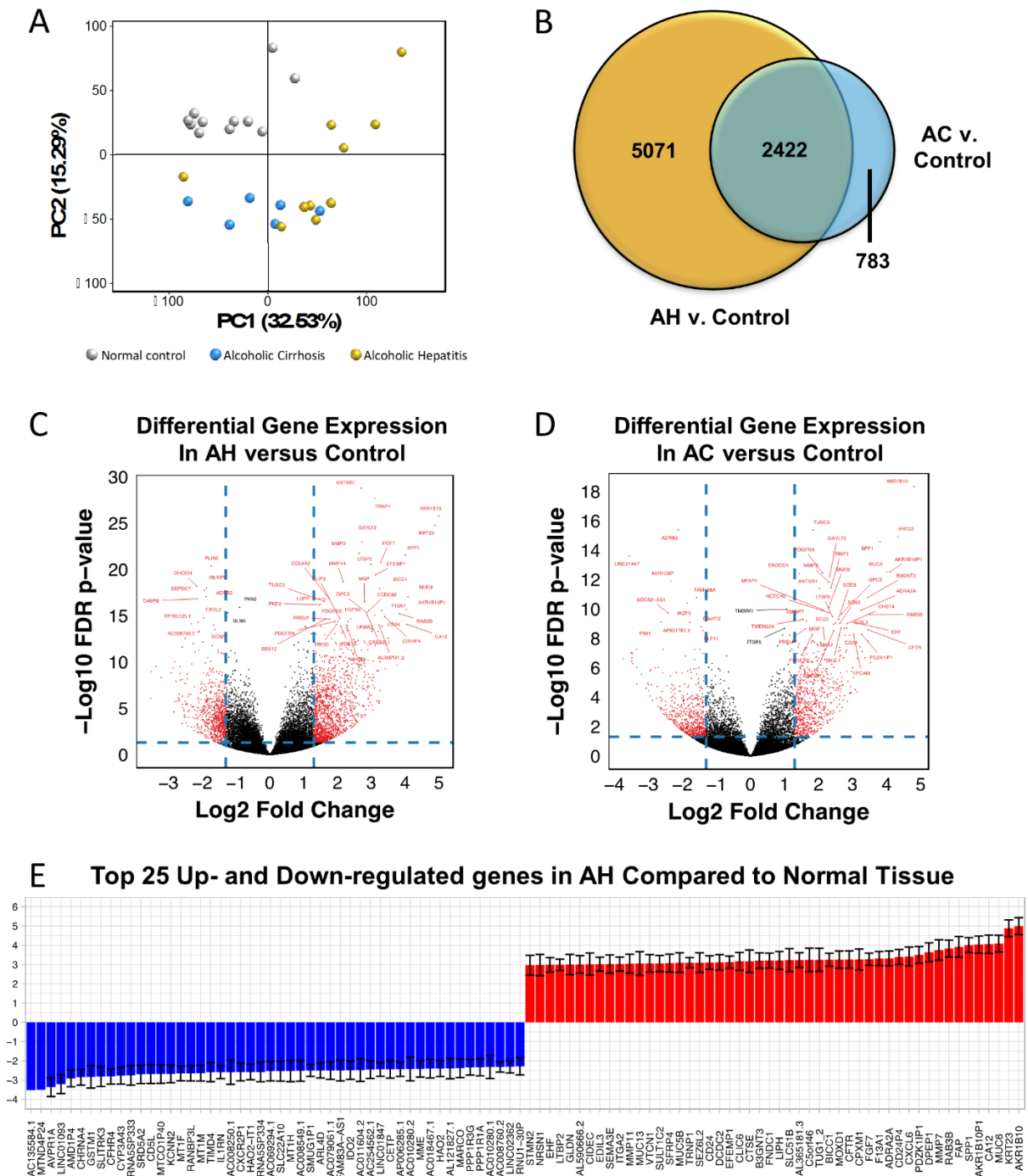


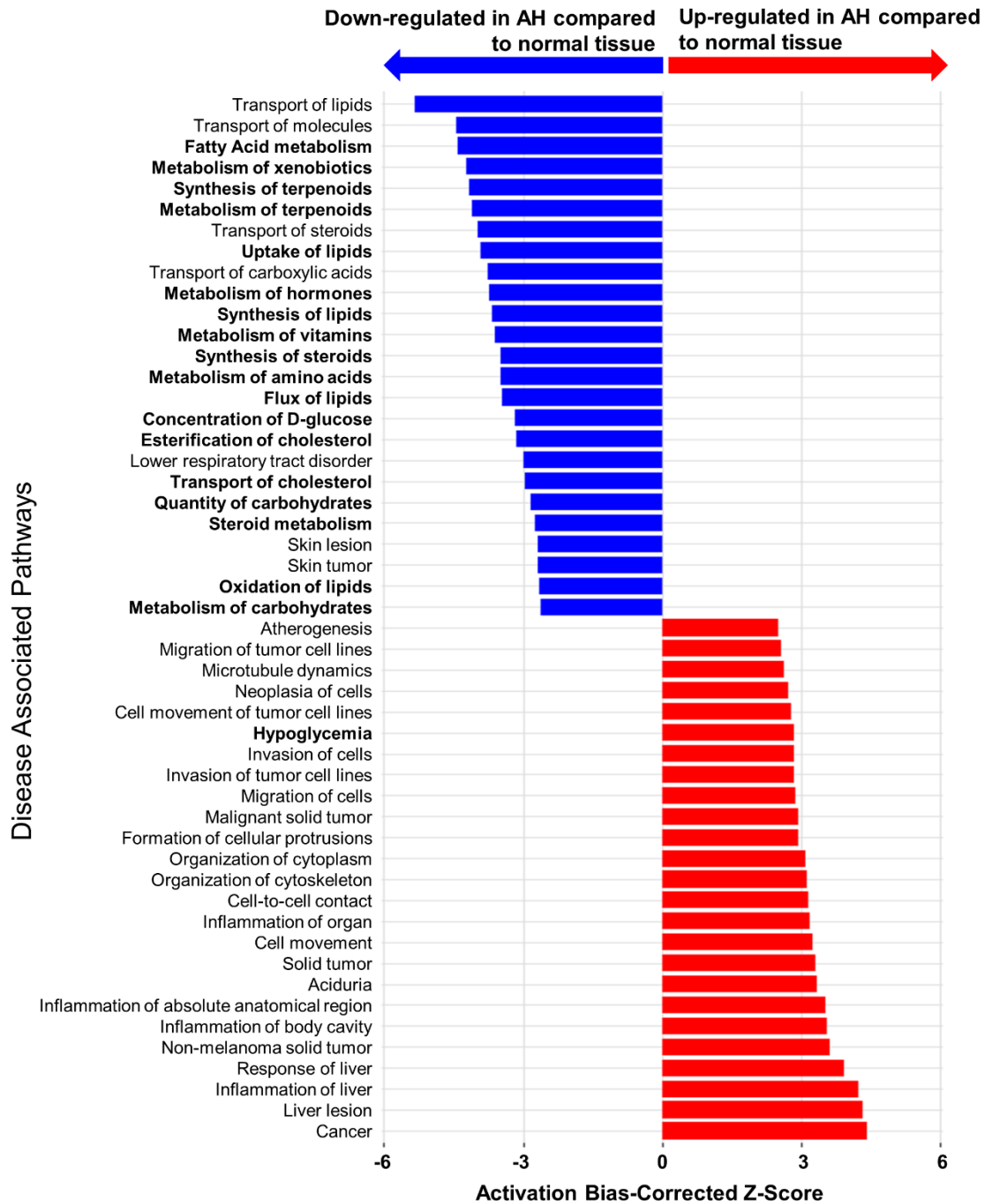
Supplementary Figures



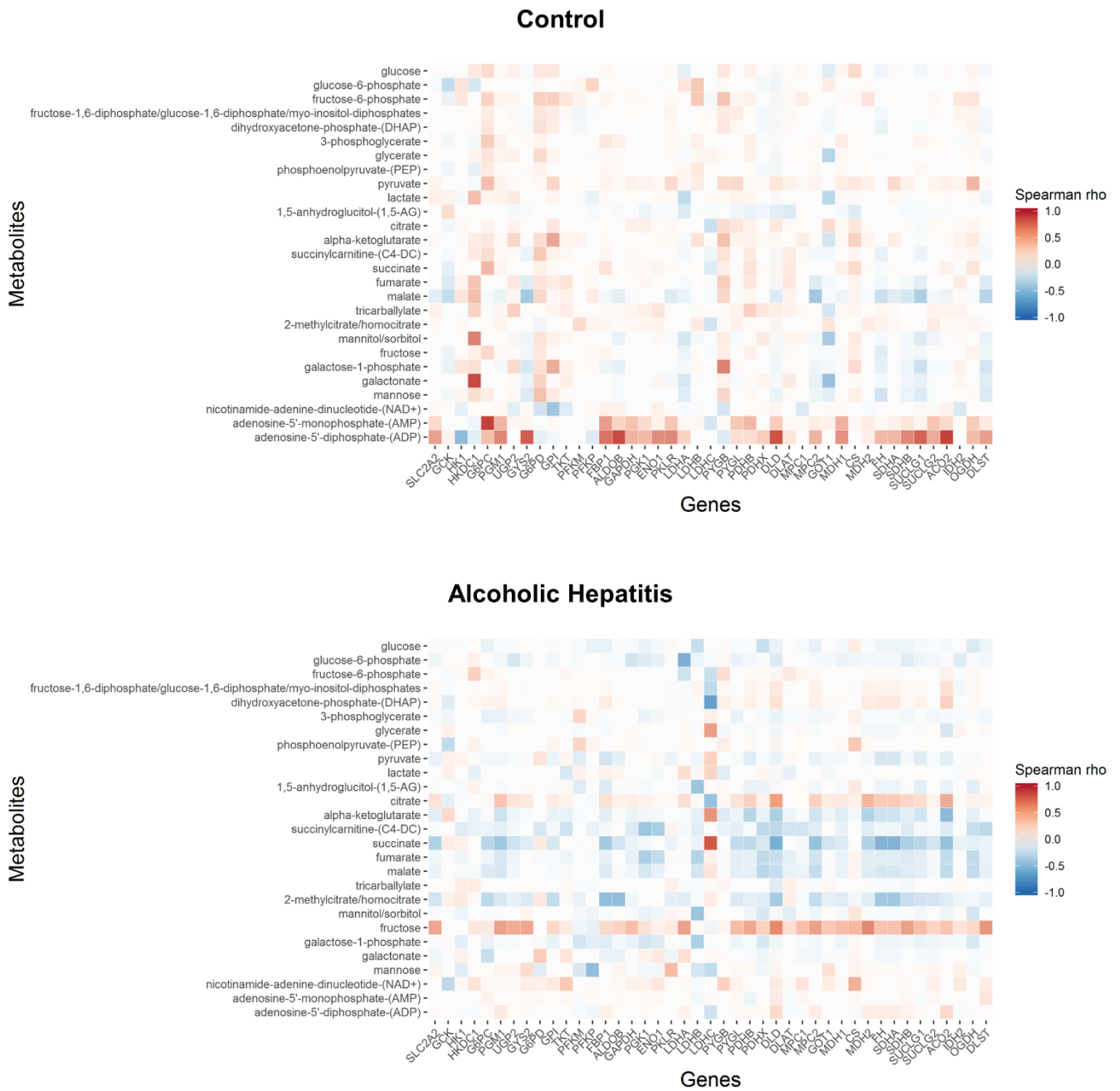
Supplementary Figure 1. The hepatic transcriptome is altered in alcoholic liver disease. Analysis of total RNA sequencing of human liver tissue was performed using the DESeq2 package in R as described in *Materials & Methods*. (A) Plot of the Principle Component Analysis (PCA) of the hepatic transcriptome. (B) Venn diagram showing the total number of transcripts changed in AH versus control (yellow) and alcoholic cirrhosis (AC) versus

