SUPPLEMENTARY INFORMATION

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Supplementary Table 1: Clinical characteristics of human hepatocellular carcinoma samples.

	Training Set (1)	Validation Set (2)
Gender		
Male	64 (70.3%)	121 (73.8%)
Female	27 (29.7%)	43 (26.2%)
Ethnicity		
Caucasian	74 (81.3%)	129 (78.7%)
Asian	4 (4.4%)	29 (17.7%)
African-American	4 (4.4%)	5 (3%)
Not known	9 (9.9%)	1 (0.6%)
Median Age (range)	65 (42-80)	67 (36-83)
Etiology		
HCV	91 (100%)	77 (47%)
HBV	0 (0%)	45 (27.4%)
Alcohol	0 (0%)	12 (7.3%)
Other	0 (0%)	24 (14.6%)
Not known	0 (0%)	6 (3.7%)
Grade of tumor differentiation		
well differentiated	20 (22%)	29 (17.7%)
moderate differentiated	43 (47.2%)	63 (38.4%)
poorly differentiated	18 (19.8%)	16 (9.8%)
Not known	10 (11%)	56 (34.1%)
Median Diameter of largest nodule (cm)	3.5 (1-22)	3.5 (0.7-13)
BCLC stage		
0	7 (7.7%)	18 (11%)

A	60 (65.9%)	133 (81.1%)
B	6 (6.6%)	9 (5.5%)
C	8 (8.8%)	1 (0.6%)
Not known	10 (11%)	3 (1.8%)

Supplementary Table 2: Clinical characteristics of 5 public HCC datasets.

	HCC-I	HCC-II	HCC-III	HCC-IV	HCC-V
Samples (n=)	90	82	60	57	118
Gender (male %)	79%	na	73%	82%	81%
Age	53 (12)	na	63	62 (14)	58 (9)
Etiology					
HBV	59%	83%	18%	30%	23%
HCV	9%	5%	67%	19%	69%
HBV+HCV	3%	-	-	-	1%
Alcohol	6%	-	-	32%	3%
Others	4%	11%	15%	-	-
Histology	G2/3/4#	na	G1/2/3#	G1/2/3/4#	W/M/P*
	8/31/1		4/45/10	7/51/35/7	24/65/16
Reference	Lee et al. Nat Genet 2004	Chen et al. Mol Biol Cell 2002	Izuka et al. Lancet 2003	Boyault et al. Hepatology 2007	Hoshida et al. Cancer Res 2009

HBV: hepatitis B virus, HCV: hepatitis C virus,
#: Edmonson-Steiner grade, *: UICC tumor differentiation (well/moderate/poor),
Mean (SD, if available)
Origin of HCC-datasets: HCC-I (GSE1528), HCC-II (http://smd.stanford.edu/cgi-bin/publication/viewPublication.pl?pub_no=107), HCC-III (http://surgery2.med.yamaguchi-u.ac.jp/research/DNAchip/hcc-recurrence/index.html), HCC-IV (E-TABM-36) and HCC-I (GSE10186).

Supplementary Table 3: Wnt-pathway mRNA list: 210 Wnt-related genes from the literature (see main manuscript Materials and Methods for details).

Symbol	Gene ID	Description
AKT1	207	v-akt murine thymoma viral oncogene homolog 1
AKT2	208	V-akt murine thymoma viral oncogene homolog 2, mRNA
AKT3	10000	v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)
ANKRD6	22881	ankyrin repeat domain 6
APC	324	adenomatous polyposis coli
APC2	10297	adenomatosis polyposis coli 2
ARRB1	408	arrestin, beta 1
ARRB2	409	arrestin, beta 2
AXIN1	8312	axin 1
AXIN2	8313	axin 2
BRD7	29117	bromodomain containing 7
BTRC	8945	beta-transducin repeat containing
PGEA1	25776	(CBY1) chibby homolog 1 (Drosophila)
CACYBP	27101	calcyclin binding protein
CAMK2A	815	calcium/calmodulin-dependent protein kinase II alpha
CAMK2B	816	calcium/calmodulin-dependent protein kinase II beta
CAMK2D	817	calcium/calmodulin-dependent protein kinase II delta
CAMK2G	818	calcium/calmodulin-dependent protein kinase II gamma
CCND1	595	cyclin D1
CCND2	894	cyclin D2
CCND3	896	Cyclin D3 (CCND3), transcript variant 3, mRNA
CDC2	983	cell division cycle 2, G1 to S and G2 to M
CDC25C	995	cell division cycle 25 homolog C (S. pombe)
CDH1	999	cadherin 1, type 1, E-cadherin (epithelial)
CDX1	1044	caudal type homeobox 1
CER1	9350	cerberus 1, cysteine knot superfamily, homolog (Xenopus laevis)
CHD8	57680	chromodomain helicase DNA binding protein 8
CHP	11261	calcium binding protein P22
CREBBP	1387	CREB binding protein
CSNK1A1	1452	Homo sapiens, clone IMAGE:4769127, mRNA
CSNK1D	1453	casein kinase 1, delta
CSNK1E	1454	casein kinase 1, epsilon
CSNK2A1	1457	casein kinase 2, alpha 1 polypeptide
CSNK2A2	1459	casein kinase 2, alpha prime polypeptide
CSNK2B	1460	casein kinase 2, beta polypeptide
CTBP1	1487	C-terminal binding protein 1
CTBP2	1488	C-terminal binding protein 2
CTNNB1	1499	catenin (cadherin-associated protein), beta 1, 88kDa

