Supplementary Tables

Supplementary Table 1. Enrichment of Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathways in Mutated Genes during Hepatocellular Carcinoma Development in Genetically Obese Mice and Wild-Type Mice

Group	KEGG Pathways	NG[a]	adjP[b]	Mutated genes	Notes
Obese (db/db)	Calcium signaling	9 (178)	3.32E-06	*Adcy4, Cacna1a, Itpr3, Pdgfra, Plce1, Prkca, Ryr2, Tacr1, Tbxa2r*	Regulation of cellular events in tumorigenesis.
	Gap junction	6 (88)	3.50E-05	***Hras**, Adcy4, Itpr3, Pdgfra, Prkca, Sos1*	Regulation of cell growth and differentiation
	Focal adhesion	6 (200)	0.0008	***Hras**, Flt4, Lama3, Pdgfra, Prkca, Sos1*	Cell motility, proliferation, differentiation and survival
	Cytokine-cytokine receptor interaction	5 (245)	0.0071	*Ccr9, Flt4, Il10ra, Il5, Pdgfra*	Cancer-related pathway
	GnRH signaling pathway[c]	5 (99)	0.0003	***Hras**, Adcy4, Itpr3, Prkca, Sos1*	Cancer proliferation, metastasis, and angiogenesis
	Chemokine signaling	4 (185)	0.0125	***Hras**, Adcy4, Ccr9, Sos1*	Tumor survival, metastasis and neovascularization.
	MAPK signaling pathway[d]	8 (268)	0.0002	***Hras**, Cacna1a, Cacna2d2, Cacna2d4, Pdgfra, Prkca, Ptpn5, Sos1*	Cell proliferation, differentiation and migration
	Pathways in cancer	6 (325)	0.0054	***Hras**, Brca2, Lama3, Pdgfra, Prkca, Sos1*	Cancer related pathway
Lean (wild-type)	MAPK signaling pathway	4 (268)	0.0342	*Cacna1f, Cdc25b, Mecom, Nfkb2*	Cell proliferation, differentiation and migration
	Pathways in cancer	7 (325)	0.0026	*Arnt2, Ctnna2, Cyct, Dvl3, Mecom, Msh2, Nfkb2*	Cancer related pathway

[a] NG, number of annotated genes in the input list (number of annotated genes in the reference list; [b] adjP, p value adjusted by the multiple test adjustment; [c] GnRH, gonadotropin-releasing hormone; [d] MAPK, mitogen-activated protein kinase.

Supplementary Table 2. Mutations in CEL identified in TCGA HCC associated with nutritional factors or viruses infection

	HCC associated with nutritional factors only		HCC associated with viruses infection only	
#	**bcr_patient_barcode**	**Mutations**	**bcr_patient_barcode**	**Mutations**
1	TCGA-BC-A10S	Arg156Cys	TCGA-DD-A114	
2	TCGA-BC-A10U		TCGA-DD-A116	
3	TCGA-BC-A10Y		TCGA-DD-A119	
4	TCGA-BC-A110	Arg156Cys	TCGA-DD-A1EA	
5	TCGA-BC-A112		TCGA-DD-A1EE	
6	TCGA-DD-A115		TCGA-DD-A1EH	
7	TCGA-DD-A11B		TCGA-DD-A1EI	
8	TCGA-DD-A11D		TCGA-EP-A12J	
9	TCGA-BC-A217		TCGA-DD-A1EL	
10	TCGA-DD-A1E9		TCGA-FV-A23B	
11	TCGA-DD-A1ED		TCGA-G3-A25T	
12	TCGA-EP-A26S		TCGA-G3-A25U	
13	TCGA-G3-A25S		TCGA-G3-A25X	
14	TCGA-G3-A25V		TCGA-G3-A25Y	
15	TCGA-BC-A3KG	Ala321Ser	TCGA-G3-A25Z	
16	TCGA-BD-A2L6		TCGA-ES-A2HT	
17	TCGA-CC-A3M9		TCGA-G3-A3CG	
18	TCGA-CC-A3MA		TCGA-G3-A3CJ	
19	TCGA-DD-A39Z		TCGA-G3-A3CK	
20	TCGA-EP-A3JL		TCGA-G3-A3CH	
21	TCGA-G3-A3CI		TCGA-FV-A495	
22	TCGA-CC-A3MC		TCGA-FV-A4ZQ	
23	TCGA-EP-A3RK		TCGA-BW-A5NO	
24	TCGA-FV-A2QQ		TCGA-BW-A5NP	
25	TCGA-FV-A3I1		TCGA-DD-A4NF	
26	TCGA-FV-A4ZP		TCGA-G3-A5SI	
27	TCGA-BW-A5NQ		TCGA-G3-A5SK	
28	TCGA-DD-A4NG		TCGA-DD-A4NO	
29	TCGA-DD-A4NH		TCGA-DD-A4NQ	
30	TCGA-DD-A4NJ		TCGA-K7-A5RF	
31	TCGA-G3-A5SL		TCGA-DD-A73D	
32	TCGA-BC-A5W4		TCGA-MI-A75C	
33	TCGA-CC-A5UC		TCGA-MI-A75H	
34	TCGA-CC-A5UD		TCGA-MI-A75I	
35	TCGA-CC-A5UE		TCGA-QA-A7B7	
36	TCGA-NI-A4U2		TCGA-UB-A7ME	
37	TCGA-BC-A69H		TCGA-UB-A7MF	
38	TCGA-DD-A4NS		TCGA-G3-A7M6	