control (blue). Overlap shows genes that were changed in both AH and AC compared to control. Volcano plots showing the differential gene expression in (C) AH compared to control tissues and (D) alcoholic cirrhosis compared to control tissues. (E) Top downregulated (blue) and 25 upregulated (red) genes in AH compared to control.

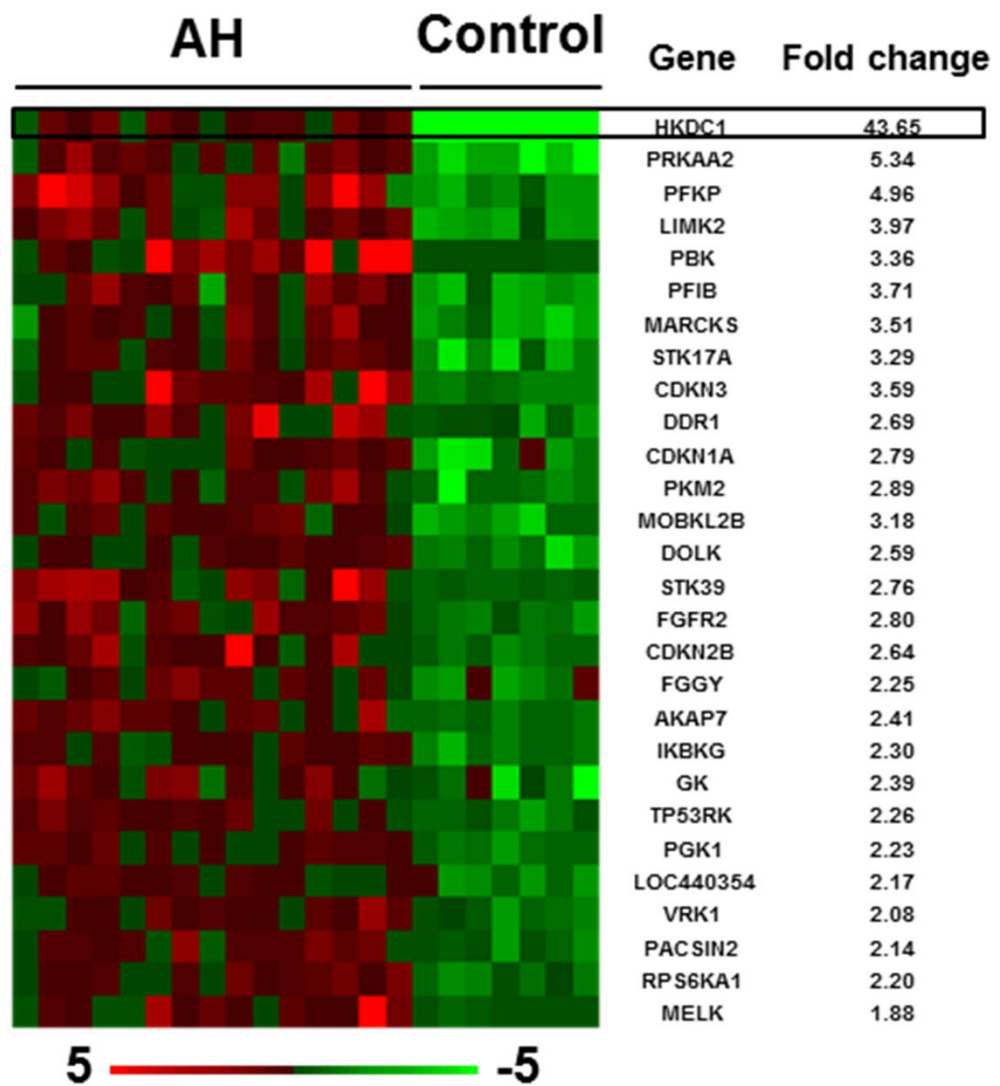
Top 25 Up- and Down-regulated Disease Associated Pathways in AH Compared to Normal Tissue



