**Supplemental Information:**

## Supplemental Results:

### PKA and transcription factors in FLHCC

Upon stress in the endoplasmic reticulum, activation of IRE1 leads to cytoplasmic non-canonical splicing of the XBP1 transcript and subsequent transcriptional regulation by XBP1. PKA phosphorylation of IRE1a in the liver bypasses stress activation of this pathway (1). While characteristic splicing of the XBP1 mRNA was increased in several FLHCC samples, it was not increased in all and there were no consistent changes in XBP1 gene sets (c3.tft Broad Institute, Fig S1). PKA also phosphorylates the p65 subunit of NFκB. However, there was no significant correlation with changes of gene expression associated with NFκB, AP-2 or GATA-3.

## Supplemental Methods

**qPCR:** We quantified the expression levels of several genes by quantitative RT-PCR (qPCR) (Fig 6A,B). Overall, qPCR fold-change (tumor vs. normal) values were very similar to those measured by RNA-Seq (Fig S4A,B, $R^2$=0.98). Fold-change values for two genes tested by qPCR could not be quantitatively compared to RNA-Seq data due to lack of amplification in normal tissue samples, likely due to absence of gene expression. RNA-Seq reported an increase in the FLHCC tissue of 7.48 ($log_2$) fold for Rho GTPase activating protein 36 (ARHGAP36) and 4.54 ($log_2$) fold for EGF. By qPCR, we observed consistent amplification FLHCC tumor samples, but no amplification in the normal tissue. Thus, although a quantitative fold-change comparison was not possible, qPCR results suggest that qualitatively, these genes are strongly induced in FLHCC (as observed in the RNA-Seq analysis).

### Western Blots

Fresh frozen tissue curls at 5 µm were solubilized in RIPA buffer (Sigma) containing protease and phosphatase inhibitors (Complete EDTA-free and Phosphostop, Roche, Indianapolis, IN). Samples were normalized using protein concentration. These were then diluted with 4X Nupage LDS sample buffer (Life technologies) containing 10% beta-mercaptoethanol. Samples were heated at 100°C for 5 minutes, and then loaded on 4-12% Bis-Tris gels and run in MOPS buffer for 50 minutes at 200V. Transfer was performed using the iBlot (Life Technologies, Carlsbad, CA). The membranes were probed with primary antibodies in 5% milk against AKAP12, ZNF703, COL11A1 (abcam, ab49849, ab137054, ab166606, respectively, 1:500); EREG, AGR2 (Cell Signaling, #12048, #13062, respectively, 1:500); PRKACA (Santa Cruz Biotechnology, sc-903, 1:200); Beta-actin (Sigma, A5316, 1:2000) and incubated overnight. After washing in TBST, membranes were incubated with horseradish peroxidase-conjugated appropriate secondary antibodies (A9917, A0545, Sigma) in 5% milk at a concentration of 1:100,000, for 1 hour. Blots were then incubated with Amersham ECL prime western blotting detection reagent (GE Healthcare) or SuperSignal West Femto maximum sensitivity Substrate (Thermo Scientific, Rockford, IL).

### Mass Spectrometry

Protein lysates were prepared from four patient replicates for each tumor and normal tissue. After removing detergent by chloroform/methanol precipitation (2), proteins were solubilized in 8M urea, cysteines reduced and alkylated with DTT/iodoacetamide, and digested with LysC (Wako Chemicals) followed by trypsin (Promega). After desalting [(3), 3 µg of peptides were analyzed by nanoLC-MS/MS. Peptides were separated on a 50 cm EasySpray C18 column across 3 h gradients from 3 to 40% solvent B (A: 0.1% formic acid, B: 100% acetonitrile, 0.1% formic acid) and analyzed on a QExactive mass spectrometer (ThermoScientific).

Data were analyzed using MaxQuant (version 1.5.0.30) and Perseus software (version 1.5.0.9) (4), searching against a Uniprot human database (July 2014). Oxidation of methionine and protein N-terminal acetylation were allowed as variable modifications, and cysteine carbamidomethyl was set as a fixed modification. Two missed cleavages were allowed for specificity: Trypsin/P. The “match between runs” option was enabled. False discovery rates at the protein and PSM level were set to 1%. Protein abundances are expressed as LFQ (label free quantitation) values (5). Only proteins quantified in at least two out of three replicates in at least one group were retained, and missing values were imputed. A t-test test was performed and corrected for multiple-hypothesis testing using a permutation-based FDR with a threshold of 0.05.