CTNNBIP1	56998	catenin, beta interacting protein 1
CUL1	8454	cullin 1
CXXC4	80319	CXXC finger 4
DAAM1	23002	dishevelled associated activator of morphogenesis 1
DAAM2	23500	dishevelled associated activator of morphogenesis 2
DAB2	1601	Differentially expressed protein
DACT1	51339	dapper, antagonist of beta-catenin, homolog 1 (Xenopus laevis)
CCDC85B	11007	coiled-coil domain containing 85B
DKK1	22943	dickkopf homolog 1 (Xenopus laevis)
DKK2	27123	dickkopf homolog 2 (Xenopus laevis)
DKK3	27122	dickkopf homolog 3 (Xenopus laevis)
DKK4	27121	dickkopf homolog 4 (Xenopus laevis)
DLG1	1739	discs, large homolog 1 (Drosophila)
DLG2	1740	discs, large homolog 2 (Drosophila)
DLG4	1742	discs, large homolog 4 (Drosophila)
DVL1	1855	dishevelled, dsh homolog 1 (Drosophila)
DVL2	1856	dishevelled, dsh homolog 2 (Drosophila)
DVL3	1857	dishevelled, dsh homolog 3 (Drosophila)
EP300	2033	E1A binding protein p300
FBXW11	23291	F-box and WD repeat domain containing 11
FBXW2	26190	F-box and WD repeat domain containing 2
FOSL1	8061	FOS-like antigen 1
FRAT1	10023	frequently rearranged in advanced T-cell lymphomas
FRAT2	23401	frequently rearranged in advanced T-cell lymphomas 2
FSTL1	11167	follistatin-like 1
FZD1	8321	frizzled homolog 1 (Drosophila)
FZD10	11211	frizzled homolog 10 (Drosophila)
FZD2	2535	frizzled homolog 2 (Drosophila)
FZD3	7976	frizzled homolog 3 (Drosophila)
FZD4	8322	frizzled homolog 4 (Drosophila)
FZD5	7855	frizzled homolog 5 (Drosophila)
FZD6	8323	frizzled homolog 6 (Drosophila)
FZD7	8324	frizzled homolog 7 (Drosophila)
FZD8	8325	frizzled homolog 8 (Drosophila)
FZD9	8326	frizzled homolog 9 (Drosophila)
GSK3A	2931	glycogen synthase kinase 3 alpha
GSK3B	2932	glycogen synthase kinase 3 beta
HDAC1	3065	histone deacetylase 1
HIPK2	28996	homeodomain interacting protein kinase 2
JUN	3725	jun oncogene
RPSA	3921	ribosomal protein SA
LDLR	3949	low density lipoprotein receptor

LEF1	51176	lymphoid enhancer-binding factor 1
LRP1	4035	low density lipoprotein-related protein 1 (alpha-2-macroglobulin receptor)
LRP5	4041	low density lipoprotein receptor-related protein 5
LRP6	4040	low density lipoprotein receptor-related protein 6
MAGI3	260425	membrane associated guanylate kinase, WW and PDZ domain containing 3
MAP1B	4131	microtubule-associated protein 1B
MAP3K4	4216	mitogen-activated protein kinase kinase kinase 4
MAP3K7	6885	mitogen-activated protein kinase kinase kinase 7
MAP3K7IP1	10454	TGF-beta activated kinase 1/MAP3K7 binding protein 1
MAPK10	5602	mitogen-activated protein kinase 10
MAPK8	5599	mitogen-activated protein kinase 8
MAPK8IP1	9479	mitogen-activated protein kinase 8 interacting protein 1
MAPK9	5601	mitogen-activated protein kinase 9
MARK2	2011	MAP/microtubule affinity-regulating kinase 2
MMP7	4316	matrix metallopeptidase 7 (matrilysin, uterine)
MVP	9961	major vault protein
MYC	4609	v-myc myelocytomatosis viral oncogene homolog (avian)
NFAT5	10725	nuclear factor of activated T-cells 5, tonicity-responsive
NFATC1	4772	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1
NFATC2	4773	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2
NFATC3	4775	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 3
NFATC4	4776	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 4
NKD1	85407	naked cuticle homolog 1 (Drosophila)
NKD2	85409	naked cuticle homolog 2 (Drosophila)
NLK	51701	nemo-like kinase
NR5A1	2516	nuclear receptor subfamily 5, group A, member 1
PAFAH1B1	5048	platelet-activating factor acetylhydrolase, isoform Ib, alpha subunit 45kDa
PAX2	5076	paired box 2
PIAS4	51588	protein inhibitor of activated STAT, 4
PIN1	5300	peptidylprolyl cis/trans isomerase, NIMA-interacting 1
PLAU	5328	plasminogen activator, urokinase
PLCB1	23236	phospholipase C, beta 1 (phosphoinositide-specific)
PLCB2	5330	phospholipase C, beta 2
PLCB3	5331	phospholipase C, beta 3 (phosphatidylinositol-specific)
PLCB4	5332	phospholipase C, beta 4
PORCN	64840	porcupine homolog (Drosophila)
PPARD	5467	peroxisome proliferator-activated receptor delta
PPP2CA	5515	protein phosphatase 2 (formerly 2A), catalytic subunit, alpha isoform
PPP2CB	5516	protein phosphatase 2 (formerly 2A), catalytic subunit, beta isoform
PPP2R1A	5518	protein phosphatase 2 (formerly 2A), regulatory subunit A, alpha isoform
PPP2R1B	5519	protein phosphatase 2 (formerly 2A), regulatory subunit A, beta isoform
PPP2R2A	5520	protein phosphatase 2 (formerly 2A), regulatory subunit B, alpha isoform

PPP2R2B	5521	protein phosphatase 2 (formerly 2A), regulatory subunit B, beta isoform
PPP2R2C	5522	protein phosphatase 2 (formerly 2A), regulatory subunit B, gamma isoform
PPP2R5B	5526	protein phosphatase 2, regulatory subunit B', beta isoform
PPP2R5C	5527	protein phosphatase 2, regulatory subunit B', gamma isoform
PPP2R5E	5529	protein phosphatase 2, regulatory subunit B', epsilon isoform
PPP3CA	5530	protein phosphatase 3 (formerly 2B), catalytic subunit, alpha isoform
PPP3CB	5532	protein phosphatase 3 (formerly 2B), catalytic subunit, beta isoform
PPP3CC	5533	protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform
PPP3R1	5534	protein phosphatase 3, regulatory subunit B, alpha
PPP3R2	5535	protein phosphatase 3 (formerly 2B), regulatory subunit B, beta isoform
PRICKLE1	144165	prickle homolog 1 (Drosophila)
PRICKLE2	166336	prickle homolog 2 (Drosophila)
PRKACA	5566	protein kinase, cAMP-dependent, catalytic, alpha
PRKACB	5567	protein kinase, cAMP-dependent, catalytic, beta
PRKACG	5568	protein kinase, cAMP-dependent, catalytic, gamma
PRKCA	5578	protein kinase C, alpha
PRKCB1	5579	protein kinase C, beta 1
PRKCD	5580	protein kinase C, delta
PRKCE	5581	protein kinase C, epsilon
PRKCG	5582	protein kinase C, gamma
PRKCH	5583	protein kinase C, eta
PRKCI	5584	protein kinase C, iota
PRKCQ	5588	protein kinase C, theta
PRKCZ	5590	Protein kinase C zeta
PRKD1	5587	protein kinase D1
PRKX	5613	protein kinase, X-linked
PRKY	5616	protein kinase, Y-linked
PSEN1	5663	presenilin 1
PTPRA	5786	protein tyrosine phosphatase, receptor type, A
RAC1	5879	MRNA, clone: PO2ST9
RAC2	5880	ras-related C3 botulinum toxin substrate 2
RAC3	5881	ras-related C3 botulinum toxin substrate 3
RBX1	9978	ring-box 1
RHOA	387	ras homolog gene family, member A
ROCK1	6093	Rho-associated, coiled-coil containing protein kinase 1
ROCK2	9475	Rho-associated, coiled-coil containing protein kinase 2
ROR2	4920	receptor tyrosine kinase-like orphan receptor 2
RUNX2	860	runt-related transcription factor 2
RUVBL1	8607	RuvB-like 1 (E. coli)
SALL1	6299	sal-like 1 (Drosophila)
SENP2	59343	SUMO1/sentrin/SMT3 specific peptidase 2
SFRP1	6422	secreted frizzled-related protein 1