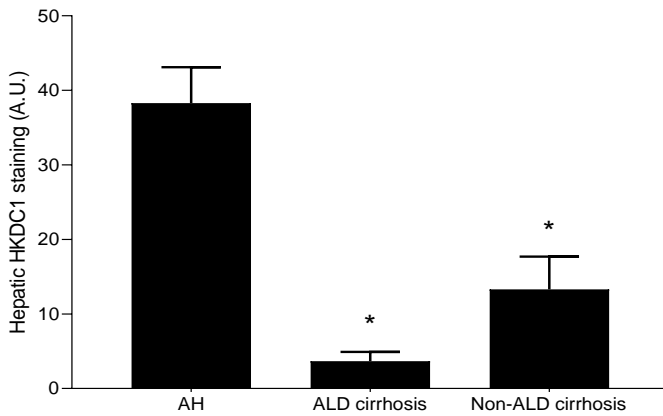
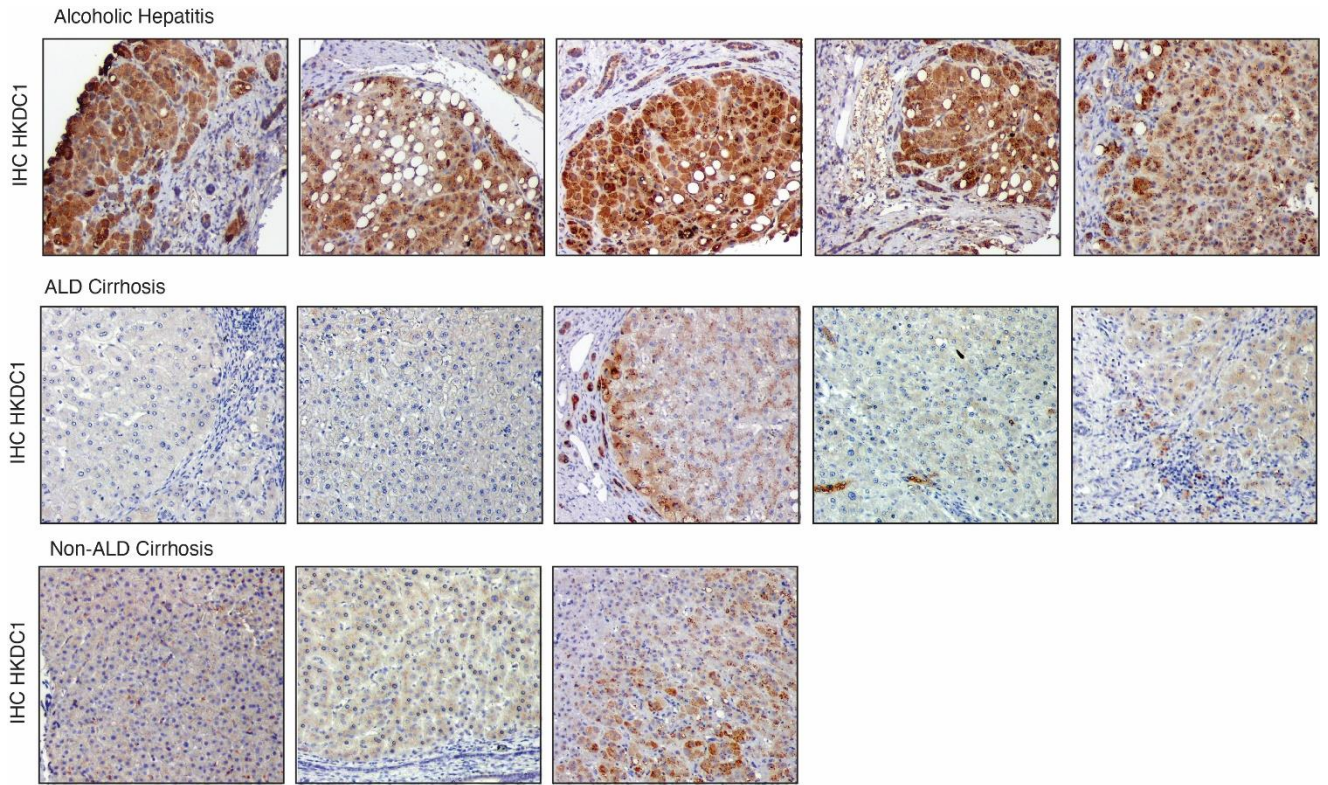
Supplementary Figure 2. Ingenuity pathway analysis of the hepatic transcriptome of alcoholic hepatitis (AH). Ingenuity pathway analysis was performed as described in *Materials and Methods*. The top 25 down-regulated (blue) and up-regulated (red) disease associated pathways identified in AH compared to normal tissue (control) are shown. Data are shown as activate bias-corrected Z-score.



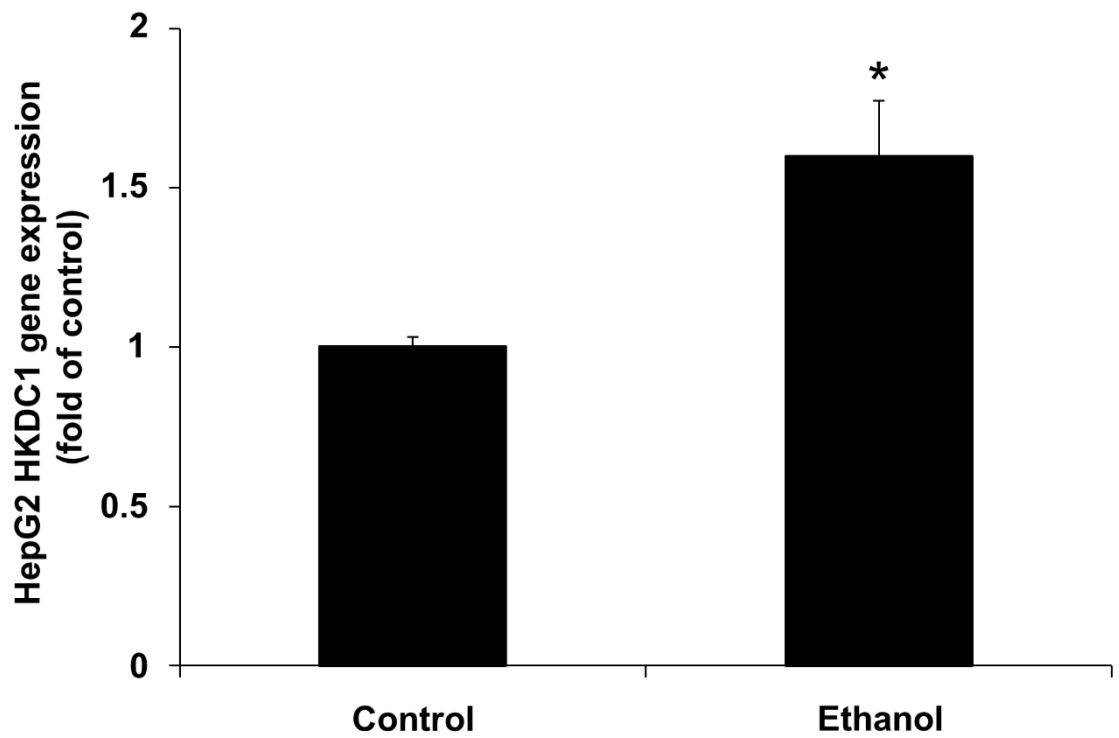
Supplementary Figure 3. Control patient samples (top) show differential correlations between key genes and metabolites involved in energetic processes, such as the TCA cycle, when compared with alcoholic hepatitis patient samples (bottom).