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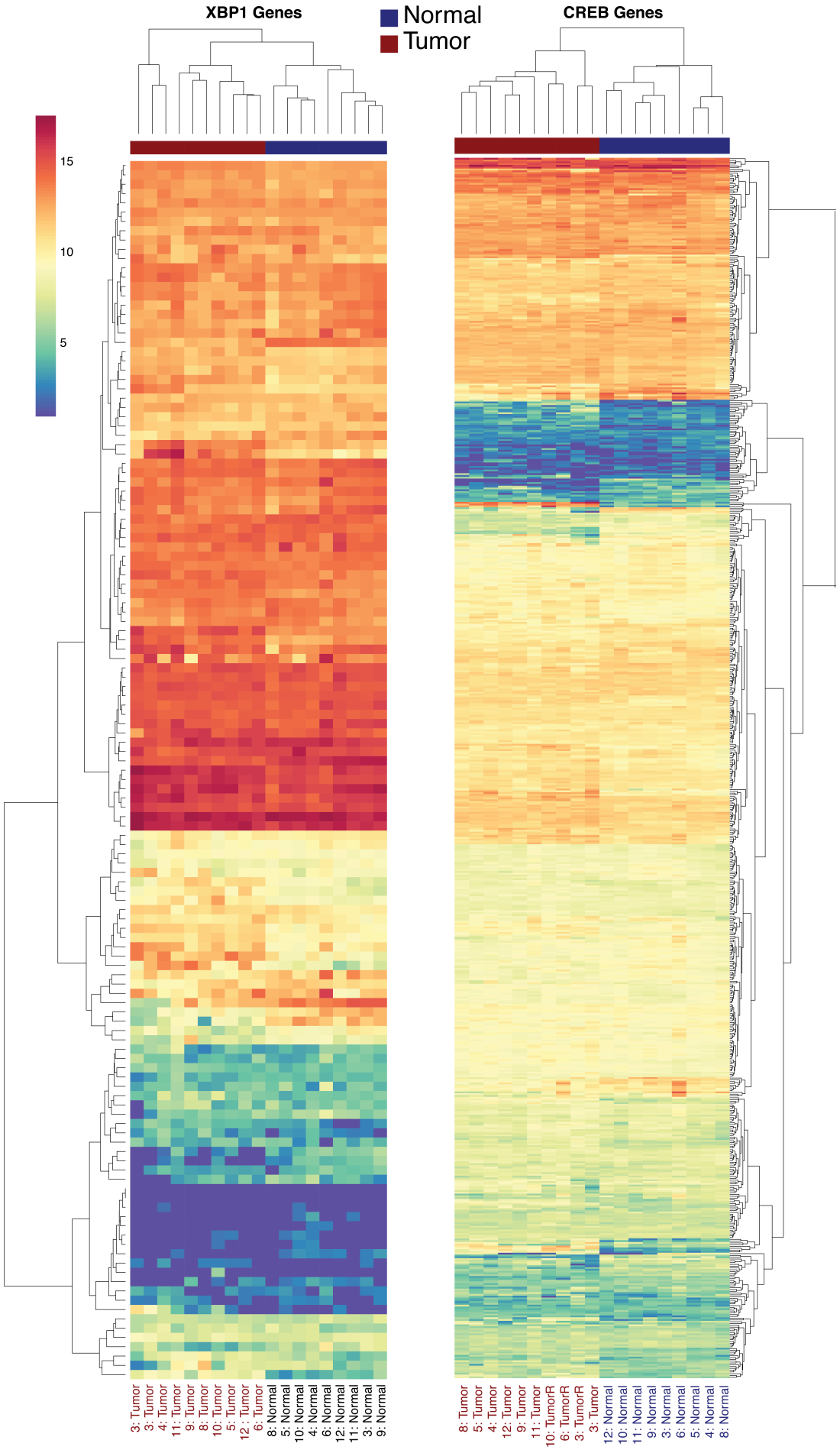
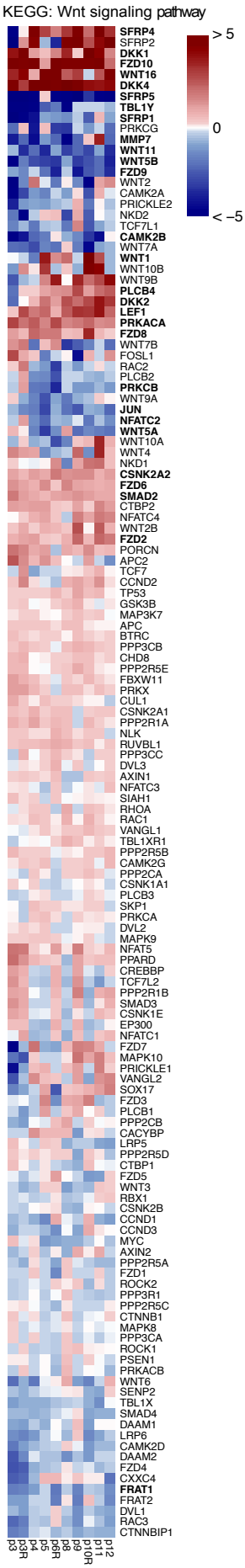
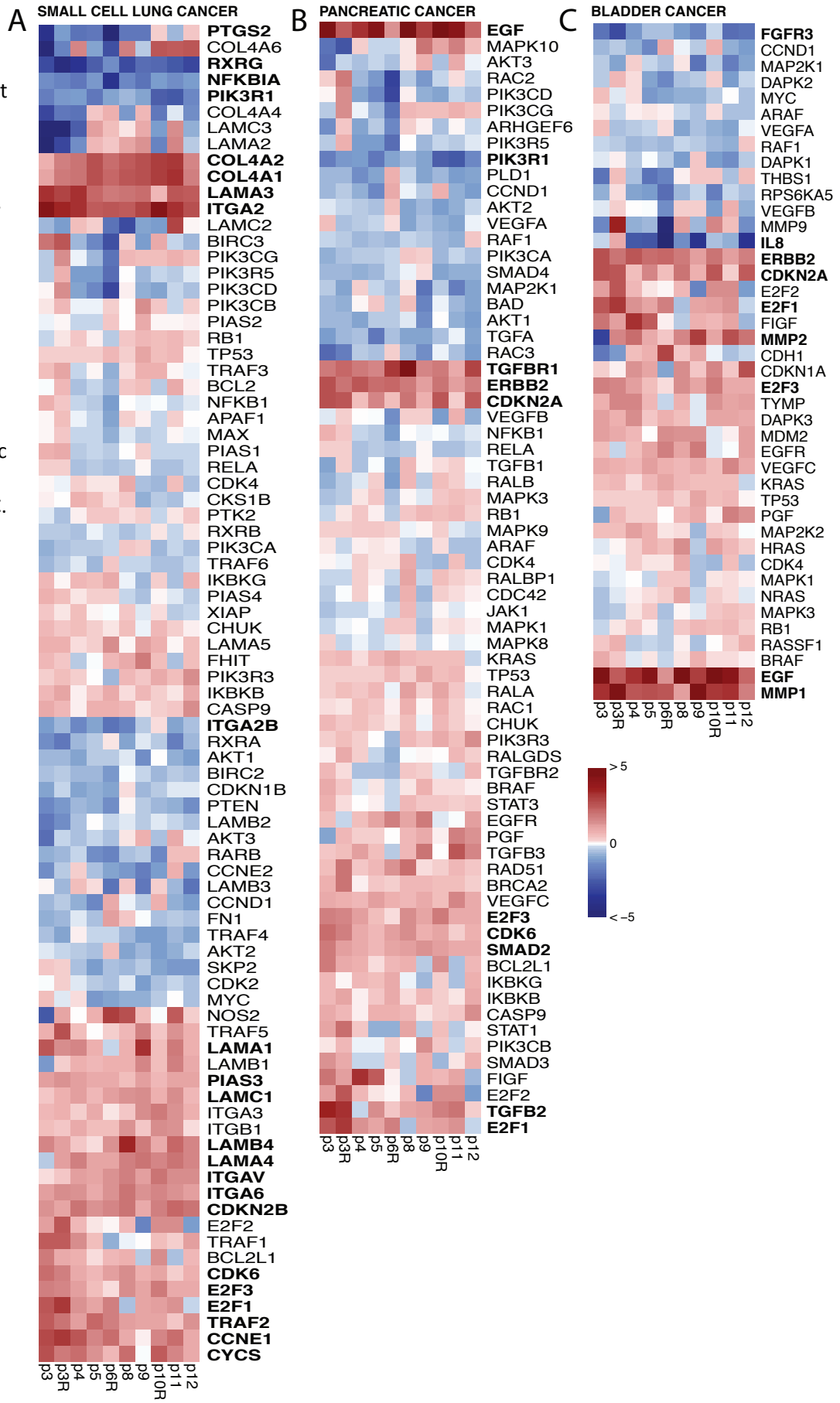



**Supplemental Figure 1: Gene level heat maps for XBP1 and CREB transcription factor target gene sets**
Variance stabilization transformed expression values for genes in XBP1 (left) and CREB (right) transcription factor target gene sets (MSigDB, c3.tft). Gene lists were generated by concatenating and collapsing all gene sets in c3.tft collection designated XBP1 and CREB, respectively. FLHCC (maroon), normal (blue).

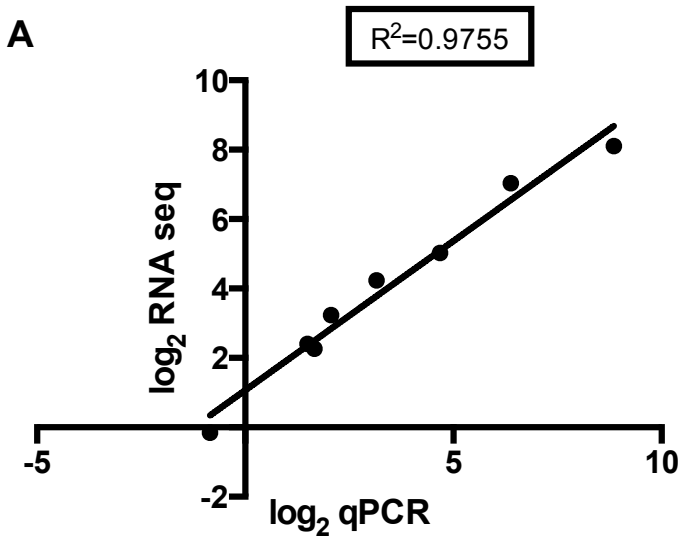
**Supplemental Figure 2: Gene expression differences in FLHCC vs. normal liver tissue for KEGG Wnt signaling pathway gene set.** For genes in KEGG Wnt signaling pathway gene set, $\log_2$ fold-change (patient-matched FL-HCC vs. normal liver) expression is plotted with heatmap color scale. Genes significantly differentially expressed (FDR 0.01, $\log_2$ fold-change > 1) are indicated in **BOLD**.

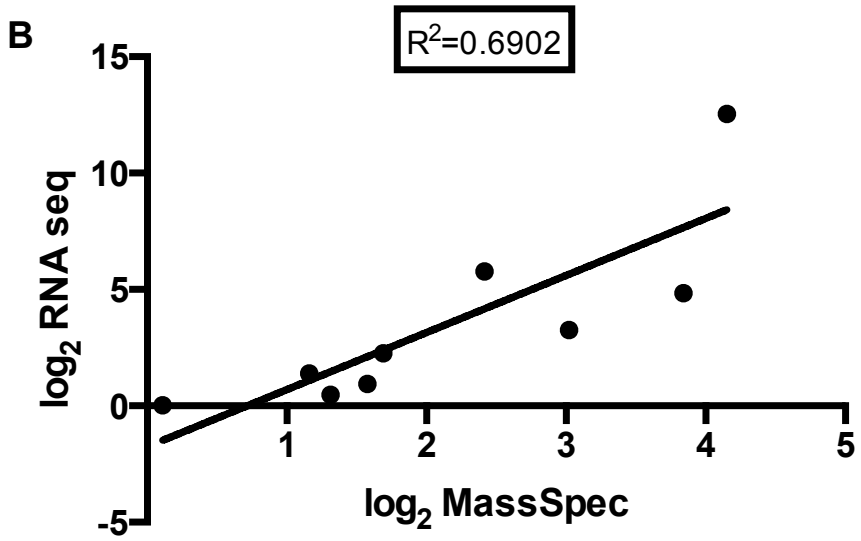


**Supplemental Figure 3**. Gene expression differences in FLHCC vs. normal liver tissue for select KEGG pathway cancer gene sets. For all genes in each collection, $\log_2$ fold-change (patient-matched FLHCC vs. normal liver) expression is plotted with heatmap color scale. Genes significantly differentially expressed (FDR 0.01, $\log_2$ fold-change > 1) are indicated in **BOLD**. A. Small Cell Lung Cancer (KEGG, GSVA adjusted p value = 0.045), B. Pancreatic Cancer (KEGG, GSVA adjusted p value = 0.046), C. Bladder Cancer (KEGG, GSVA adjusted p value = 0.003).