SFRP2	6423	secreted frizzled-related protein 2
SFRP4	6424	secreted frizzled-related protein 4
SFRP5	6425	secreted frizzled-related protein 5
SIAH1	6477	seven in absentia homolog 1 (Drosophila)
SKP1A	6500	S-phase kinase-associated
SMAD2	4087	SMAD family member 2
SMAD3	4088	SMAD family member 3
SMAD4	4089	CDNA FLJ59261 complete cds
SOX1	6656	SRY (sex determining region Y)-box 1
SOX17	64321	SRY (sex determining region Y)-box 17
TAX1BP3	30851	Tax1 (human T-cell leukemia virus type I) binding protein 3
TBL1X	6907	transducin (beta)-like 1X-linked
TBL1XR1	79718	transducin (beta)-like 1 X-linked receptor 1
TBL1Y	90665	transducin (beta)-like 1Y-linked
TBP	6908	TATA box binding protein
TCF1	6927	ranscription factor 1
TCF3	6929	transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47)
TCF4	6925	transcription factor 4
TCF7	6932	transcription factor 7 (T-cell specific, HMG-box)
TCF7L1	83439	transcription factor 7-like 1 (T-cell specific, HMG-box)
TCF7L2	6934	transcription factor 7-like 2 (T-cell specific, HMG-box)
TFAP2A	7020	transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)
TLE1	7088	transducin-like enhancer of split 1 (E(sp1) homolog, Drosophila)
TP53	7157	tumor protein p53
TSHB	7252	thyroid stimulating hormone, beta
VANGL1	81839	vang-like 1 (van gogh, Drosophila)
VANGL2	57216	vang-like 2 (van gogh, Drosophila)
WIF1	11197	WNT inhibitory factor 1
WNT1	7471	wingless-type MMTV integration site family, member 1
WNT10A	80326	wingless-type MMTV integration site family, member 10A
WNT10B	7480	wingless-type MMTV integration site family, member 10B
WNT11	7481	wingless-type MMTV integration site family, member 11
WNT16	51384	wingless-type MMTV integration site family, member 16
WNT2	7472	wingless-type MMTV integration site family member 2
WNT2B	7482	wingless-type MMTV integration site family, member 2B
WNT3	7473	wingless-type MMTV integration site family, member 3
WNT4	54361	wingless-type MMTV integration site family, member 4
WNT5A	7474	wingless-type MMTV integration site family, member 5A
WNT5B	81029	wingless-type MMTV integration site family, member 5B
WNT6	7475	wingless-type MMTV integration site family, member 6
WNT7A	7476	wingless-type MMTV integration site family, member 7A
WNT7B	7477	wingless-type MMTV integration site family, member 7B

WNT8A	7478	wingless-type MMTV integration site family, member 8A
WNT8B	7479	wingless-type MMTV integration site family, member 8B
WNT9A	7483	wingless-type MMTV integration site family, member 9A
WNT9B	7484	wingless-type MMTV integration site family, member 9B

Supplementary Table 4: Wnt-pathway miRNA list: 49 Wnt-related miRNAs from the literature

Symbol	Role in Wnt/β-Catenin Pathway	Supplementary References
miR-let-7c	Downregulated after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-9	Regulates *CDH1* and activates Wnt-signaling	(4)
miR-15/16	Downregulated by active Wnt-Signaling	(5)
miR-17	Downregulation inhibits *CDH1*	(6)
miR-18a	Upregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium	(3)
miR-21	Targets *Wnt1*	(7)
miR-23b	Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-24-1	Upregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium; Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-27b	Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-29a/c	Modulates Wnt-signaling	(8)
miR-30a	Downregulated after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-30e	Transactivated by β-Catenin/TCF4	(9)
miR-31	Increases *Wnt5a*	(10)
miR-106b	Downregulation inhibits *CDH1*	(6)
miR-122a	Targets Wnt-signaling	(11)
miR-135a	Activates Wnt-signaling through *APC*	(12)
miR-135b	Activates Wnt-signaling	(12)
miR-145	Inhibits β-Catenin through *MUC1*	(13)
miR-146b	Downregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium	(3)
miR-148a	Downregulated after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-181a-1	Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3, 14)

miR-181b	Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3, 14)
miR-181d	Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3, 14)
miR-183	Upregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium	(3)
miR-186	Upregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium	(3)
miR-194	Downregulated after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-196a	Downregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium	(3)
miR-200a	Activates Wnt-signaling	(15)
miR-200c	Activates Wnt-signaling	(15)
miR-203	Targets *Lef1*	(16)
miR-210	Represses Wnt-Signaling	(3)
miR-214	Downregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium	(3)
miR-222	Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-301a	Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-315	Activates Wnt Signaling	(17)
miR-320	Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-322	Downregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium; downregulated after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-335	Downregulated after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-344	Upregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium; Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-351	Downregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium	(3)
miR-375	Expression correlated to that of beta-catenin-targeted genes	(18)
miR-449	Targets WNT1-inducible signaling pathway protein 2 (*WISP2*)	(19)
miR-450a	Downregulated after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-468	Downregulated after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)

miR-503	Downregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium	(3)
miR-542-5p	Downregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium; Downregulated after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)
miR-582-5p	Upregulated in Microarray after Wnt-signaling Activation of pre-adipocytes with Lithium	(3)
miR-714	Upregulated in Microarray after Wnt-signaling Activation in Lithium + MDI cells vs. MDI cells	(3)

Supplementary Table 5: Significantly differentially expressed Wnt-related genes in CTNNB1- and Wnt-TGFβ-class samples of the training set.

