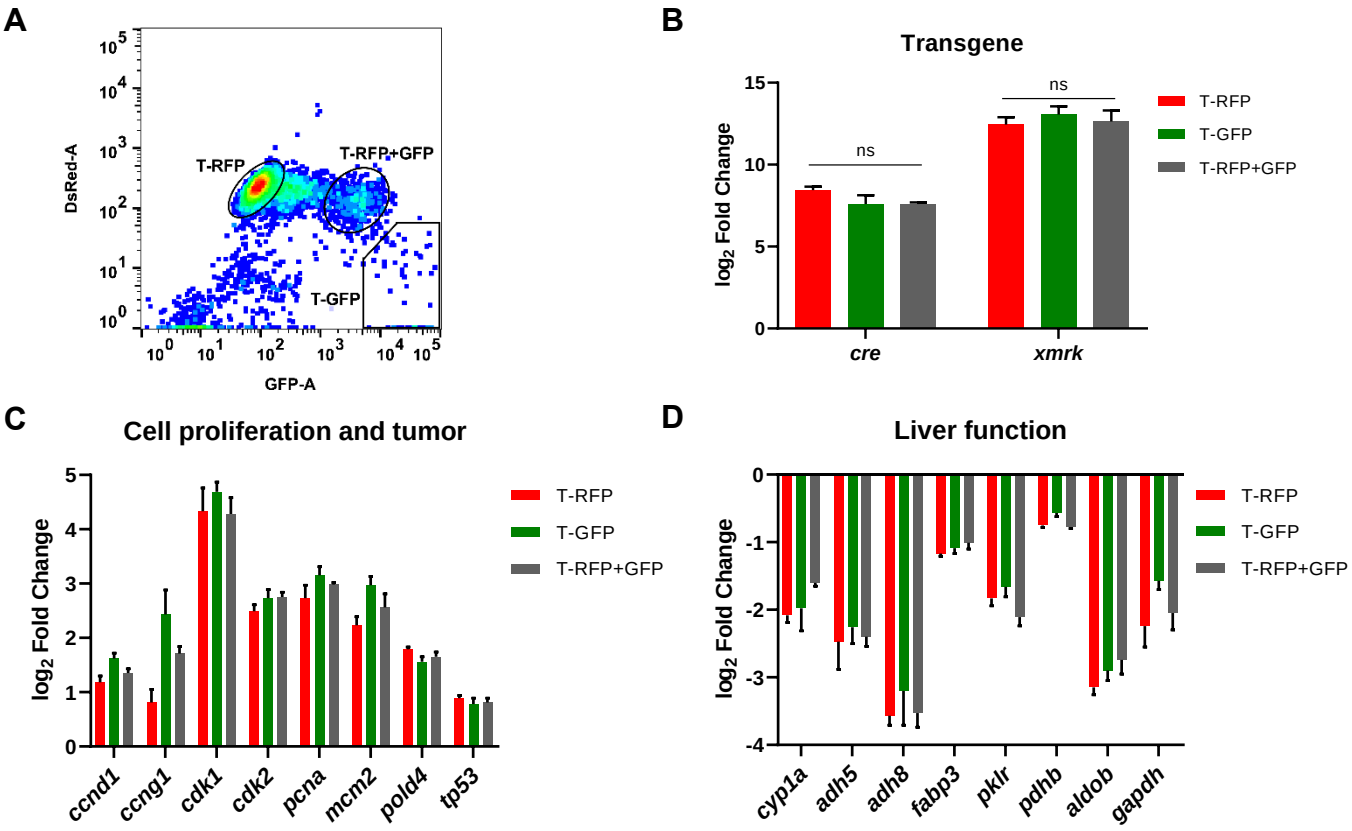

Fig. S2. Comparison of RFP+ (T-RFP), GFP+ (T-GFP), and double-positive (T-RFP+GFP) hepatocytes after Dox and 4-OHT treatments at 6 wpi from *CreER/xmrk* fish. (A) T-GFP cells (which failed to undergo loxP recombination and color switch) and T-RFP+GFP cells (which have undergone loxP recombination but with GFP protein not fully degraded) express comparable levels of *cre* and *xmrk* compared to T-RFP+ cells. (B) Genes involved in cell proliferation and tumor were up-regulated in all three population of cells at comparable levels. (C) Genes that are associated with liver function (detoxification metabolism, lipid and glucose metabolism) were down-regulated in all three population of cells at comparable levels. The fold changes are relative to the levels in the normal control hepatocytes. These results indicate that the T-GFP+ and T-RFP+GFP cells at 6 wpi are molecularly equivalent to T-RFP+ tumor cells. The GFP+ cells are likely the tumor hepatocytes that didn't undergo loxP recombination and color switch, rather than newly differentiated hepatocytes.