**Supplemental Figure 4: A.** The transcriptional changes as assayed by RNA-seq (n=10) were correlated with transcriptional changes as assayed by qPCR as shown in Fig 6A (n= 5-8; error bars=SD). Scatter plot showing the correlation of the results ($R^2$=0.98). **B.** Transcriptional changes as assayed by RNA-seq (n=10) were correlated with changes in the proteome as assayed by mass spectrometry (n=4) as shown in Figure 6B. Scatter plot showing the correlation of the results ($R^2$=0.68).



**Excel Spreadsheet:**

**Data Set 1, Differentially expressed protein-coding genes, FLHCC vs. normal tissue:** DESeq2 (6) was used with transcript annotations from GENCODE v74 to examine protein-coding genes in FLHCC versus adjacent normal tissue. Using an FDR threshold of 0.01 and a fold-change threshold of 2, we detected 3439 protein-coding genes differentially expressed (1408 upregulated, 2031 downregulated).

**Data Set 2, Canonical Pathway gene sets with positive enrichment:** Gene set variation analysis (GSVA) was used to identify significantly enriched pathway gene sets (7). Among these sets of "Canonical Pathways" in the Molecular Signatures Database (Broad institute, c2.cp), we identified 205 pathway gene sets positively enriched in FLHCC vs. normal (adj P val <= 0.05).

**Data Set 3, Canonical Pathway gene sets with negative enrichment:** Gene set variation analysis (GSVA) was used to identify significantly enriched pathway gene sets Among these sets of "Canonical Pathways" in the Molecular Signatures Database (Broad institute, c2.cp), we identified 159 pathway gene sets negatively enriched in FLHCC vs. normal (adj P val <= 0.05).

**Data Set 4: Differences in gene expression changes: FLHCC vs HCC, tumor vs. normal.**

Differential expression analysis of the differences in FLHCC (tumor vs. normal) to differences in HCC (tumor vs. normal). Using an FDR threshold of 0.01 and a fold-change threshold of 2, we detected 3708 protein-coding genes as differentially induced or repressed between tumor types.

**Supplemental Table 1 Differentially expressed collagen genes in FLHCC vs adjacent normal tissue.** FDR 0.01, $\log_2$fold-change ≥ 1 or ≤ -1.

**Supplemental Table 2 Differentially expressed fibronectin genes in FLHCC vs adjacent normal tissue.** FDR 0.01, $\log_2$fold-change ≥ 1 or ≤ -1.

**Supplemental Table 3: Differentially expressed keratin genes in FLHCC vs adjacent normal tissue.** FDR 0.01, $\log_2$fold-change ≥ 1 or ≤ -1.

**Supplemental Table 4: Differentially expressed cell-cell interactions genes in FLHCC vs adjacent normal tissue.** FDR 0.01, $\log_2$fold-change ≥ 1 or ≤ -1.)

**Supplemental Table 5: Transcription factor target gene sets (MSigDB, c3.tft) with positive enrichment.** GSVA analysis, adj P val ≤0.05**.**

**Supplemental Table 6: Transcription factor target gene sets (MSigDB, c3.tft) with negative enrichment.** GSVA analysis, adj P val ≤ 0.05**.**

**Supplemental Table 7: Differential expression of NRG2 in FLHCC vs adjacent normal tissue in nine tumor samples** GSVA analysis, adj P val ≤ 0.05**.**

**Supplemental Table 8: Differentially expressed Solute Transporter genes in FLHCC vs. normal tissue.** GSVA analysis, adj P val ≤ 0.05**.**

**Supplement Table 9: Different expressed *wnt* signaling pathway genes in FLHCC vs. adjacent normal tissue** GSVA analysis, adj P val ≤ 0.05**.**

**Supplemental Table 10: Transcription factors increased by more than 2-fold** adj P val ≤ 0.02

**Supplemental Table 11: Transcription factors decreased by more than 2-fold** adj P val ≤ 0.02

**Supplemental Table 12: Transcripts differentially expressed in FLHCC correlated with Kegg Cancer Pathways sets** Among gene sets from the "Canonical Pathways" collection in the Molecular Signatures Database (Broad institute, c2.cp), found to be differentially enriched (GSVA, FDR 0.05) in FL-HCC versus normal tissue were three "cancer sets" from the KEGG collection: bladder cancer, pancreatic cancer and small cell lung cancer.

**Supplemental Table 13: Differential expression of breast cancer associated genes in FLHCC vs adjacent normal tissue.**

**Supplemental Table 14: Comparison with previous reports on FLHCC**. Previous studies of proteomics or transcriptomics of FLHCC have previously reported candidates altered in FHLCC. These previous reports were compared with the results of the gene expression profiles in this study.

**Supplemental Table 15: Primers used for qPCR.**

**Supplemental Table 1 Differentially expressed collagen genes in FLHCC vs adjacent normal tissue.** FDR 0.01, $log_2$fold-change ≥ 1 or ≤ -1

| Gene | Name | $\Delta Log_2$ | pAdj |
|---|---|---|---|
| collagen, type I, alpha 1 | COL1A1 | 3.13 | 9.11E-08 |
| collagen, type I, alpha 2 | COL1A2 | 2.51 | 8.55E-06 |
| collagen, type III, alpha 1 | COL3A1 | 1.47 | 2.22E-02 |
| collagen, type IV, alpha 1 | COL4A1 | 2.61 | 1.07E-35 |
| collagen, type IV, alpha 2 | COL4A2 | 2.51 | 2.36E-27 |
| collagen, type V, alpha 1 | COL5A1 | 1.72 | 6.47E-04 |
| collagen, type V, alpha 2 | COL5A2 | 1.45 | 4.88E-03 |
| collagen, type V, alpha 3 | COL5A3 | 1.42 | 1.37E-07 |
| collagen, type VI, alpha 3 | COL6A3 | 1.69 | 1.67E-04 |
| collagen, type VI, alpha 5 | COL6A5 | 3.46 | 2.56E+04 |
| collagen, type VIII, alpha 1 | COL8A1 | 3.35 | 3.85E-07 |
| collagen, type IX, alpha 1 | COL9A1 | 2.78 | 2.03E-05 |
| collagen, type X, alpha 1 | COL10A1 | 4.39 | 7.88E-09 |
| collagen, type XI, alpha 1 | COL11A1 | 6.95 | 1.05E-32 |
| collagen, type XV, alpha 1 | COL15A1 | 4.12 | 1.44E-28 |
| collagen, type XVII, alpha 1 | COL17A1 | 2.27 | 6.04E-04 |
| collagen, type XXII, alpha 1 | COL22A1 | 2.32 | 6.76E-06 |

**Supplemental Table 2 Differentially expressed fibronectin genes in FLHCC vs adjacent normal tissue.** FDR 0.01, $log_2$fold-change ≥ 1 or ≤ -1.

| Name | Gene ID | $\Delta Log_2$ | pAdj |
|---|---|---|---|
| fibronectin 1 | FN1 | -0.24 | 3.88E-01 |
| fibronectin leucine rich transmembrane protein 1 | FLRT1 | -2.69 | 2.57E-03 |
| fibronectin leucine rich transmembrane protein 2 | FLRT2 | -0.21 | 8.20E-01 |
| fibronectin leucine rich transmembrane protein 3 | FLRT3 | 0.95 | 1.79E-02 |
| fibronectin type III and ankyrin repeat domains 1 | FANK1 | 0.88 | 3.18E-02 |
| fibronectin type III and SPRY domain containing 1 | FSD1 | -0.99 | 5.50E-02 |
| fibronectin type III and SPRY domain containing 1-like | FSD1L | 1.34 | 8.22E-12 |
| fibronectin type III and SPRY domain containing 2 | FSD2 | -1.19 | 1.13E-01 |
| fibronectin type III domain containing 1 | FNDC1 | 2.64 | 2.90E-04 |
| fibronectin type III domain containing 3A | FNDC3A | 1.22 | 6.53E-06 |
| fibronectin type III domain containing 3B | FNDC3B | -0.35 | 2.72E-02 |
| fibronectin type III domain containing 4 | FNDC4 | 0.57 | 1.11E-02 |
| fibronectin type III domain containing 5 | FNDC5 | -3.73 | 2.20E-09 |
| fibronectin type III domain containing 7 | FNDC7 | 0.73 | 1.85E-01 |
| fibronectin type III domain containing 8 | FNDC8 | 0.56 | NA |
| fibronectin type III domain containing 9 | FNDC9 | 1.86 | 1.77E-01 |