Over-expressed in CTNNB1

Gene Symbol	Score	FDR
NKD1	8.049	<0.001
AXIN2	8.017	<0.001
ROCK2	7.771	<0.001
SALL1	7.200	<0.001
TLE1	4.845	<0.001
DVL2	4.758	<0.001
CTNNBIP1	4.585	<0.001
SMAD3	4.551	<0.001
TCF7	4.483	<0.001
BRD7	4.000	<0.001
DAAM1	3.834	<0.001
CUL1	3.585	<0.001
PPP3CB	3.406	0.023
DLG1	2.842	0.042
RUVBL1	2.830	0.028
TBL1XR1	2.826	0.033
SENP2	2.801	0.042

Under-expressed in CTNNB1

Gene Symbol	Score	FDR
CTBP2	-6.207	<0.001
WNT4	-5.930	<0.001
TCF7L1	-5.627	<0.001
ARRB1	-4.983	<0.001
MAP1B	-4.389	<0.001
NFATC1	-3.980	<0.001
PLAU	-3.912	<0.001
WNT2	-3.726	<0.001
FSTL1	-3.689	<0.001
CXXC4	-3.639	<0.001
CDH1	-3.467	<0.001
FZD1	-3.379	0.017
PRKCD	-3.167	0.023
PLCB2	-3.150	0.017
CSNK1E	-3.037	0.023
PRKCB1	-3.027	0.028
NKD2	-2.776	0.023
WNT10A	-2.623	0.042
FZD10	-2.326	0.033

Over-expressed in Wnt-TGFβ

Gene Symbol	Score	FDR
DAB2	6.464	<0.001
PLAU	5.983	<0.001
TAX1BP3	5.912	<0.001
RUNX2	5.826	<0.001
RAC2	5.785	<0.001
FZD2	4.525	<0.001
PRKCD	4.353	<0.001
MMP7	4.304	<0.001
PRKX	4.241	<0.001
FZD7	4.060	<0.001
FRAT2	3.732	<0.001
CDC2	3.701	<0.001
HDAC1	3.576	<0.001
CACYBP	3.531	0.009
FZD6	3.518	0.016
DKK2	3.214	0.000
MVP	3.051	0.016
PRKCI	2.645	0.037
MAP1B	2.463	0.019
SFRP4	2.403	0.019
TCF4	2.363	0.029
ARRB2	2.292	0.048
CCND3	2.180	0.037

Under-expressed in Wnt-TGFβ

Gene Symbol	Score	FDR
TCF1	-6.600	<0.001
LRP6	-5.191	<0.001
LRP1	-4.182	<0.001
PRKCE	-4.053	<0.001
WNT16	-4.015	<0.001
FZD4	-4.010	<0.001
SALL1	-3.794	<0.001
WNT1	-3.678	<0.001
CAMK2A	-3.550	0.009
NR5A1	-3.483	0.019
WNT8B	-3.448	0.019
CREBBP	-3.314	0.009
DVL1	-2.979	0.019
SOX1	-2.923	0.016
PRKCA	-2.899	0.019
TSHB	-2.837	0.035
WNT10B	-2.824	0.029
NFATC3	-2.783	0.016
NFATC2	-2.775	0.037
CDX1	-2.705	0.037
PRKACG	-2.336	0.048

PLCB4	2.109	0.019
DKK3	1.993	0.048
ROR2	1.914	0.029
AKT3	1.880	0.048

Supplementary Table 6: Summary of dysregulated CTNNB1- and Wnt-TGFβ-Wnt-genes according to their cellular localization and their known or suspected function

		CTNNB1		**Wnt-TGFβ**	
		pathway activation	**pathway inhibition**	**pathway activation**	**pathway inhibition**
Membrane	**activators**		FZD10 ↓ FZD1 ↓ WNT2 ↓ WNT4 ↓ WNT10A ↓	FZD2 ↑ FZD7 ↑ FZD6 ↑	FZD4 ↓ WNT1 ↓ WNT8B ↓ WNT10B ↓ WNT16 ↓ LRP6 ↓
	inhibitors	CDH1 ↓		LRP1 ↓	SFRP4 ↑ DKK2 ↑ DKK3 ↑
Cytoplasm	**activators**	BRD7 ↑ DVL2 ↑	FSTL1 ↓ CSNK1E ↓	FRAT2 ↑ ARRB2 ↑ AKT3 ↑	
	inhibitors	ARRB1 ↓ CXXC4 ↓	AXIN2 ↑ DLG1 ↑ PPP3CB ↑ CUL1 ↑ TBL1XR1 ↑	DVL1 ↓	CACYBP ↑ DAB2 ↑
Nucleus	**activators**	SMAD3 ↑ RUVBL1 ↑	TCF7L1 ↓ FSTL1 ↓	HDAC1 ↑ TCF4 ↑	TCF1 ↓
	inhibitors	CTBP2 ↓	SALL1 ↑ TLE1 ↑ CTNNBIP1 ↑ TCF7 ↑ SENP2 ↑	SALL1 ↓ SOX1 ↓ CDX1 ↓	TAX1BP3 ↑
	target genes	---	PLAU ↓	PLAU ↑ RUNX2 ↑ MMP7 ↑ CDC2 ↑	---

				CCND3 ↑	
Non-Canonical Ca^{2+}	**activators**	---	PLCB2 ↓ NFATC1 ↓	PLCB4 ↑	CAMK2A ↓ NFATC2 ↓ NFATC3 ↓
Non-Canonical PCP	**activators**	DAAM1 ↑ ROCK2 ↑	MAP1B ↓	MAP1B ↑ ROR2 ↑ RAC2 ↑	---

↑ over-expression ↓ down-regulation

Supplementary Table 7: Expression of known liver-related Wnt-target-genes.