	HCC associated with nutritional factors only		HCC associated with viruses infection only	
#	**bcr_patient_barcode**	**Mutations**	**bcr_patient_barcode**	**Mutations**
39	TCGA-DD-A4NV		TCGA-KR-A7K2	
40	TCGA-ED-A627		TCGA-RC-A7S9	
41	TCGA-ED-A66X		TCGA-RG-A7D4	
42	TCGA-DD-A73A		TCGA-RC-A7SB	
43	TCGA-T1-A6J8		TCGA-RC-A7SF	
44	TCGA-CC-A7IF		TCGA-RC-A7SK	
45	TCGA-CC-A7IG		TCGA-CC-A9FU	
46	TCGA-CC-A7IH		TCGA-G3-AAV0	
47	TCGA-CC-A7II		TCGA-YA-A8S7	
48	TCGA-G3-A6UC		TCGA-G3-AAV1	
49	TCGA-CC-A7IJ		TCGA-G3-AAV4	
50	TCGA-CC-A7IK		TCGA-G3-AAV7	
51	TCGA-CC-A7IL		TCGA-RC-A7SH	
52	TCGA-G3-A7M5		TCGA-ZP-A9CZ	
53	TCGA-G3-A7M8		TCGA-ZP-A9D2	
54	TCGA-G3-A7M7		TCGA-3K-AAZ8	
55	TCGA-CC-A8HT		TCGA-5C-AAPD	
56	TCGA-MR-A8JO		TCGA-DD-AADP	
57	TCGA-NI-A8LF		TCGA-DD-AADW	
58	TCGA-CC-A9FS		TCGA-DD-AAC8	
59	TCGA-CC-A9FV		TCGA-DD-AAC9	
60	TCGA-CC-A9FW		TCGA-DD-AACA	
61	TCGA-G3-AAV5		TCGA-DD-AACB	
62	TCGA-ZP-A9D0		TCGA-DD-AACC	
63	TCGA-2Y-A9GS		TCGA-DD-AACD	
64	TCGA-2Y-A9GV		TCGA-DD-AACE	
65	TCGA-2Y-A9GW		TCGA-DD-AACF	
66	TCGA-2Y-A9GX		TCGA-DD-AACG	
67	TCGA-2Y-A9H2		TCGA-DD-AACH	
68	TCGA-4R-AA8I		TCGA-DD-AACK	
69	TCGA-CC-A7IE		TCGA-DD-AACL	
70	TCGA-ED-A97K		TCGA-DD-AACM	
71	TCGA-UB-AA0U		TCGA-DD-AACN	
72	TCGA-ZP-A9CY		TCGA-DD-AACO	
73	TCGA-ZP-A9D1		TCGA-DD-AACQ	
74	TCGA-2Y-A9H6		TCGA-DD-AACS	
75	TCGA-2Y-A9H8		TCGA-DD-AACT	
76	TCGA-2Y-A9HB		TCGA-DD-AACU	
77	TCGA-DD-AACP		TCGA-DD-AACY	
78	TCGA-DD-AACV		TCGA-DD-AAD0	

	HCC associated with nutritional factors only		HCC associated with viruses infection only	
#	**bcr_patient_barcode**	**Mutations**	**bcr_patient_barcode**	**Mutations**
79	TCGA-DD-AADU		TCGA-DD-AAD1	
80	TCGA-DD-AAW2		TCGA-DD-AAD2	
81			TCGA-DD-AAD6	
82			TCGA-DD-AAD8	
83			TCGA-DD-AADA	
84			TCGA-DD-AADB	
85			TCGA-DD-AADC	
86			TCGA-DD-AADD	
87			TCGA-DD-AADE	
88			TCGA-DD-AADF	
89			TCGA-DD-AADI	
90			TCGA-DD-AADK	
91			TCGA-DD-AADY	
92			TCGA-DD-AAE0	
93			TCGA-DD-AAE1	
94			TCGA-DD-AAE2	
95			TCGA-DD-AAE4	
96			TCGA-DD-AAE8	
97			TCGA-DD-AAEE	
98			TCGA-DD-AAEI	
99			TCGA-DD-AAEK	
100			TCGA-DD-AAVP	
101			TCGA-DD-AAVQ	
102			TCGA-DD-AAVR	
103			TCGA-DD-AAVS	
104			TCGA-DD-AAVU	
105			TCGA-DD-AAVW	
106			TCGA-DD-AAVX	
107			TCGA-DD-AAVZ	
108			TCGA-DD-AAW0	