**Supplemental Table 3: Differentially expressed keratin genes in FLHCC vs adjacent normal tissue.** FDR 0.01, $log_2$fold-change ≥ 1 or ≤ -1

| name | Gene | $\Delta Log_2$ | pAdj |
|---|---|---|---|
| keratin 1 | KRT1 | -3.15 | 6.56E-04 |
| keratin 19 | KRT19 | -2.71 | 9.49E-04 |
| keratin 222 | KRT222 | 2.44 | 7.48E-14 |
| keratin 7 | KRT7 | 4.08 | 5.95E-10 |
| keratin 72 | KRT72 | -2.61 | 9.80E-03 |
| keratin 73 | KRT73 | -3.10 | 7.82E-03 |
| keratin 81 | KRT81 | 3.43 | 2.90E-04 |
| keratin 83 | KRT83 | 4.08 | 1.31E-02 |
| keratin 86 | KRT86 | 5.02 | 8.65E-15 |

**Supplemental Table 4: Differentially expressed cell-cell interactions genes in FLHCC vs adjacent normal tissue.** FDR 0.01, $log_2$fold-change ≥ 1 or ≤ -1.)

| Gene | Name | $\Delta Log_2$ | Padj |
|---|---|---|---|
| gap junction protein, gamma 1, 45kDa | GJC1 | 2.38 | 1.59E-31 |
| gap junction protein, alpha 5, 40kDa | GJA5 | 2.41 | 4.92E-12 |
| integrin, alpha 7 | ITGA7 | 2.30 | 1.54E-16 |
| integrin, alpha 5 | ITGAV | 1.36 | 1.99E-12 |
| roundabout, axon guidance receptor, homolog 1 | ROBO1 | 1.30 | 2.03E-06 |
| slit homolog 2 (Drosophila) | SLIT2 | 1.88 | 1.31E-08 |
| jagged 1 | JAG1 | 1.19 | 9.31E-07 |
| Cadherin-13 | CDH13 | 2.90 | 6.27E-25 |
| Cluster of Differentiation 90 | THY1 | 3.07 | 2.33E-18 |

**Supplemental Table 5: Transcription factor target gene sets (MSigDB, c3.tft) with positive enrichment.** GSVA analysis, adj P val ≤ 0.05**.**