Training Set

	CTNNB1 vs. Wnt-TGFβ		CTNNB1 vs. Rest		Wnt-TGFβ vs. Rest	
Gene Symbol	Score	FDR	Score	FDR	Score	FDR
MERTK	5.922	<0.001	5.661	<0.001	-3.770	0.018
GLUL	5.715	<0.001	6.570	<0.001	-2.111	0.180
SPARCL1	4.602	<0.001	5.688	<0.001	-1.861	0.180
EPHB2	4.075	<0.001	4.460	<0.001	-2.091	0.241
LGR5	4.045	<0.001	5.099	<0.001	-1.318	0.303
TBX3	3.903	0.005	4.316	<0.001	-2.079	0.180
REG3A	2.935	0.005	3.696	<0.001	-0.790	0.430
LEF1	0.060	0.944	1.014	0.244	0.763	0.430
LAMA1	-1.325	0.196	-2.224	0.036	0.977	0.427

Validation Set

	CTNNB1 vs. Wnt-TGFβ		CTNNB1 vs. Rest		Wnt-TGFβ vs. Rest	
Gene Symbol	Score	FDR	Score	FDR	Score	FDR
GLUL	18.765	<0.001	22.324	<0.001	-2.470	0.036
TBX3	16.299	<0.001	18.880	<0.001	-4.479	<0.001
LGR5	13.059	<0.001	13.268	<0.001	-5.017	<0.001
MERTK	7.758	<0.001	10.827	<0.001	5.323	<0.001
SPARCL1	6.594	<0.001	8.648	<0.001	-0.750	0.468
REG3A	5.097	<0.001	6.674	<0.001	0.445	0.702
EPHB2	5.098	<0.001	5.793	<0.001	-1.954	0.108
LEF1	-0.804	0.446	3.302	0.007	-0.947	0.468
LAMA1	-1.019	0.335	-2.421	0.03	-0.881	0.468

Supplementary Table 8: Correlation of Wnt-related transcription factors to Wnt-target-genes in the training set.

		CTNNB1 target genes							Wnt-TGFβ target genes				
		REG3A	**LGR5**	**MERTK**	**TBX3**	**EPHB2**	**SPARCL1**	**GLUL**	**RUNX3**	**CDC2**	**MMP7**	**CCND3**	**PLAU**
CTNNB1 nuclear factors	**SMAD3**	0.003 .258	<0.001 .557	<0.001 .388	<0.001 .354	<0.001 .456	<0.001 .332	<0.001 .570	n.s.	n.s.	0.022 -.200	n.s.	n.s.
	RUVBL1	0.031 .188	<0.001 .416	0.014 .213	<0.001 .304	n.s.	0.003 .259	<0.001 .496	0.001 -.279	<0.001 .577	n.s.	<0.001 -.414	n.s.
	TCF7L1	0.001 -.278	<0.001 -.369	0.023 -.197	0.002 -.268	<0.001 -.313	n.s.	<0.001 -.314	n.s.	n.s.	n.s.	n.s.	n.s.
	FSTL1	0.007 -.235	0.001 -.296	0.030 -.189	<0.001 -.390	<0.001 -.306	n.s.	<0.001 -.374	<0.001 .353	n.s.	<0.001 .563	<0.001 .307	<0.001 .400
	CTBP2	0.045 -.175	<0.001 -.401	<0.001 -.348	<0.001 -.337	n.s.	0.002 -.266	<0.001 -.374	0.006 .239	<0.001 -.306	0.002 .268	0.001 .281	n.s.
	SENP2	n.s.	0.046 .174	0.005 .242	0.001 .292	n.s.	n.s.	0.014 .212	0.009 -.226	0.001 .305	n.s.	<0.001 -.364	0.018 .205
	TLE1	0.001 .291	<0.001 .396	<0.001 .393	<0.001 .375	0.003 .260	0.001 .283	<0.001 .514	0.003 -.259	0.002 .263	<0.001 .477	0.021 -.200	<0.001 -.354
	CTNNBIP1	n.s.	0.004 .250	<0.001 .362	<0.001 .391	<0.001 .387	0.015 .211	<0.001 .353	<0.001 -.345	n.s.	<0.001 -.376	0.001 -.299	<0.001 -.306
	TCF7	<0.001 .339	<0.001 .490	<0.001 .356	<0.001 .427	<0.001 .521	<0.001 .344	<0.001 .518	n.s.	n.s.	n.s.	n.s.	n.s.
	SALL1	n.s.	<0.001 .392	<0.001 .536	<0.001 .414	0.017 .208	<0.001 .299	<0.001 .374	0.006 -.237	n.s.	0.004 -.248	n.s.	<0.001 -.391
Wnt-TGFβ nuclear factors	**TCF1**	n.s.	n.s.	0.040 .179	<0.001 .350	0.002 .268	n.s.	0.001 .281	0.001 -.279	n.s.	<0.001 -.507	0.019 -.204	<0.001 -.529
	HDAC1	n.s.	n.s.	0.003 -.257	n.s.	0.007 -.234	n.s.	n.s.	0.045 .175	<0.001 .559	n.s.	n.s.	0.004 .252
	CDX1	n.s.	n.s.	n.s.	n.s.	0.001 .283	0.013 -.216	n.s.	0.006 -.289	<0.001 -.321	0.029 -.190	0.027 -.193	0.026 -.194
	SOX1	n.s.	n.s.	n.s.	n.s.	<0.001 .308	n.s.	n.s.	<0.001 -.312	0.017 -.208	n.s.	0.020 -.202	n.s.
	TAXIPB3	n.s.	n.s.	n.s.	n.s.	n.s.	0.007 .234	n.s.	n.s.	0.003 .253	<0.001 .371.	n.s.	<0.001 .503
	TCF4	n.s.	n.s.	n.s.	0.001 -.362	n.s.	n.s,	0.004 -.246	<0.001 .389	n.s.	0.004 .251	<0.001 .335	n.s.

Numbers shown are p-values and Spearman coefficients (grey shading if correlation is significant and in the right direction)

Supplementary Table 9. Frequency of β-catenin IHC positive samples and CTNNB1 mutations Wnt-related and non-Wnt-related subclasses of HCC in the in training (T) and validation (V) sets.

	CTNNB1 class		**Wnt-TGFβ class**		**non-Wnt**		
	T	**V**	**T**	**V**	**T**	**V**	
β-catenin IHC nucl and cyto	63.6% 14/22	82.4% 28/34	20.0% 4/20	16.0% 5/32	29.5% 13/44	17.3% 13/75	*
***CTNNB1* mutations** **(T: Sanger Seq, V: Mutation signature)**	62.5% 15/24	n.d.	9.5% 2/21	n.d.	26.6% 12/45	n.d.	*

* Ratios correspond to positive samples/total number of samples with available data (see Fig. 2 and Suppl Fig. 1)

n.d.: not determined

Supplementary Table 10: Differentially expressed Wnt-related-miRNAs in 89 HCC samples of the training set.