Supplementary Figure 4. Hepatic expression of HKDC1 is increased in alcoholic hepatitis patients. (A) Heatmap showing hierarchical clustering using expression profiles of kinases genes. Distances were measured using Pearson correlation.



Supplementary Figure 5. HKDC1 expression is markedly increased in hepatocytes in alcoholic hepatitis. HKDC1 immunostaining (original magnification, 200X) in livers from patients with alcoholic hepatitis (AH), alcoholic liver disease (ALD) cirrhosis and non-ALD cirrhosis. The intensity of HKDC1 staining was quantified using ImageJ and presented in the bar chart. * $p < 0.05$, AH vs ALD cirrhosis and non-ALD cirrhosis. A. U.: arbitrary units.



Supplementary Figure 6. Ethanol treatment increases HKDC1 gene expression in HepG2 cells. Cells were cultured in the presence or the absence of 15 mM ethanol for 48 hours. Data are representative of 6 different experiments. Data are shown as the mean \pm standard error. * $p < 0.05$ compared to control.

Supplementary Tables

	Normal livers n=11	Cirrhosis n=10	AH n=10
Demographics			
Age - median (IQR)	60(55-71)	51 (41.5-62)	58.5 (31.25-60.5)
Gender - male n (%)	6 (54.5)	6 (60)	6 (60)
Severity scores – median (IQR)			
Child-Pugh	N/A	11 (9.75-12)	12 (10.75-13)
MELD	N/A	25 (23.5-29.5)	29.5 (24.87-35)
ABIC	N/A	N/A	8.68 (7.44-10.21)
Maddrey	N/A	N/A	66.66 (50.4-92.1)
Lille	N/A	N/A	0.83 (0.71-0.9)
Lille response n (%)	N/A	N/A	1(10)
Lab parameters - median (IQR)			
Hemoglobin g/dL	13.5 (12.7-14.15)	8.2 (7.6-11.6)	9.2 (8.9-11.7)
WBC x10 ⁹ /L	6.19 (4.97-8.74)	6.68 (5.30-8.81)	13.25 (7.02-18.22)
Platelets x10 ⁹ /L	153 (135-398.5)	92 (62.5-134.5)	115 (97-161)
AST (U/L)	30 (29-38.5)	71 (41.5-79)	113.5 (91.75-152.5)
ALT (U/L)	27 (20-34)	35 (19.5-43)	41 (26.5-67)
Bilirubin mg/dL	0.6 (0.3-0.8)	7.55 (3.22-11.12)	16.5 (10.22-27.92)
GGT (U/L)	95 (59.5-249.5)	21 (16-51.5)	101 (53-367)
ALP (U/L)	163 (84.5-177)	127 (102-195)	218 (114-260)
Albumin (g/dL)	4 (3.8-4.55)	3.05 (2.42-3.92)	2.5 (2.4-2.65)
Creatinine mg/dL	0.89 (0.7-1.04)	0.9 (0.67-1.21)	0.8 (0.6-1.4)
Sodium (mEq/L)	137 (136-138.5)	134 (125-137)	124.5 (119.25-126.75)
INR	1.1 (1-1.15)	1.65 (1.39-2.37)	2.05 (1.73-3.5)
PT (Quick Index, %)	98 (86-100)	40.5 (34.25-56.75)	34.5 (23.5-43.5)

Supplementary Table 1. Baseline characteristics of patients and controls.

HVPG: Hepatic Venous Pressure Gradient; GI: Gastro Intestinal; SIRS: Systemic Inflammatory Response Syndrome; WBC: White blood count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma Glutamyl Transpeptidase; ALP: Alkaline Phosphatase; INR: International Normalized Ratio; PT: Prothrombin Time

Supplementary Table 2. Metabolites uniquely changed in alcoholic hepatitis compared to control