| Gene sets | logFC | AveExpr | t | P.Value | adj.P.Val | B | FC | FC base 10 |
|---|---|---|---|---|---|---|---|---|
| V$HTF_01 | 0.597 | -0.011 | 6.706 | 2.10E-11 | 1.29E-08 | 15.487 | 1.51 | 3.95 |
| CGGAARNGGCNG_UNKNOWN | 0.468 | -0.030 | 5.256 | 1.50E-07 | 2.31E-05 | 7.017 | 1.38 | 2.93 |
| V$EVI1_01 | 0.424 | 0.021 | 4.764 | 1.92E-06 | 2.36E-04 | 4.613 | 1.34 | 2.65 |
| V$MEF2_04 | 0.405 | 0.020 | 4.556 | 5.28E-06 | 5.19E-04 | 3.664 | 1.32 | 2.54 |
| SNACANNNYSYAGA_UNKNOWN | 0.403 | -0.051 | 4.532 | 5.91E-06 | 5.19E-04 | 3.558 | 1.32 | 2.53 |
| CYTAGCAAY_UNKNOWN | 0.398 | -0.039 | 4.471 | 7.85E-06 | 6.03E-04 | 3.292 | 1.32 | 2.50 |
| YRTCANNRCGC_UNKNOWN | 0.373 | -0.051 | 4.194 | 2.76E-05 | 1.70E-03 | 2.119 | 1.30 | 2.36 |
| V$PAX3_01 | 0.363 | -0.031 | 4.082 | 4.49E-05 | 2.51E-03 | 1.667 | 1.29 | 2.31 |
| GAANYNYGACNY_UNKNOWN | 0.358 | -0.036 | 4.027 | 5.70E-05 | 2.92E-03 | 1.447 | 1.28 | 2.28 |
| V$AR_03 | 0.352 | 0.007 | 3.962 | 7.47E-05 | 3.10E-03 | 1.196 | 1.28 | 2.25 |
| V$AP1_Q6_01 | 0.352 | -0.003 | 3.954 | 7.75E-05 | 3.10E-03 | 1.163 | 1.28 | 2.25 |
| V$XBP1_01 | 0.350 | -0.058 | 3.931 | 8.53E-05 | 3.10E-03 | 1.075 | 1.27 | 2.24 |
| TMTCGCGANR_UNKNOWN | 0.350 | -0.045 | 3.929 | 8.58E-05 | 3.10E-03 | 1.068 | 1.27 | 2.24 |
| V$HSF1_01 | 0.347 | -0.001 | 3.902 | 9.60E-05 | 3.28E-03 | 0.965 | 1.27 | 2.22 |
| CRGAARNNNNCGA_UNKNOWN | 0.343 | -0.068 | 3.859 | 1.14E-04 | 3.65E-03 | 0.804 | 1.27 | 2.20 |
| V$TCF11MAFG_01 | 0.342 | -0.037 | 3.850 | 1.19E-04 | 3.65E-03 | 0.767 | 1.27 | 2.20 |
| V$PAX4_03 | 0.337 | 0.004 | 3.788 | 1.53E-04 | 4.40E-03 | 0.536 | 1.26 | 2.17 |
| GGARNTKYCCA_UNKNOWN | 0.336 | -0.014 | 3.780 | 1.58E-04 | 4.40E-03 | 0.508 | 1.26 | 2.17 |
| V$HOXA3_01 | 0.326 | -0.047 | 3.663 | 2.50E-04 | 6.68E-03 | 0.083 | 1.25 | 2.12 |
| V$ELK1_02 | 0.320 | -0.044 | 3.602 | 3.17E-04 | 7.51E-03 | -0.133 | 1.25 | 2.09 |
| V$TAXCREB_02 | 0.320 | 0.007 | 3.602 | 3.18E-04 | 7.51E-03 | -0.136 | 1.25 | 2.09 |
| V$ATF1_Q6 | 0.319 | -0.022 | 3.588 | 3.34E-04 | 7.60E-03 | -0.182 | 1.25 | 2.09 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| KRCTCNNNNMANAGC_UNKNOWN | 0.317 | -0.036 | 3.559 | 3.74E-04 | 7.82E-03 | -0.284 | 1.25 | 2.07 |
| YGTCCTTGR_UNKNOWN | 0.314 | -0.042 | 3.525 | 4.25E-04 | 7.82E-03 | -0.401 | 1.24 | 2.06 |
| V$E2F_Q6 | 0.312 | -0.084 | 3.508 | 4.53E-04 | 7.88E-03 | -0.459 | 1.24 | 2.05 |
| SGCGSSAAA_V$E2F1DP2_01 | 0.312 | -0.104 | 3.503 | 4.62E-04 | 7.88E-03 | -0.478 | 1.24 | 2.05 |
| TCCCRNNRTGC_UNKNOWN | 0.310 | -0.048 | 3.487 | 4.91E-04 | 8.15E-03 | -0.533 | 1.24 | 2.04 |
| V$AP1_Q6 | 0.308 | -0.017 | 3.459 | 5.45E-04 | 8.81E-03 | -0.628 | 1.24 | 2.03 |
| RYTGCNNRGNAAC_V$MIF1_01 | 0.306 | -0.050 | 3.435 | 5.95E-04 | 9.37E-03 | -0.708 | 1.24 | 2.02 |
| SCGGAAGY_V$ELK1_02 | 0.302 | -0.041 | 3.392 | 6.96E-04 | 1.07E-02 | -0.850 | 1.23 | 2.00 |
| V$AP1FJ_Q2 | 0.295 | -0.016 | 3.317 | 9.13E-04 | 1.37E-02 | -1.097 | 1.23 | 1.97 |
| TGACGTCA_V$ATF3_Q6 | 0.283 | -0.047 | 3.182 | 1.47E-03 | 2.14E-02 | -1.525 | 1.22 | 1.92 |
| V$AP1_01 | 0.282 | -0.012 | 3.176 | 1.50E-03 | 2.14E-02 | -1.545 | 1.22 | 1.92 |
| V$CREBP1CJUN_01 | 0.282 | -0.045 | 3.167 | 1.54E-03 | 2.15E-02 | -1.571 | 1.22 | 1.91 |
| V$NRF2_Q4 | 0.280 | -0.043 | 3.144 | 1.67E-03 | 2.19E-02 | -1.643 | 1.21 | 1.90 |
| V$NRF1_Q6 | 0.278 | -0.033 | 3.128 | 1.76E-03 | 2.25E-02 | -1.690 | 1.21 | 1.90 |
| V$GATA2_01 | 0.276 | -0.041 | 3.106 | 1.90E-03 | 2.38E-02 | -1.758 | 1.21 | 1.89 |
| V$MIF1_01 | 0.276 | -0.039 | 3.099 | 1.94E-03 | 2.39E-02 | -1.778 | 1.21 | 1.89 |
| V$NFY_Q6_01 | 0.273 | -0.060 | 3.071 | 2.14E-03 | 2.56E-02 | -1.865 | 1.21 | 1.88 |
| V$E2F1DP1_01 | 0.272 | -0.100 | 3.056 | 2.25E-03 | 2.56E-02 | -1.909 | 1.21 | 1.87 |
| V$E2F1DP2_01 | 0.272 | -0.100 | 3.056 | 2.25E-03 | 2.56E-02 | -1.909 | 1.21 | 1.87 |
| V$E2F4DP2_01 | 0.272 | -0.100 | 3.056 | 2.25E-03 | 2.56E-02 | -1.909 | 1.21 | 1.87 |
| CCGNMNNTNACG_UNKNOWN | 0.271 | -0.079 | 3.048 | 2.31E-03 | 2.58E-02 | -1.933 | 1.21 | 1.87 |
| MCAATNNNNNGCG_UNKNOWN | 0.269 | 0.000 | 3.018 | 2.55E-03 | 2.74E-02 | -2.020 | 1.20 | 1.86 |
| V$GABP_B | 0.267 | -0.054 | 3.003 | 2.68E-03 | 2.84E-02 | -2.066 | 1.20 | 1.85 |
| V$PAX3_B | 0.266 | -0.024 | 2.990 | 2.79E-03 | 2.90E-02 | -2.102 | 1.20 | 1.85 |
| V$E2F4DP1_01 | 0.266 | -0.101 | 2.986 | 2.83E-03 | 2.90E-02 | -2.116 | 1.20 | 1.84 |
| V$E2F_01 | 0.263 | -0.064 | 2.953 | 3.16E-03 | 3.09E-02 | -2.212 | 1.20 | 1.83 |
| TGASTMAGC_V$NFE2_01 | 0.262 | -0.032 | 2.949 | 3.20E-03 | 3.09E-02 | -2.222 | 1.20 | 1.83 |
| RCGCANGCGY_V$NRF1_Q6 | 0.262 | -0.037 | 2.945 | 3.24E-03 | 3.09E-02 | -2.234 | 1.20 | 1.83 |
| V$STAT1_02 | 0.262 | -0.057 | 2.941 | 3.28E-03 | 3.09E-02 | -2.247 | 1.20 | 1.83 |
| CGTSACG_V$PAX3_B | 0.261 | -0.028 | 2.936 | 3.33E-03 | 3.09E-02 | -2.259 | 1.20 | 1.82 |
| GCTNWTTGK_UNKNOWN | 0.261 | -0.020 | 2.936 | 3.33E-03 | 3.09E-02 | -2.260 | 1.20 | 1.82 |
| AAGWWRNYGGC_UNKNOWN | 0.261 | -0.032 | 2.932 | 3.38E-03 | 3.09E-02 | -2.271 | 1.20 | 1.82 |
| TGACCTTG_V$SF1_Q6 | 0.260 | -0.065 | 2.924 | 3.47E-03 | 3.13E-02 | -2.295 | 1.20 | 1.82 |
| V$NFE2_01 | 0.259 | -0.030 | 2.912 | 3.60E-03 | 3.14E-02 | -2.329 | 1.20 | 1.82 |
| V$TITF1_Q3 | 0.259 | -0.020 | 2.911 | 3.61E-03 | 3.14E-02 | -2.331 | 1.20 | 1.82 |
| V$RFX1_01 | 0.259 | -0.057 | 2.909 | 3.63E-03 | 3.14E-02 | -2.336 | 1.20 | 1.81 |
| CACGTG_V$MYC_Q2 | 0.257 | -0.024 | 2.890 | 3.86E-03 | 3.23E-02 | -2.390 | 1.20 | 1.81 |
| MGGAAGTG_V$GABP_B | 0.257 | -0.069 | 2.886 | 3.91E-03 | 3.23E-02 | -2.401 | 1.19 | 1.81 |
| V$HEN1_01 | 0.256 | 0.030 | 2.880 | 3.98E-03 | 3.23E-02 | -2.419 | 1.19 | 1.80 |
| V$ROAZ_01 | 0.256 | -0.084 | 2.876 | 4.04E-03 | 3.23E-02 | -2.431 | 1.19 | 1.80 |
| V$E2F_Q3 | 0.256 | -0.078 | 2.875 | 4.05E-03 | 3.23E-02 | -2.434 | 1.19 | 1.80 |
| V$ARNT_02 | 0.255 | -0.041 | 2.870 | 4.12E-03 | 3.24E-02 | -2.448 | 1.19 | 1.80 |
| V$COMP1_01 | 0.254 | -0.030 | 2.860 | 4.24E-03 | 3.25E-02 | -2.474 | 1.19 | 1.80 |
| AACWWCAANK_UNKNOWN | 0.254 | -0.007 | 2.860 | 4.24E-03 | 3.25E-02 | -2.474 | 1.19 | 1.80 |
| V$USF_Q6_01 | 0.253 | -0.043 | 2.841 | 4.51E-03 | 3.38E-02 | -2.528 | 1.19 | 1.79 |
| V$NRF2_01 | 0.251 | -0.054 | 2.820 | 4.81E-03 | 3.52E-02 | -2.585 | 1.19 | 1.78 |
| V$MZF1_01 | 0.250 | -0.011 | 2.806 | 5.02E-03 | 3.63E-02 | -2.624 | 1.19 | 1.78 |
| V$WHN_B | 0.249 | -0.003 | 2.797 | 5.16E-03 | 3.68E-02 | -2.648 | 1.19 | 1.77 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| V$E2F1_Q3 | 0.247 | -0.078 | 2.782 | 5.42E-03 | 3.82E-02 | -2.691 | 1.19 | 1.77 |
| AACYNNNNTTCCS_UNKNOWN | 0.245 | -0.032 | 2.750 | 5.97E-03 | 4.12E-02 | -2.775 | 1.18 | 1.76 |
| V$BRN2_01 | 0.244 | -0.031 | 2.743 | 6.10E-03 | 4.16E-02 | -2.796 | 1.18 | 1.75 |
| V$SREBP1_01 | 0.241 | -0.065 | 2.714 | 6.65E-03 | 4.49E-02 | -2.871 | 1.18 | 1.74 |
| V$AP1_Q2 | 0.241 | -0.031 | 2.704 | 6.85E-03 | 4.57E-02 | -2.898 | 1.18 | 1.74 |
| GCCATNTTG_V$YY1_Q6 | 0.240 | -0.051 | 2.695 | 7.04E-03 | 4.63E-02 | -2.921 | 1.18 | 1.74 |
| V$E2F1_Q6 | 0.240 | -0.082 | 2.693 | 7.09E-03 | 4.63E-02 | -2.928 | 1.18 | 1.74 |
| TTCYRGAA_UNKNOWN | 0.237 | -0.005 | 2.668 | 7.64E-03 | 4.94E-02 | -2.993 | 1.18 | 1.73 |
| RNGTGGGC_UNKNOWN | 0.236 | -0.015 | 2.655 | 7.93E-03 | 4.98E-02 | -3.026 | 1.18 | 1.72 |
| GTGACGY_V$E4F1_Q6 | 0.236 | -0.034 | 2.655 | 7.93E-03 | 4.98E-02 | -3.026 | 1.18 | 1.72 |
| V$SF1_Q6 | 0.236 | -0.022 | 2.655 | 7.95E-03 | 4.98E-02 | -3.028 | 1.18 | 1.72 |