	Wnt-TGFβ vs. CTNNB1		**Wnt-TGFβ vs. Rest**		**CTNNB1 vs. Rest**	
	Score*	FDR	Score*	FDR	Score^	FDR
hmr-miR-181b_rfam7.0	4.976	0.003	2.82	<0.001	-4.739	<0.001
hmr-miR-181a_rfam7.0	4.599	0.003	1.809	0.197	-5.073	<0.001
h-miR-181d_rfam7.0	4.29	0.003	2.658	0.034	-3.156	0.023
hmr-miR-214_rfam7.0	4.014	0.006	1.361	0.349	-5.51	<0.001
hmr-miR-203_rfam7.0	3.262	0.003	1.466	0.218	-3.234	0.009
hmr-miR-145_rfam7.0	2.496	0.023	1.906	0.166	-1.24	0.234
hmr-miR-183_rfam7.0	2.475	0.028	-0.414	0.899	-3.548	0.026
hmr-miR-18a_rfam7.0	2.422	0.015	2.003	0.068	-0.593	0.742
h-miR-503_rfam7.0	2.419	0.039	0.058	0.97	-2.439	0.047
hm-miR-375_rfam7.0	2.11	0.012	1.402	0.214	-2.744	0.048
hm-miR-9*_rfam7.0	1.753	0.056	1.903	<0.001	1.521	0.112
hmr-miR-210_rfam7.0	1.234	0.279	1.507	0.218	-0.057	0.97
hmr-miR-196a_rfam7.0	1.08	0.347	1.027	0.363	-0.485	0.742
hmr-miR-320_rfam7.0	0.34	0.69	-0.413	0.899	-0.917	0.523
hmr-miR-222_rfam7.0	-0.084	0.912	0.5	0.789	0.54	0.617
h-miR-146b_rfam7.0	-0.995	0.397	-0.093	0.97	1.016	0.367
hmr-miR-24_rfam7.0	-1.134	0.306	0.613	0.789	2.183	0.049
hmr-miR-186_rfam7.0	-1.817	0.121	0.194	0.899	2.563	0.029
hmr-miR-16_rfam7.0	-2.002	0.067	-0.256	0.899	2.087	0.062
hmr-miR-135a_rfam7.0	-2.069	0.023	-0.06	0.97	2.067	0.009
hmr-miR-27b_rfam7.0	-2.704	0.012	-1.009	0.544	1.918	0.087
hmr-miR-335_rfam7.0	-2.728	0.02	-3.013	0.034	0.287	0.754
hm-miR-15a_rfam7.0	-2.731	0.02	-0.286	0.899	2.895	0.012
hmr-let-7c_rfam7.0	-2.77	0.025	-1.317	0.363	2.099	0.062
hmr-miR-23b_rfam7.0	-2.799	0.015	-0.291	0.899	3.074	0.009
hmr-miR-29c_rfam7.0	-2.808	0.028	-0.319	0.899	3.191	0.012
hmr-miR-29a_rfam7.0	-3.093	0.012	-0.462	0.899	3.056	0.009
hmr-miR-30a-5p_rfam7.0	-3.54	<0.001	-1.077	0.544	2.878	0.012
hmr-miR-122a_rfam7.0	-3.614	0.006	-2.153	0.198	2.227	0.047
hmr-miR-106b_rfam7.0	-3.715	0.006	-2.025	0.198	2.113	0.062
hmr-miR-30e-5p_rfam7.0	-4.035	0.003	-2.577	0.128	2.288	0.043
hmr-miR-194_rfam7.0	-4.27	0.003	-2.737	0.068	2.369	0.041
hm-miR-148a_rfam7.0	-7.3	0.003	-3.052	0.041	5.551	<0.001

* positive value: up in Wnt-TGFβ; negative value: down in Wnt-TGFβ

^ positive value: up in CTNNB1; negative value: down in CTNNB1

Supplementary Table 11: Enrichment of samples identified by CTNNB1-, Wnt-TGFβ-WntGenes- and *CTNNB1*-mutation-signature in CTNNB1 and Wnt-TGFβ subclasses in 5 independent datasets (Fisher's Exact Test).

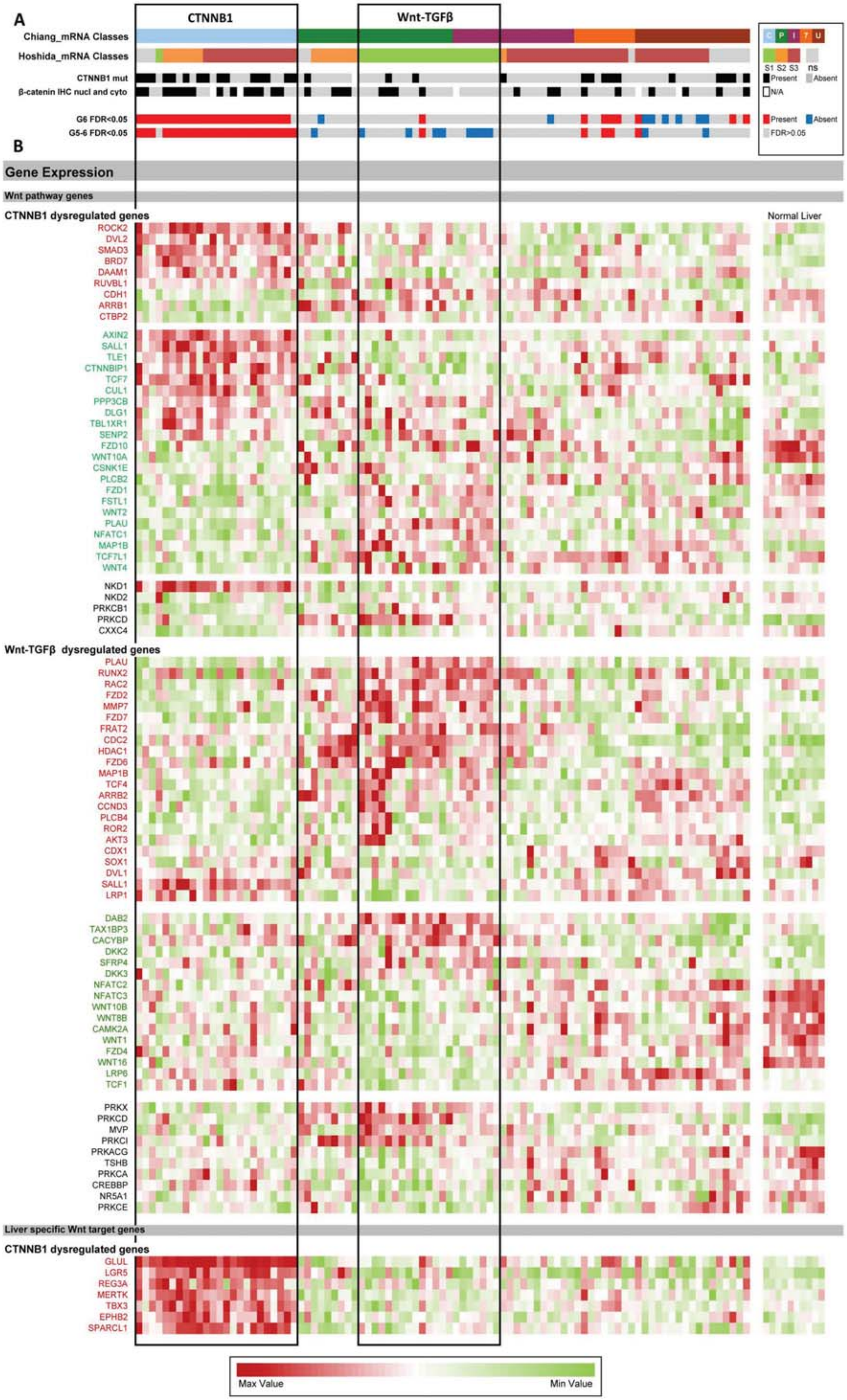
		CTNNB1-WntGenes signature	Wnt-TGFβ-WntGenes signature	*CTNNB1*-mutation-signature
HCC-I	CTNNB1	0.001	n.s.	<0.001
	Wnt-TGFβ	n.s.	<0.001	n.s.
HCC-II	CTNNB1	0.001	n.s.	<0.001
	Wnt-TGFβ	n.s.	<0.001	n.s.
HCC-III	CTNNB1	n/a	n.s.	<0.001
	Wnt-TGFβ	n.s.	<0.001	n.s.
HCC-IV	CTNNB1	<0.001	n.s.	<0.001
	Wnt-TGFβ	n.s.	<0.001	n.s.
HCC-V	CTNNB1	<0.001	n.s.	<0.001
	Wnt-TGFβ	n.s.	<0.001	n.s.