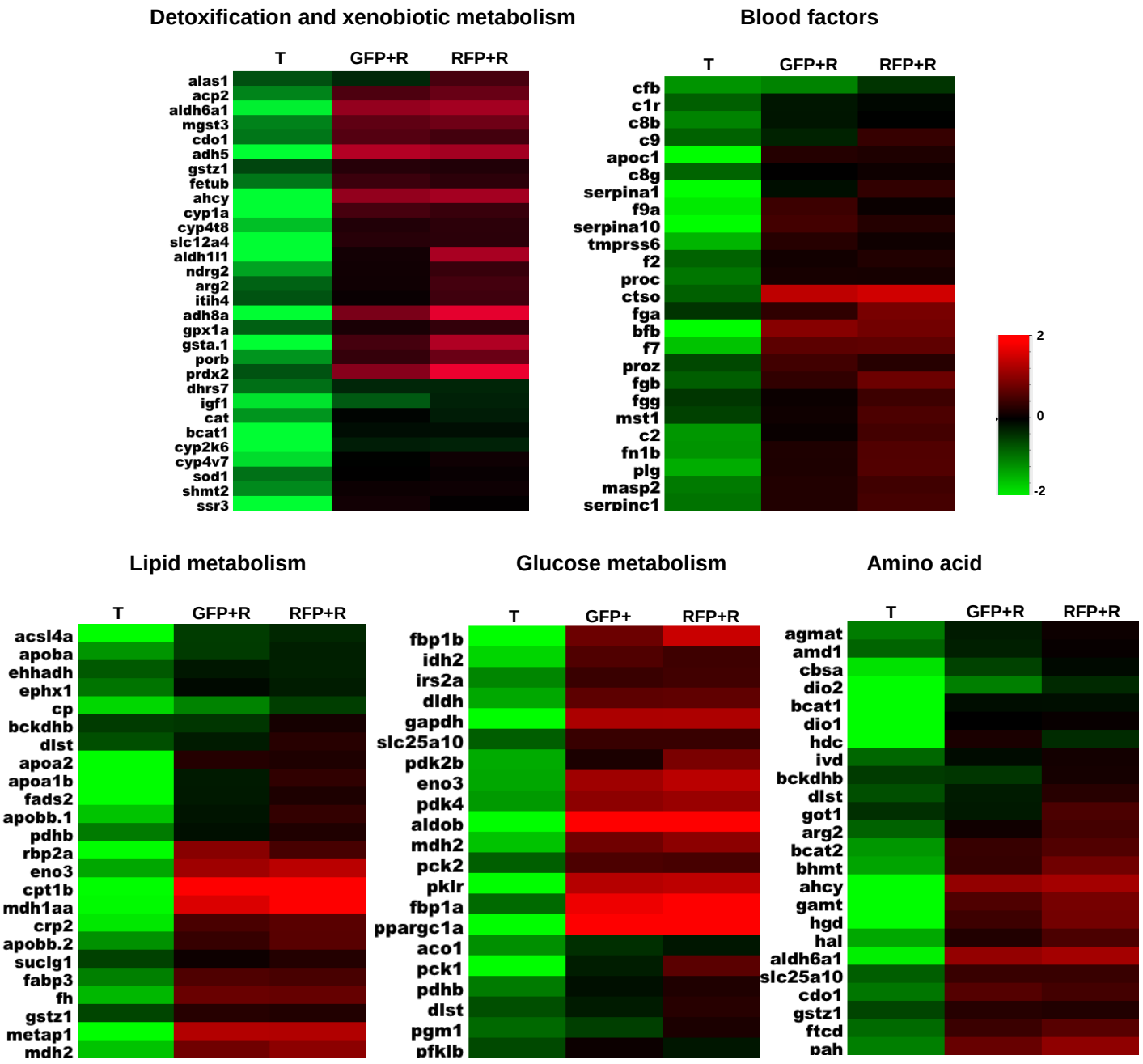

Fig. S3. Expression profiles of selected genes that are associated with liver function: Detoxification and xenobiotic metabolism, Blood factors, Lipid metabolism, Glucose metabolism, and Amino acid metabolism. The expression data was based on RNA-Seq analyses and fold changes are relative to the levels in the normal control samples, i.e. T vs C; GFP+R and RFP+R vs CR. The scale represents log2 Fold Change of 2 to -2.