**Supplemental Table 6 Transcription factor target gene sets (MSigDB, c3.tft) with negative enrichment.**
GSVA analysis, adj P val ≤ 0.05**.**

| | logFC | AveExpr | t | P.Value | adj.P.Val | B |
|---|---|---|---|---|---|---|
| RGTTAMWNATT_V$HNF1_01 | -0.529 | 0.014 | -5.945 | 2.85E-09 | 8.74E-07 | 10.788 |
| V$STAT3_01 | -0.483 | -0.030 | -5.430 | 5.75E-08 | 1.18E-05 | 7.929 |
| V$HNF1_01 | -0.375 | 0.040 | -4.218 | 2.49E-05 | 1.70E-03 | 2.217 |
| V$ALX4_01 | -0.351 | 0.028 | -3.944 | 8.07E-05 | 3.10E-03 | 1.126 |
| V$LMO2COM_02 | -0.321 | 0.029 | -3.605 | 3.14E-04 | 7.51E-03 | -0.124 |
| CAGNYGKNAAA_UNKNOWN | -0.317 | -0.047 | -3.568 | 3.62E-04 | 7.82E-03 | -0.254 |
| V$HNF1_C | -0.315 | 0.037 | -3.544 | 3.95E-04 | 7.82E-03 | -0.335 |
| V$HNF1_Q6 | -0.314 | 0.052 | -3.529 | 4.18E-04 | 7.82E-03 | -0.387 |
| V$PAX8_01 | -0.313 | 0.004 | -3.523 | 4.28E-04 | 7.82E-03 | -0.408 |
| V$PAX5_02 | -0.313 | -0.038 | -3.520 | 4.33E-04 | 7.82E-03 | -0.418 |
| V$HNF4_Q6 | -0.281 | -0.034 | -3.159 | 1.59E-03 | 2.16E-02 | -1.595 |
| V$CEBP_Q3 | -0.280 | 0.003 | -3.147 | 1.65E-03 | 2.19E-02 | -1.633 |
| YRCCAKNNGNCGC_UNKNOWN | -0.269 | 0.022 | -3.025 | 2.49E-03 | 2.73E-02 | -2.000 |
| V$AHRARNT_02 | -0.256 | -0.031 | -2.878 | 4.01E-03 | 3.23E-02 | -2.425 |
| V$RORA2_01 | -0.253 | -0.017 | -2.842 | 4.49E-03 | 3.38E-02 | -2.525 |
| V$GATA_C | -0.252 | -0.012 | -2.831 | 4.65E-03 | 3.44E-02 | -2.556 |
| V$HNF4_01 | -0.246 | -0.013 | -2.766 | 5.69E-03 | 3.97E-02 | -2.734 |

**Supplemental Table 7: Differential expression of NRG2 in FLHCC vs adjacent normal tissue in nine tumor samples** GSVA analysis, adj P val ≤ 0.05**.**

| PATIENT | $\Delta Log_2$ |
|---|---|
| 3 | 4.49 |
| 4 | 4.42 |
| 5 | 5.85 |
| 6 | 5.63 |
| 8 | 5.48 |
| 9 | 5.58 |
| 10 | 6.20 |
| 11 | 6.41 |
| 12 | 4.24 |

**Supplemental Table 8: Differentially expressed Solute Transporter genes in FLHCC vs. normal tissue.** GSVA analysis, adj P val ≤ 0.05**.**

| gene_id | description | Δlog2 | padj | function |
|---|---|---|---|---|
| SLC16A14 | solute carrier family 16, member 14 | 7.43 | 3.69E-142 | monocarboxylic acid |
| SLC6A3 | solute carrier family 6 (neurotransmitter transporter), member 3 | 6.31 | 1.22E-07 | dopamine transporter which is a member of the sodium- and chloride-dependent neurotransmitter transporter family |
| SLC6A11 | solute carrier family 6 (neurotransmitter transporter), member 11 | 5.66 | 1.66E-09 | GABA transporter phosphorylated by PKA |
| SLC22A12 | solute carrier family 22 (organic anion/urate transporter), member 12 | 5.60 | 4.11E-05 | Urate transporter found in the kidney |
| SLC7A11 | solute carrier family 7 (anionic amino acid transporter light chain, xc- system), member 11 | 5.00 | 8.38E-51 | heteromeric Na(+)-independent anionic amino acid transport system highly specific for cystine and glutamate |
| SLC22A11 | solute carrier family 22 (organic anion/urate transporter), member 11 | 3.59 | 3.91E-08 | sodium-independent transport and excretion of organic anions in kidney and placenta |
| SLC6A17 | solute carrier family 6 (neutral amino acid transporter), member 17 | 3.22 | 8.19E-07 | specific transporters for neurotransmitters, amino acids, and osmolytes like betaine, taurine, and creatine |
| SLC6A8 | solute carrier family 6 (neurotransmitter transporter), member 8 | 3.14 | 1.11E-14 | Sodium- and chloride-dependent creatine transporter 1 |
| SLC7A5 | solute carrier family 7 (amino acid transporter light chain, L system), member 5 | 2.67 | 1.23E-17 | large neutral amino acids transporter small subunit 1 |
| SLC7A1 | solute carrier family 7 (cationic amino acid transporter, y+ system), member 1 | 2.44 | 6.88E-14 | Cationic amino acid transporter |
| SLC38A1 | solute carrier family 38, member 1 | 2.39 | 1.04E-32 | Sodium-coupled neutral amino acid transporter 1 - essential roles in the uptake of nutrients, production of energy, chemical metabolism, detoxification |
| SLC22A15 | solute carrier family 22, member 15 | 2.31 | 2.63E-07 | Probably transports organic cations By similarity |
| SLC35G2 | solute carrier family 35, member G2 | 2.29 | 1.22E-51 | nothing known |
| SLC5A6 | solute carrier family 5 (sodium/multivitamin and iodide cotransporter), member 6 | 2.03 | 5.64E-08 | Sodium-dependent multivitamin transporter |
| SLC7A6 | solute carrier family 7 (amino acid transporter light chain, y+L system), member 6 | 2.02 | 3.76E-17 | cationic amino acid transporter, y+ system or Y+L amino acid transporter 2 |
| SLC35C1 | solute carrier family 35 (GDP-fucose transporter), member C1 | 2.00 | 9.89E-14 | GDP-fucose transporter 1 |
| SLC52A3 | solute carrier family 52 (riboflavin transporter), member 3 | 1.94 | 5.15E-04 | Riboflavin transport |
| SLC22A31 | solute carrier family 22, member 31 | 1.81 | 1.12E-02 | Organic anion transporter |
| SLC4A11 | solute carrier family 4, sodium borate transporter, member 11 | 1.78 | 2.06E-04 | bicarbonate transporters |
| SLC6A6 | solute carrier family 6 (neurotransmitter transporter), member 6 | 1.76 | 1.50E-04 | Sodium- and chloride-dependent taurine transporter |

| | | | | |
|---|---|---|---|---|
| SLC2A5 | solute carrier family 2 (facilitated glucose/fructose transporter), member 5 | 1.73 | 3.13E-04 | fructose transporter |
| SLC2A1 | solute carrier family 2 (facilitated glucose transporter), member 1 | 1.62 | 1.83E-12 | Facilitative glucose transporter |
| SLC51B | solute carrier family 51, beta subunit | 1.47 | 1.25E-02 | bile acid export from enterocytes into portal blood; transport radiolabeled estrone-3-sulfate |
| SLC44A3 | solute carrier family 44, member 3 | 1.44 | 5.40E-09 | similar to choline transporters |
| SLC7A2 | solute carrier family 7 (cationic amino acid transporter, y+ system), member 2 | 1.37 | 7.81E-04 | Low-affinity, high capacity permease involved in the transport of the cationic amino acids (arginine, lysine and ornithine). |
| SLC25A12 | solute carrier family 25 (aspartate/glutamate carrier), member 12 | 1.29 | 8.18E-06 | Catalyzes the calcium-dependent exchange of cytoplasmic glutamate with mitochondrial aspartate across the mitochondrial inner membrane. May have a function in the urea cycle |
| SLC45A1 | solute carrier family 45, member 1 | 1.25 | 3.29E-04 | Mediates glucose uptake along the pH gradient. |
| SLC6A9 | solute carrier family 6 (neurotransmitter transporter, glycine), member 9 | 1.18 | 6.59E-04 | Sodium- and chloride-dependent glycine transporter 1 |
| SLC27A4 | solute carrier family 27 (fatty acid transporter), member 4 | 1.18 | 2.30E-05 | Long-chain fatty acid transport protein 4 |
| SLC16A11 | solute carrier family 16, member 11 | 1.17 | 9.64E-03 | Proton-linked monocarboxylate transporter. Hepatic lipid metabolism |
| SLC22A5 | solute carrier family 22 (organic cation/carnitine transporter), member 5 | 1.15 | 2.57E-06 | high affinity carnitine transporter |
| SLC35B4 | solute carrier family 35 (UDP-xylose/UDP-N-acetylglucosamine transporter), member B4 | 1.15 | 9.32E-08 | UDP-xylose and UDP-N-acetylglucosamine transporter that moves sugars into Golgi |
| SLC25A15 | solute carrier family 25 (mitochondrial carrier; ornithine transporter) member 15 | 1.14 | 5.27E-04 | Transports ornithine from the cytosol into the mitochondria in the urea cycle |
| SLC26A7 | solute carrier family 26 (anion exchanger), member 7 | 1.13 | 2.72E-05 | Anion exchange transporter |
| SLC35E4 | solute carrier family 35, member E4 | 1.12 | 1.91E-05 | A drug-metabolite transporter |
| SLC22A23 | solute carrier family 22, member 23 | 1.09 | 8.72E-05 | A member of a family of organic ion transporters |
| SLC36A1 | solute carrier family 36 (proton/amino acid symporter), member 1 | 1.04 | 9.68E-07 | Transport of small amino acids (e.g. glycine, alanine and proline) |