*Prediction of CTNNB1 and Wnt-TGFβ subclasses as previously published in main manuscript reference[18].

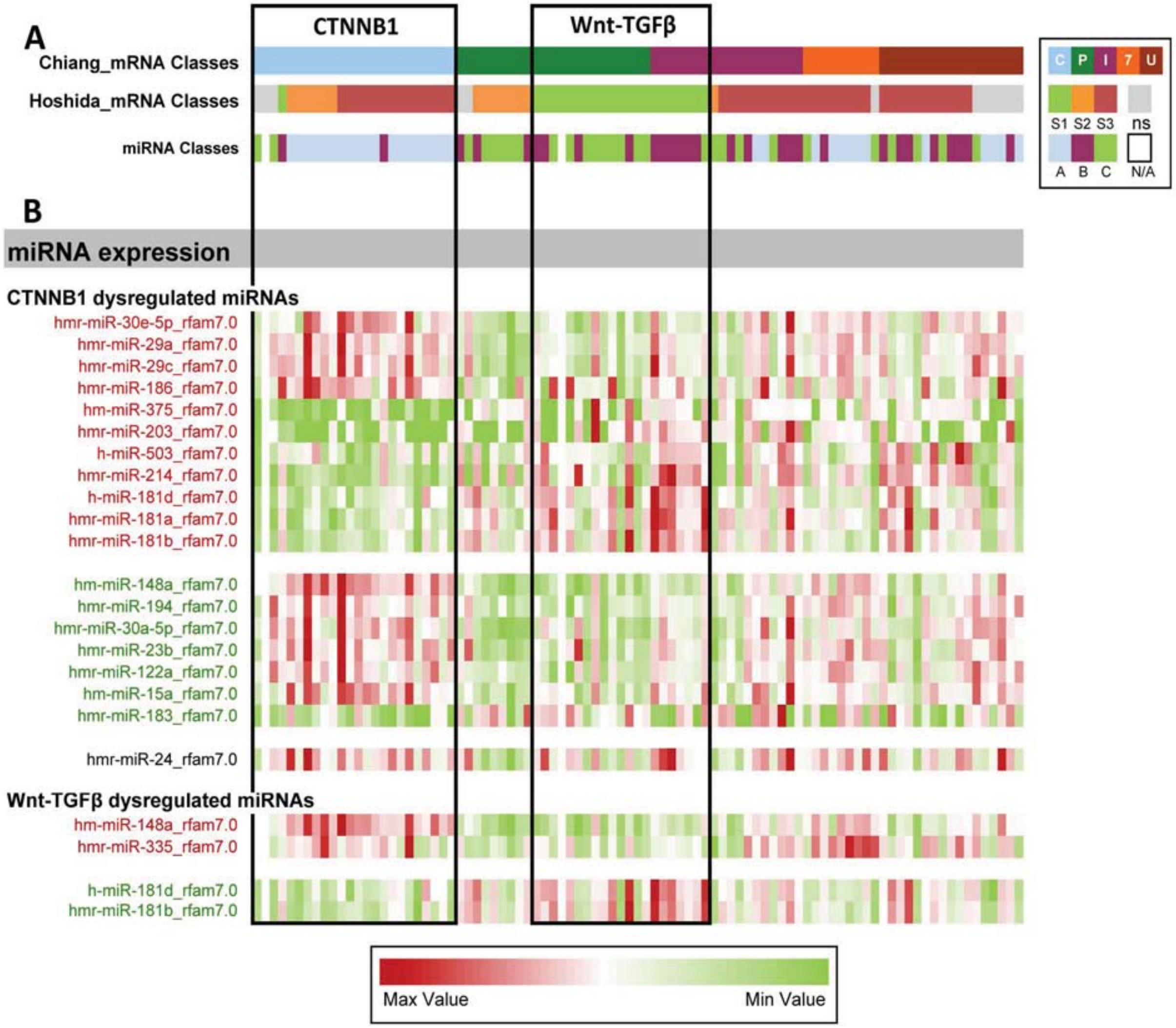
Supplementary Table 12: 21 Liver Cancer cell lines analyzed by GSEA for gene expression profiles similar to either CTNNB1 or Wnt-TGFβ class.