Supplementary Table 3. Whole-Exome Sequencing in NAFLD-HCCs

Sample ID	Effective data (Mb)	Mean depth	Coverage (%)
Db1-N	5055	151	97.5
Db1-T	5416	165	97.6
Db2-N	7007	207	97.6
Db2-T	7502	183	97.6
Wt1-N	4559	141	97.7
Wt1-T	5390	158	97.8
Wt2-N	5743	174	97.8
Wt2-T	9956	237	97.8
Mean		177.0 ± 31.6	97.7 ± 0.1%

T, Tumor; N, non-tumor.

Supplementary Table 4. Primer list

Primer name	Nucleotide sequence (5'->3')	Size/note
Cel-F1	GTATGCACACACATGACCTT	341 bp
Cel-R1	CATGTTGCACTGGGCTTCAT	
Cel-F2	GGCGGAAGTAGCCTCAGCTA	1161 bp
Cel-R2	CCTGTCCCATAGTTTAGCTT	
Cel-F3	GCACATTGACTGTTAATCTCTA	883 bp
Cel-R3	ACTGGAAGACATCTCTTTACTA	
Cel-F4	CCCTATCACTAGCTGATTGT	731 bp
Cel-R4	GTTTAGTGAGCCAAGAGAACTA	
Cel-F5	CCACACAGATGCCTCTACTT	349 bp
Cel-R5	GCTACCAAGGCTTGAGGATA	
Cel-F6	GCACATGAGCAGGAGAACT	753 bp
Cel-R6	GCCAAGTGCCTGTCACCAT	
Hras-F1	CCTTGGCTAAGTGTGCTTCTC	648 bp
Hras-R1	AAGACATAAAGCCTCAGTGTGC	
Hras-F2	TGTGCACACTGAGGCTTTATG	453 bp
Hras-R2	CTGCGGTCTGGGAGACTTAC	
Hras-F3	CAGACAGCACCCCTTTTCTC	236 bp
Hras-R3	CATCTGGCTAGCTGAGGTCAC	
CEL D454E-F	CAAATGGGTGGGGGCCGAGCATGCAGATGACATTCAG	For site directed mutagenesis
CEL D454E-R	CTGCTGAATGTCATCTGCATGCTCGGCCCCCACCCATTTG	
CEL D555N-F	GCGCTGCCCACAGTGACCAACCAGGCGGCCACCCCTG	
CEL D555N-R	CAGGGGTGGCCTCCTGGTTGGTCACTGTGGGCAGCGC	

Supplementary Table 5. Antibodies used in this study

Antibody	Cat. No.	Company	Dilution
Akt (5G3)	#2966	Cell Signaling Technology	1:1000
Phospho-Akt (Thr308) (D25E6)	#13038	Cell Signaling Technology	1:1000
CEL (E-4)	sc377087	Santa Cruz	1:250
c-Jun (60A8)	#9165	Santa Cruz	1:200
Phospho-c-Jun (Ser63) (54B3)	#2361	Cell Signaling Technology	1:1000
ERK1/2	sc-292838	Santa Cruz	1:400
GAPDH	sc-25778	Santa Cruz	1:500
GRP78	sc-13968	Santa Cruz	1:500
His-probe (H-15)	sc-803	Santa Cruz	1:1000
H-Ras (F235)	sc-29	Santa Cruz	1:400
IRE1α (14C10)	#3294	Cell Signaling Technology	1:1000
pIRE1a (ser725)	NB100-2323	novusbio	1:1000
JNK	#9252	Cell Signaling Technology	1:1000
Phospho-SAPK/JNK (Thr183/Tyr185) (81E11)	#4668	Cell Signaling Technology	1:1000
MEK1/2	#9122	Cell Signaling Technology	1:400
Phospho-MEK1/2 (Ser221) (166F8)	#2338	Cell Signaling Technology	1:1000
PI3-kinase p85 α (3H2838)	sc-71892	Santa Cruz	1:200
Phospho-PI3 Kinase p85 (Tyr458)	#4228	Cell Signaling Technology	1:1000
PDK1 (C-20)	sc-7140	Santa Cruz	1:500
Phospho-PDK1 (Ser241) (C49H2)	#3438	Cell Signaling Technology	1:1000