**Supplemental Table 9: Different expressed *wnt* signaling pathway genes in FLHCC vs. adjacent normal tissue**

GSVA analysis, adj P val ≤ 0.05**.**

| Gene | ∆log2 | padj | Description |
|---|---|---|---|
| DKK4 | 6.52 | 3.99E-19 | dickkopf WNT signaling pathway inhibitor 4 |
| FZD10 | 6.13 | 3.08E-20 | frizzled family receptor 10 |
| WNT16 | 4.40 | 3.04E-03 | wingless-type MMTV integration site family, member 16 |
| Wnt1 | 3.64 | 1.55E-01 | wingless-type MMTV integration site family, member 1 |
| SFRP2 | 3.25 | 5.84E-03 | secreted frizzled-related protein 2 |
| LEF1 | 2.66 | 7.57E-12 | lymphoid enhancer-binding factor 1 |
| DKK1 | 2.45 | 8.83E-05 | dickkopf WNT signaling pathway inhibitor 1 |
| PRKACA | 2.23 | 6.55E-23 | protein kinase, cAMP-dependent, catalytic, alpha |
| DKK2 | 2.17 | 5.34E-05 | dickkopf WNT signaling pathway inhibitor 2 |
| WNT9B | 1.91 | 2.46E-02 | wingless-type MMTV integration site family, member 9B |
| FZD8 | 1.46 | 3.98E-06 | frizzled family receptor 8 |
| PLCB4 | 1.34 | 1.02E-03 | phospholipase C, beta 4 |
| FZD2 | 1.32 | 4.98E-04 | frizzled family receptor 2 |
| CSNK2A2 | 1.31 | 5.68E-15 | casein kinase 2, alpha prime polypeptide |
| SMAD2 | 1.17 | 3.32E-08 | SMAD family member 2 |
| FZD6 | 1.10 | 1.09E-14 | frizzled family receptor 6 |
| WNT2B | 1.02 | 2.36E-03 | wingless-type MMTV integration site family, member 2B |
| CTBP2 | 0.99 | 6.11E-10 | C-terminal binding protein 2 |
| NFATC4 | 0.93 | 6.79E-05 | nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 4 |

Supplemental Table 10: Transcription factors $log_2$fold-change ≥ 1 ($p<0.02$)

| Transcription Factor | Gene name | $\Delta Log_2$ | $P_{adj}$ |
|---|---|---|---|
| cAMP responsive element binding protein 3-like 1 | CREB3L1 | 4.85 | 3.12E-27 |
| Cellular repressor of E1A-stimulated genes 2 | CREG2 | 3.72 | 3.31E-05 |
| E2F transcription factor 1 | E2F1 | 1.28 | 5.47E-05 |
| E2F transcription factor 3 | E2F3 | 1.19 | 1.06E-08 |
| E2F transcription factor 5, p130-binding | E2F5 | 1.74 | 3.16E-18 |
| E2F transcription factor 7 | E2F7 | 1.67 | 1.10E-04 |
| E2F transcription factor 8 | E2F8 | 2.07 | 4.26E-07 |
| early B-cell factor 2 | EBF2 | 3.22 | 2.99E-08 |
| ETS Variant gene 1 | ETV1 | 1.85 | 3.35E-10 |
| forkhead box C1 | FOXC1 | 1.31 | 1.39E-05 |
| forkhead box C2 (MFH-1, mesenchyme forkhead 1) | FOXC2 | 1.78 | 1.26E-02 |
| forkhead box E1 (thyroid transcription factor 2) | FoxE1 | 4.2 | 2.3E-03 |
| forkhead box F2 | FoxF2 | 3.39 | 4.33E-06 |
| forkhead box L1 | FoxL1 | 2.13 | 4.46E-05 |
| forkhead box Q1 | FoxQ1 | 3.91 | 8.95E-15 |
| forkhead box S1 | FoxS1 | 2.01 | 4.63E-05 |
| general transcription factor IIE, polypeptide 1, alpha 56kDa | GTF2E1 | 1.01 | 1.29E-05 |
| homeobox D1 | HOXD1 | 3.69 | 3.84e-03 |
| homeobox D3 | HOXD3 | 2.58 | 2.42E-06 |
| homeobox D9 | HOXD9 | 3.62 | 1.18E-07 |
| heat shock transcription factor 4 | HSF4 | 1.63 | 8.46E-09 |
| Iroquois homeobox protein 3 | IRX3 | 3.23 | 2.66E-05 |
| iroquois homeobox 5 | IRX5 | 4.69 | 5.11E-06 |
| maternal embryonic leucine zipper kinase | MELK | 2.51 | 6.65E-15 |
| neuronal PAS domain protein 2 | NPAS2 | 2.75 | 5.49E-11 |
| Paired-like homeodomain transcription factor 1 | PITX1 | 4.69 | 2.29E-10 |
| PR domain containing 7 | PRDM7 | 2.45 | 0.0012 |
| paired related homeobox 1 | PRRX1 | 3.12 | 4.36E-09 |
| runt-related transcription factor 1 | RUNX1 | 1.12 | 4.10E-4 |
| Scm-like with four mbt domains 2 | SFMBT2 | 2.53 | 1.10E-10 |
| SIX homeobox 1 | SIX1 | 6.96 | 8.50E-09 |
| SIX homeobox 2 | SIX2 | 5.10 | 9.19E-3 |
| SIX homeobox 4 | SIX4 | 2.45 | 6.71E-07 |
| SRY (sex determining region Y)-box 11 | SOX11 | 5.86 | 2.68E-07 |
| Sp6 transcription factor | SP6 | 1.52 | 2.32e-04 |
| SPOC domain containing 1 | SPOCD1 | 2.76 | 5.32E-08 |
| transcription factor 23 | TCF23 | 4.33 | 3.00E-09 |
| transducin-like enhancer of split 6 (E(sp1) homolog, Drosophila) | TLE6 | 3.44 | 5.71E-35 |
| ventral anterior homeobox 2 | VAX2 | 3.38 | 1.46E-05 |
| visual system homeobox 1 | VSX1 | 3.23 | 2.73E-07 |
| zinc finger, MYND-type containing 15 [Source:HGNC Symbol;Acc:20997] | ZMYND15 | 1.95 | 1.18E-14 |
| zinc finger protein 233 | ZNF233 | 3.19 | 9.52E-17 |
| zinc finger protein 703 | ZNF703 | 3.58 | 3.24E-24 |

Supplemental Table 11: Transcription factors that are decreased by > 2-fold (p<0.02)

| Gene | Gene Name | $\Delta Log_2$ | Padj |
|---|---|---|---|
| activating transcription factor 3 | ATF3 | -1.56 | 1.52E-06 |
| activating transcription factor 5 | ATF5 | -1.55 | 6.485E-04 |
| activating transcription factor 7 interacting protein 2 | ATF7IP2 | -1.18 | 1.42E-09 |
| BTB and CNC homology 1, basic leucine zipper transcription factor 2 | BACH2 | -1.43 | 4.84E-06 |
| E74-like factor 5 (ets domain transcription factor) | ELF5 | -4.33 | 1.55e-4 |
| forkhead box A2 | FOXA2 | -1.11 | 9.57E-06 |
| forkhead box A3 | FOXA3 | -2.28 | 5.28E-16 |
| forkhead box D3 | FOXD3 | -4.47 | 1.09E-03 |
| growth factor independent 1B transcription repressor | GFI1B | -3.79 | 2.47E-03 |
| ripply transcriptional repressor 1 | RIPPLY1 | -1.22 | 5.20E-03 |
| ripply transcriptional repressor 3 | RIPPLY3 | -2.42 | 6.28E-03 |
| Spi-B transcription factor (Spi-1/PU.1 related) | SPIB | -1.94 | 0.01049661 |
| Spi-C transcription factor (Spi-1/PU.1 related) | SPIC | -4.00 | 1.26E-09 |
| transcription elongation factor A (SII), 3 | TCEA3 | -2.24 | 4.89E-06 |
| transcription elongation factor A (SII)-like 2 | TCEAL2 | -3.96 | 0.001997562 |
| transcription elongation factor A (SII)-like 7 | TCEAL7 | -1.34 | 0.016655587 |
| transcription factor 21 | TCF21 | -2.23 | 2.23E-03 |
| transcription factor 7-like 1 (T-cell specific, HMG-box) | TCF7L1 | -1.05 | 6.36E-03 |