Biochemical Name	Super Pathway	Sub Pathway	AH vs AC		AH vs Control		AC vs Control	
			FC	P value	FC	P value	FC	P value
betaine	Amino Acid	Glycine, Serine and Threonine Metabolism	1.61	0.0006	1.23	0.0747	1.31	0.1072
N-acetylthreonine	Amino Acid	Glycine, Serine and Threonine Metabolism	1.31	0.0444	0.92	0.8941	1.42	0.0874
N-acetylglutamate	Amino Acid	Glutamate Metabolism	1.22	0.0269	0.96	0.1541	1.28	0.4869
pyroglutamine*	Amino Acid	Glutamate Metabolism	0.47	0.0106	0.89	0.4502	0.53	0.0952
N-acetylhistidine	Amino Acid	Histidine Metabolism	0.51	0.0034	0.72	0.2095	0.71	0.1127
trans-urocanate	Amino Acid	Histidine Metabolism	19.35	0.0420	0.96	0.9556	20.12	0.0577
2-aminoadipate	Amino Acid	Lysine Metabolism	2.81	0.0067	1.24	0.3214	2.28	0.1075
isovalerylcarnitine (C5)	Amino Acid	Leucine, Isoleucine and Valine Metabolism	0.11	0.0045	0.19	0.0578	0.61	0.3851
2-hydroxy-3-methylvalerate	Amino Acid	Leucine, Isoleucine and Valine Metabolism	1.67	0.0061	1.52	0.0730	1.10	0.3844
cystine	Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	1.59	0.0141	1.61	0.1019	0.99	0.4661
N-acetylcitrulline	Amino Acid	Urea cycle; Arginine and Proline Metabolism	1.79	0.0190	1.58	0.0734	1.13	0.6433
acisoga	Amino Acid	Polyamine Metabolism	0.74	0.0451	0.87	0.3674	0.85	0.3193
glutathione, oxidized (GSSG)	Amino Acid	Glutathione Metabolism	0.05	0.0017	1.40	0.0555	0.04	0.2433
5-methylglutathione	Amino Acid	Glutathione Metabolism	0.09	0.0050	2.52	0.1782	0.04	0.1698
cysteinyglycine	Amino Acid	Glutathione Metabolism	0.58	0.0336	0.76	0.3192	0.77	0.3061
5-oxoproline	Amino Acid	Glutathione Metabolism	0.56	0.0031	0.72	0.2075	0.78	0.1071
gamma-glutamylalanine	Peptide	Gamma-glutamyl Amino Acid	0.39	0.0006	0.59	0.0570	0.66	0.1324
gamma-glutamylhistidine	Peptide	Gamma-glutamyl Amino Acid	0.59	0.0146	0.65	0.0852	0.90	0.5274
Ac-Ser-Asp-Lys-Pro-OH	Peptide	Polypeptide	1.74	0.0022	1.28	0.0500	1.36	0.2997
1,5-anhydroglucitol (1,5-AG)	Carbohydrate	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism	0.63	0.0472	0.66	0.2312	0.96	0.4887
pyruvate	Carbohydrate	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism	1.96	0.0070	1.58	0.1295	1.24	0.2721
lactate	Carbohydrate	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism	1.18	0.0078	1.09	0.1342	1.09	0.2813
UDP-glucose	Carbohydrate	Nucleotide Sugar	0.21	0.0281	0.33	0.1849	0.64	0.4381
acetylphosphate	Energy	Oxidative Phosphorylation	0.60	0.0008	0.77	0.0747	0.78	0.1270
3-hydroxybutyryl CoA	Lipid	Fatty Acid Metabolism	0.35	0.0230	0.73	0.6184	0.48	0.1033
5-dodecenolate (12:1n7)	Lipid	Medium Chain Fatty Acid	1.69	0.0206	1.82	0.0736	0.93	0.6654
2-hydroxyadipate	Lipid	Fatty Acid, Dicarboxylate	2.34	0.0233	1.58	0.0845	1.49	0.6530
3-hydroxybutyrylcarnitine (2)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	1.79	0.0077	1.26	0.1123	1.43	0.3201
adipoylcarnitine (C6-DC)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.45	0.0075	0.83	0.5691	0.54	0.0508
arachidonoylcarnitine (C20:4)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	3.86	0.0004	1.91	0.0756	2.02	0.0840
docosahexaenoylcarnitine (C22:6)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	2.05	0.0485	1.11	0.4731	1.84	0.2542
4-hydroxybutyrate (GHB)	Lipid	Fatty Acid, Monohydroxy	1.84	0.0020	1.28	0.1037	1.44	0.1622
glycerophosphoinositol*	Lipid	Phospholipid Metabolism	0.63	0.0476	0.90	0.6327	0.70	0.1707
1-palmitoyl-2-stearoyl-GPC (16:0/18:0)	Lipid	Phosphatidylcholine (PC)	1.37	0.0021	1.12	0.2581	1.22	0.0646
1-palmitoyl-2-oleoyl-GPG (16:0/18:1)	Lipid	Phosphatidylglycerol (PG)	0.71	0.0034	0.90	0.3015	0.80	0.0740
1-palmitoyl-2-arachidonoyl-GPI (16:0/20:4)*	Lipid	Phosphatidylinositol (PI)	0.61	0.0015	0.84	0.1419	0.74	0.1003
2-palmitoleoyl-GPC (16:1)*	Lipid	Lysophospholipid	2.06	0.0153	2.00	0.1075	1.03	0.4683
1-palmitoyl-GPS (16:0)*	Lipid	Lysophospholipid	0.37	0.0162	0.53	0.1241	0.69	0.4383
1-{1-eryl-palmitoyl}-2-palmitoyl-GPC (P-16:0/16:0)	Lipid	Plasmalogen	1.40	0.0027	1.22	0.1191	1.15	0.1702
pregnen-diol disulfate C21H34O8S2*	Lipid	Progesterin Steroids	0.45	0.0272	0.59	0.1783	0.76	0.4424
glycolithocholate sulfate*	Lipid	Secondary Bile Acid Metabolism	0.43	0.0047	0.73	0.0610	0.58	0.3800
glycocholenate sulfate*	Lipid	Secondary Bile Acid Metabolism	0.55	0.0125	0.71	0.2117	0.77	0.2493
allantoin	Nucleotide	Purine Metabolism, (Hypo)Xanthine/Inosine containing	0.42	0.0019	0.65	0.1509	0.64	0.1080
uracil	Nucleotide	Pyrimidine Metabolism, Uracil containing	1.39	0.0182	1.16	0.1557	1.20	0.3959
ascorbate (Vitamin C)	Cofactors and Vitamins	Ascorbate and Aldarate Metabolism	1.61	0.0271	1.37	0.1226	1.18	0.5660
5-methyltetrahydrofolate (5MeTHF)	Cofactors and Vitamins	Folate Metabolism	0.42	0.0332	0.49	0.1052	0.84	0.6767
protoporphyrin IX	Cofactors and Vitamins	Hemoglobin and Porphyrin Metabolism	0.36	0.0029	0.62	0.1424	0.58	0.1489
retinol (Vitamin A)	Cofactors and Vitamins	Vitamin A Metabolism	0.45	0.0129	0.82	0.4046	0.55	0.1256
3-hydroxyhippurate	Xenobiotics	Benzoate Metabolism	0.26	0.0245	0.48	0.3088	0.54	0.2607
4-hydroxyhippurate	Xenobiotics	Benzoate Metabolism	0.80	0.0253	0.53	0.1022	1.50	0.6094
1,7-dimethylurate	Xenobiotics	Xanthine Metabolism	0.14	0.0010	0.44	0.0925	0.31	0.1141
retinal	Xenobiotics	Food Component/Plant	0.13	0.0004	0.43	0.0538	0.31	0.1004
beta-cryptoxanthin	Xenobiotics	Food Component/Plant	0.28	0.0048	0.41	0.1008	0.69	0.2690
2-ketogluconate	Xenobiotics	Food Component/Plant	0.28	0.0021	0.69	0.1245	0.41	0.1396
carotene diol (3)	Xenobiotics	Food Component/Plant	0.38	0.0038	0.57	0.0828	0.68	0.2777
tramadol	Xenobiotics	Drug	142.03	0.0286	12.28	0.2023	11.56	0.4131
O-desmethytramadol	Xenobiotics	Drug	33.84	0.0290	4.23	0.1918	7.99	0.4338
lanthionine	Xenobiotics	Chemical	0.63	0.0209	0.83	0.4473	0.76	0.1541