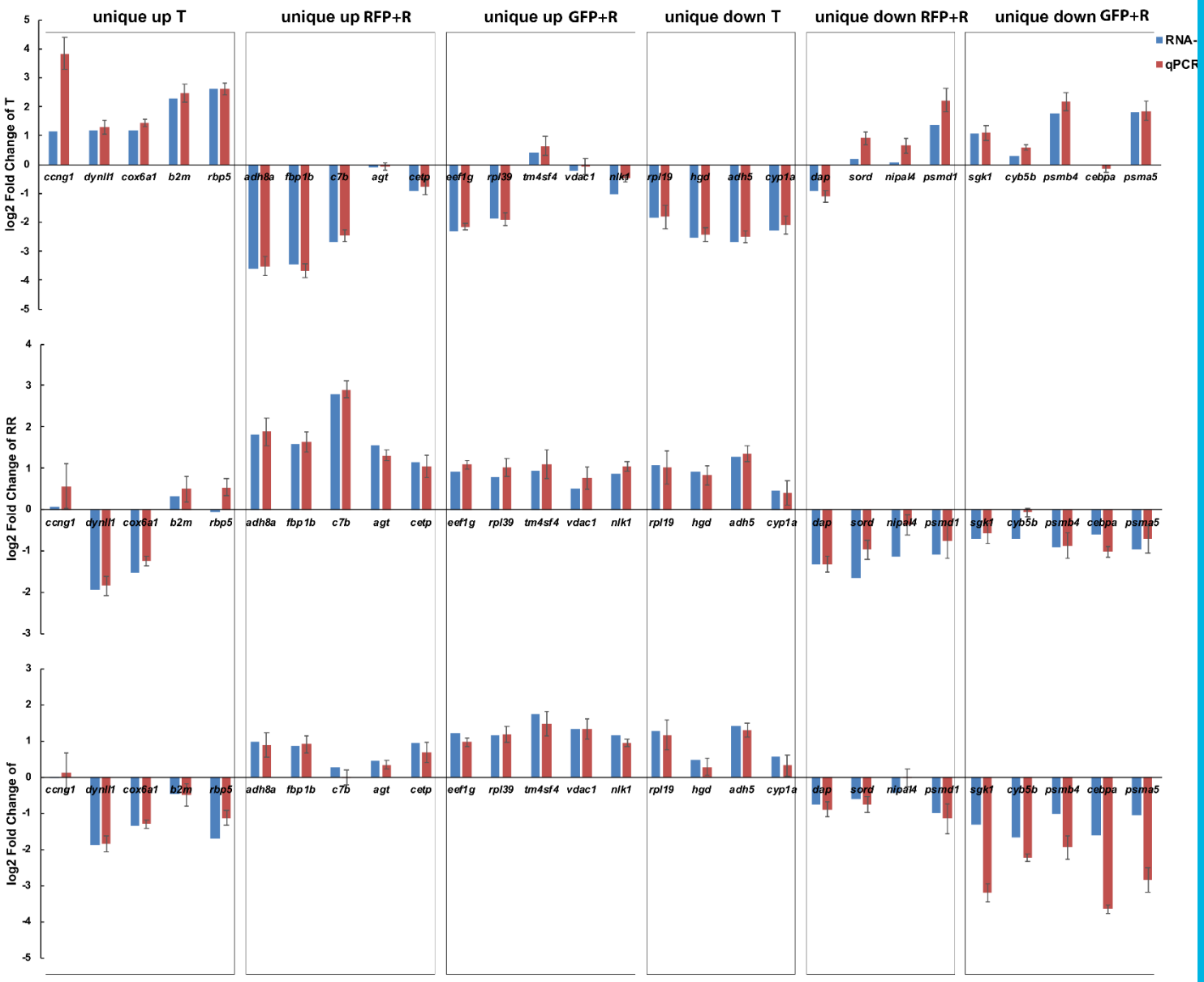

Fig. S4. qPCR validation of RNA-seq data. 4-5 genes were selected from each uniquely upregulated or downregulated category in T, RFP+R and GFP+R, as shown in the Venn diagram of Fig. 5 A-B. Genes with different abundance levels (FPKM 10 to 1000) were covered and majority of the genes tested showed good concordance between RT-qPCR and RNA-seq.