**Supplemental Table 12: Transcripts differentially expressed in FLHCC correlated with Kegg Cancer Pathways sets**

Among gene sets from the "Canonical Pathways" collection in the Molecular Signatures Database (Broad institute, c2.cp), found to be differentially enriched (GSVA, FDR 0.05) in FL-HCC versus normal tissue were three "cancer sets" from the KEGG collection: bladder cancer, pancreatic cancer and small cell lung cancer.

| Pathway | logFC | Ave Expr | t | P.Value | Adj P.Val | B |
|---|---|---|---|---|---|---|
| KEGG_BLADDER_CANCER | 0.47 | -0.03 | 3.88 | 0.00 | 0.00 | -0.26 |
| KEGG_PANCREATIC_CANCER | 0.34 | -0.04 | 2.67 | 0.01 | 0.04 | -3.43 |
| KEGG_SMALL_CELL_LUNG_CANCER | 0.32 | -0.01 | 2.62 | 0.01 | 0.04 | -3.54 |
| KEGG_PROSTATE_CANCER | 0.28 | -0.03 | 2.30 | 0.03 | 0.08 | -4.23 |
| KEGG_CHRONIC_MYELOID_LEUKEMIA | 0.27 | -0.06 | 2.12 | 0.04 | 0.10 | -4.60 |
| KEGG_GLIOMA | 0.20 | -0.05 | 1.64 | 0.11 | 0.22 | -5.44 |
| KEGG_PATHWAYS_IN_CANCER | 0.19 | -0.04 | 1.61 | 0.12 | 0.22 | -5.49 |
| KEGG_ENDOMETRIAL_CANCER | 0.19 | -0.08 | 1.56 | 0.13 | 0.24 | -5.56 |
| KEGG_COLORECTAL_CANCER | 0.14 | -0.06 | 1.08 | 0.29 | 0.44 | -6.18 |
| KEGG_NON_SMALL_CELL_LUNG_CANCER | 0.13 | -0.07 | 1.01 | 0.32 | 0.47 | -6.25 |
| KEGG_MELANOMA | 0.12 | -0.04 | 0.98 | 0.33 | 0.48 | -6.28 |
| KEGG_THYROID_CANCER | 0.12 | -0.08 | 0.91 | 0.37 | 0.52 | -6.34 |
| KEGG_RENAL_CELL_CARCINOMA | 0.08 | -0.05 | 0.65 | 0.52 | 0.65 | -6.54 |
| KEGG_BASAL_CELL_CARCINOMA | 0.05 | 0.02 | 0.42 | 0.68 | 0.77 | -6.67 |
| KEGG_ACUTE_MYELOID_LEUKEMIA | 0.00 | -0.03 | -0.02 | 0.98 | 0.99 | -6.76 |

## Supplemental Table 13: Transcripts increased in expression in FLHCC that have been implicated in breast cancer.

| Gene | Gene Name | $DLog_2$ | Padj | notes |
|---|---|---|---|---|
| v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 | ERBB2 | 2.15 | 6.44E-34 | Increased in 30% of breast cancers (14) |
| ZNF703 | ZNF703 | 3.58 | 3.24E-24 | a luminal B breast cancer oncogene (15) |
| Aurora Kinase A | AURKA | 2.65 | 3.52E-18 | Determinant of tamoxifen resistance through phosphorylation of ERα (16) |
| breast cancer anti-estrogen resistance 1 | BCAR1 | 1.00 | 7.67E-08 | Important for transformation of ERBB2 in breast cancer (17) |
| p21-Activated Kinase 3 | PAK3 | 7.91 | 2.84E-141 | PAK3 responsible for phosphorylation of ERK (18) |
| cytochrome P450, family 19, subfamily A, polypeptide 1 (aromatase ) | CYP19A1 | 5.95 | 4.25E-26 | A driver for some forms of breast cancer (19) |
| platelet isoform of phosphofructokinas | PFKP | 3.09 | 8.31E-15 | Drives the proliferation of breast tumors (20) |
| Lactate dehydrogenase B | LDHB | 2.25 | 7.19E-17 | Essential for triple-negative breast cancer (21) |
| Jagged-1 | JAG1 | 1.19 | 9.31E-07 | poor prognosis in breast cancer (22) |
| iroquois homeobox 5 | IRX5 | 4.69 | 5.11E-06 | Increased in breast cancer (23) |
| neuronal PAS domain protein 2 | NPAS2 | 2.75 | 5.49E-11 | Prognostic for breast cancer (24) |
| Paired-like homeodomain transcription factor 1 | PITX1 | 4.69 | 2.29E-10 | Upregulated in ER-positive breast cancer (low in prostate, bladder and colon tumor lines (25) |

## Supplemental Table 14: Comparison with previous reports on FLHCC

| Protein | Gene | $\Delta Log_2$ | pAdj | Reference |
|---|---|---|---|---|
| anterior gradient 2 | AGR2 | 7.77 | 1.27E-37 | Reported increased: (26) |
| CD44 molecule (Indian blood group) | CD44 | NS | NS | Reported increased: (27) |
| CD68 | CD68 | NS | NS | Reported increased: (28) |
| CD99 molecule | CD99 | -0.70 | 4.43E-03 | Reported increased: (29) |
| cyclin-dependent kinase inhibitor 2A | CDKN2A | 1.72 | 5.07E-06 | Reported increased: (30) |
| cytochrome P450, family 19, subfamily A, polypeptide 1 (aromatase – estrogen synthase) | CYP19A1 | 5.95 | 4.25E-26 | Reported increased levels of aromatase (31-34) |
| endothelin 1 | EDN1 | -1.27 | 4.71E-05 | Reported increase: (35) |
| endothelin 3 | EDN3 | NS | NS | Reported increase: (35) |
| Epidermal growth factor receptor | EGFR | .086 | 3.18E-03 | Reported increased in 54% of FLHCC (36); reported increased in 92% (37)and increased in (38) |
| v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 | ERBB2 | 2.15 | 6.44E-34 | |
| fibrinogen alpha chain | FGA | 0.78 | 7.17E-03 | Reported increased: (39) (40) |
| fibrinogen beta chain | FGB | 0.58 | 1.10E-01 | Reported increased: (39) (40) |
| glypican 3 | GPC3 | NS | NS | Reported increased: (41) |
| P21Ras | hras, nras, kras | NS | NS | Reported increased: (42) |
| antigen identified by monoclonal antibody Ki-67 | MKI67 | 2.89 | 5.80E-12 | (30) |
| neurotensin | NTS | 7.55 | 1.67E-26 | Reported increased: (43) (44) (45) |
| proprotein convertase subtilisin/kexin type 1 | PCSK1 | 10.64 | 4.20E-100 | Reported increased: (46) |
| peroxisome proliferator-activated receptor gamma | PPARG | -0.719 | 5.73E-04 | Reported absent: (27) |
| prominin 1 | PROM1 | -2.97 | 3.86E-05 | Reported increased: (27) |
| transcobalamin I (vitamin B12 binding protein, R binder family) | TCN1 | 3.98 | 7.67E-08 | Reported increased: (47) (48) (49) |
| transforming growth factor, beta 1 | TGFB1 | -0.151 | 5.76E-01 | Reported increased: (50) |

## Supplemental Table 15: Primers used for qPCR

| | Forward Primer | Reverse Primer |
|---|---|---|
| PRKACA (exon 8-9) | GCCCTGGGGGTTCTTATCTA | AGCTGAAGTGGGAAGGGAAG |
| DNAJB1 (exon 2-3) | ACCTCCAACAACATTCCAGC | AGTGGGGACGTTCACTGTG |