Supplementary Table 3. Metabolites uniquely changed in alcoholic hepatitis compared to alcoholic cirrhosis

Biochemical Name	Super Pathway	Sub Pathway	AH vs AC		AH vs Control		AC vs Control	
			FC	P value	FC	P value	FC	P value
1-methylimidazoleacetate	Amino Acid	Histidine Metabolism	0.89	0.3485	1.42	0.1251	0.63	0.0242
4-hydroxyphenylpyruvate	Amino Acid	Tyrosine Metabolism	1.11	0.3299	0.51	0.1127	2.17	0.0197
cysteamine	Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	1.57	0.0829	0.91	0.5525	1.72	0.0356
cyano-alanine	Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	0.74	0.1686	2.11	0.0551	0.35	0.0032
proline	Amino Acid	Urea cycle; Arginine and Proline Metabolism	1.02	0.6523	0.86	0.0614	1.20	0.0306
tryptophylglycine	Peptide	Dipeptide	1.39	0.1564	0.40	0.0621	3.46	0.0034
maltose	Carbohydrate	Glycogen Metabolism	0.84	0.6369	0.33	0.0809	2.53	0.0391
palmitoleate (16:1n7)	Lipid	Long Chain Fatty Acid	1.39	0.2155	0.91	0.2100	1.53	0.0242
adrenate (22:4n6)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	1.51	0.1020	0.82	0.2290	1.85	0.0110
2-hydroxybehenate	Lipid	Fatty Acid, Monohydroxy	1.12	0.5043	0.64	0.0914	1.76	0.0299
1-palmitoyl-2-oleoyl-GPE (16:0/18:1)	Lipid	Phosphatidylethanolamine (PE)	0.95	0.5417	1.17	0.0545	0.81	0.0193
1-linoleoyl-2-arachidonoyl-GPE (18:2/20:4)*	Lipid	Phosphatidylethanolamine (PE)	0.78	0.0647	1.17	0.2188	0.67	0.0061
1-stearoyl-2-oleoyl-GPI (18:0/18:1)*	Lipid	Phosphatidylinositol (PI)	0.80	0.0576	1.30	0.1038	0.61	0.0019
2-myristoylglycerol (14:0)	Lipid	Monoacylglycerol	0.99	0.4355	0.55	0.0618	1.81	0.0153
palmitoleoyl-oleoyl-glycerol (16:1/18:1) [1]*	Lipid	Diacylglycerol	1.89	0.4488	1.12	0.1373	1.68	0.0392
sphingomyelin (d18:2/24:2)*	Lipid	Sphingolipid Metabolism	1.14	0.3969	0.74	0.0665	1.54	0.0142
sphingomyelin (d18:0/20:0, d16:0/22:0)*	Lipid	Sphingolipid Metabolism	0.94	0.2980	1.61	0.0662	0.58	0.0091
sphingomyelin (d18:0/18:0, d19:0/17:0)*	Lipid	Sphingolipid Metabolism	0.82	0.1708	1.38	0.2439	0.60	0.0222
N-stearoyl-sphinganine (d18:0/18:0)*	Lipid	Sphingolipid Metabolism	1.00	0.7935	1.58	0.0677	0.63	0.0494
adenosine 3'-monophosphate (3'-AMP)	Nucleotide	Purine Metabolism, Adenine containing	0.74	0.0875	1.26	0.2011	0.58	0.0077
N1-methylguanosine	Nucleotide	Purine Metabolism, Guanine containing	1.43	0.0706	0.80	0.0813	1.78	0.0017
pyridoxal phosphate	Cofactors and Vitamins	Vitamin B6 Metabolism	0.67	0.1450	1.31	0.1551	0.51	0.0098

Supplementary Table 4. Metabolites uniquely changed in alcoholic cirrhosis compared to control

Biochemical Name	Super Pathway	Sub Pathway	AH vs AC		AH vs Control		AC vs Control	
			FC	P value	FC	P value	FC	P value
N-acetylglycine	Amino Acid	Glycine, Serine and Threonine Metabolism	0.96	0.8899	0.72	0.0441	1.32	0.0704
carboxethyl-GABA	Amino Acid	Glutamate Metabolism	1.13	0.3782	1.29	0.0327	0.87	0.1972
3-methylglutaconate	Amino Acid	Leucine, Isoleucine and Valine Metabolism	0.74	0.3629	0.48	0.0346	1.54	0.2145
2-methylbutyrylcarnitine (C5)	Amino Acid	Leucine, Isoleucine and Valine Metabolism	1.43	0.1122	1.76	0.0140	0.81	0.3269
N-acetylvaline	Amino Acid	Leucine, Isoleucine and Valine Metabolism	0.62	0.1581	0.37	0.0056	1.69	0.1394
N-acetylcysteine	Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	0.78	0.0976	0.63	0.0145	1.24	0.3669
2-oxoarginine*	Amino Acid	Urea cycle; Arginine and Proline Metabolism	1.35	0.4018	2.47	0.0267	0.55	0.1588
N-acetylarginine	Amino Acid	Urea cycle; Arginine and Proline Metabolism	1.39	0.0622	2.21	0.0025	0.63	0.1814
N-methylproline	Amino Acid	Urea cycle; Arginine and Proline Metabolism	1.35	0.2289	2.86	0.0148	0.47	0.1888
guanidinoacetate	Amino Acid	Creatine Metabolism	0.78	0.3436	0.58	0.0154	1.34	0.1270
gamma-glutamylleucine	Peptide	Gamma-glutamyl Amino Acid	0.83	0.6388	0.55	0.0179	1.52	0.0602
gamma-glutamylthreonine	Peptide	Gamma-glutamyl Amino Acid	0.78	0.2457	0.64	0.0285	1.22	0.2738
gamma-glutamylvaline	Peptide	Gamma-glutamyl Amino Acid	0.69	0.2007	0.50	0.0085	1.37	0.1471
anserine	Peptide	Dipeptide Derivative	1.42	0.1409	2.69	0.0080	0.53	0.1952
UDP-galactose	Carbohydrate	Nucleotide Sugar	0.81	0.2453	1.44	0.0492	0.56	0.3875
N-acetylglucosamine/N-acetylgalactosamine	Carbohydrate	Aminosugar Metabolism	0.68	0.0589	0.71	0.0374	0.96	0.7680
myristate (14:0)	Lipid	Long Chain Fatty Acid	0.69	0.3464	0.72	0.0421	0.97	0.2580
10-heptadecenoate (17:1n7)	Lipid	Long Chain Fatty Acid	0.70	0.2617	0.56	0.0037	1.25	0.0611
nonadecanoate (19:0)	Lipid	Long Chain Fatty Acid	0.81	0.1084	0.69	0.0047	1.18	0.1722
docosahexaenoate (DHA; 22:6n3)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.50	0.0560	0.36	0.0017	1.39	0.1518
15-methylpalmitate	Lipid	Fatty Acid, Branched	0.68	0.1855	0.73	0.0158	0.93	0.2385
ximenoylcarnitine (C26:1)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.76	0.1300	0.70	0.0274	1.07	0.4323
oleoyl ethanolamide	Lipid	Endocannabinoid	0.68	0.1075	0.63	0.0446	1.08	0.6252
inositol 1-phosphate (1IP)	Lipid	Inositol Metabolism	0.70	0.0637	0.53	0.0006	1.32	0.0726
1-palmitoleoyl-GPC (16:1)*	Lipid	Lysophospholipid	0.71	0.0996	0.59	0.0175	1.21	0.4018
1-oleoyl-GPE (18:1)	Lipid	Lysophospholipid	0.73	0.1919	0.56	0.0441	1.31	0.4357
N-palmitoyl-sphingadienine (d18:2/16:0)*	Lipid	Sphingolipid Metabolism	0.78	0.0678	0.60	0.0006	1.31	0.0658
sphingomyelin (d17:2/16:0, d18:2/15:0)*	Lipid	Sphingolipid Metabolism	0.81	0.2656	0.61	0.0298	1.32	0.2629
beta-sitosterol	Lipid	Sterol	1.11	0.8161	2.39	0.0407	0.46	0.0781
Salpha-androstan-3beta,17beta-diol disulfate	Lipid	Androgenic Steroids	0.57	0.3036	0.43	0.0480	1.32	0.3190
glycochenodeoxycholate	Lipid	Primary Bile Acid Metabolism	1.28	0.1500	2.17	0.0226	0.59	0.3512
glycochenodeoxycholate sulfate	Lipid	Primary Bile Acid Metabolism	1.05	0.1666	1.60	0.0159	0.66	0.2617
deoxycholate	Lipid	Secondary Bile Acid Metabolism	16.78	0.3139	17.66	0.0208	0.95	0.1746
glycohyocholate	Lipid	Secondary Bile Acid Metabolism	1.90	0.1058	5.66	0.0013	0.34	0.0759
nicotinamide riboside	Cofactors and Vitamins	Nicotinate and Nicotinamide Metabolism	0.48	0.5137	0.32	0.0480	1.51	0.1832
dihydrobiopterin	Cofactors and Vitamins	Tetrahydrobiopterin Metabolism	0.61	0.0621	0.56	0.0339	1.08	0.7189