Cell Line	Histology	HBV/HCV
C3A	derivative of HepG2	neg.
HEP3B212	HCC	HBV
HepG2	hepatoblastoma	neg.
HLE	HCC	neg.
HLF	HCC	neg.
Huh1	HCC	HBV
Huh7	HCC	HCV
JHH1	HCC	neg.
JHH2	HCC	neg.
JHH4	HCC	neg.
JHH5	HCC	neg.
JHH7	HCC	HBV
PLCPRF5	HCC	HBV
SKHEP1	Adenocarcinoma	neg.
SNU182	HCC	HBV
SNU387	HCC	HBV
SNU398	HCC	HBV
SNU423	HCC	HBV
SNU449	HCC	HBV
SNU475	HCC	HBV
SNU878	HCC	HBV

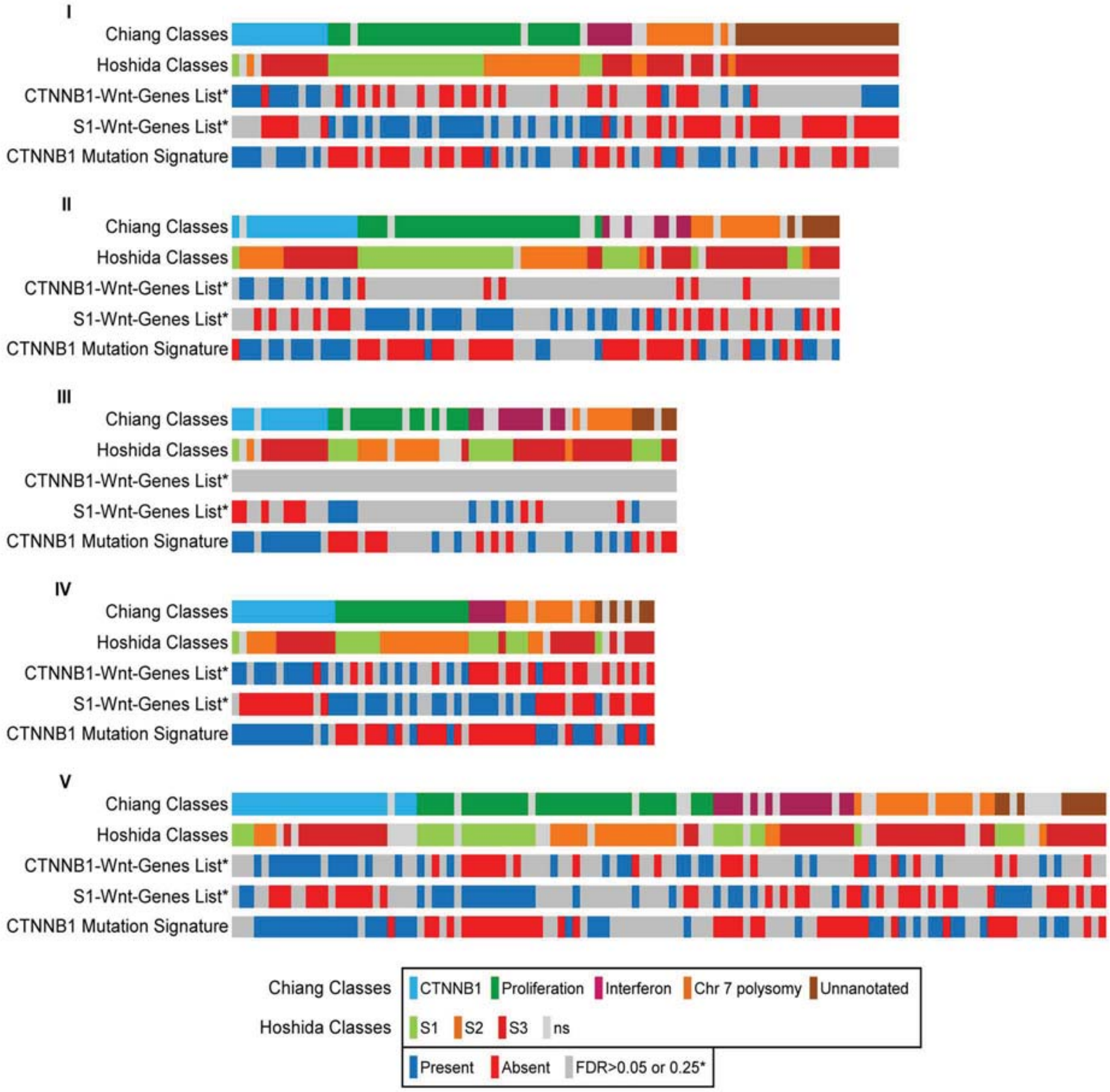
Supplementary Figure 1



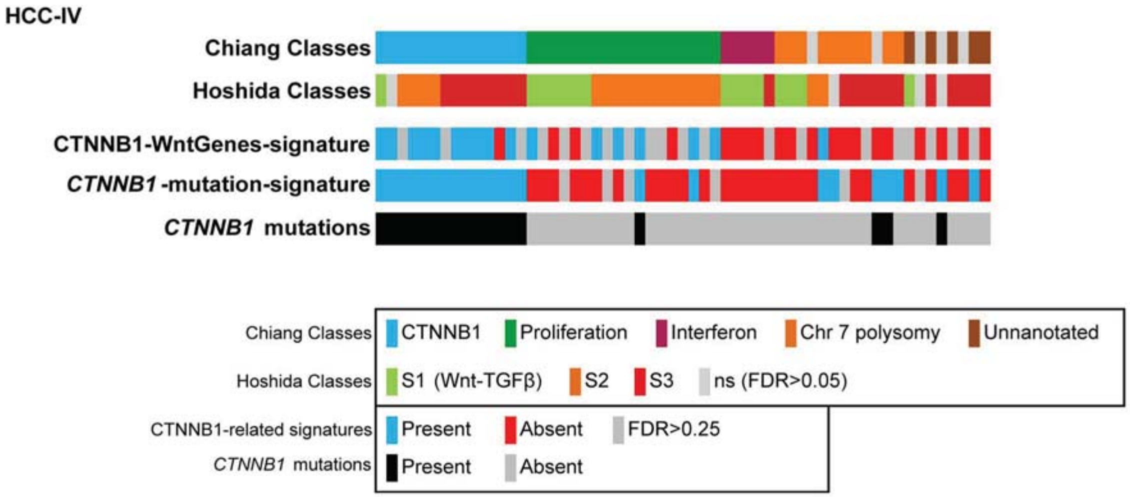
Supplementary Figure 2



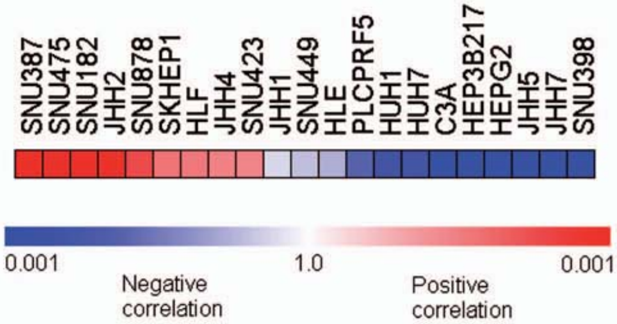
Supplementary Figure 3



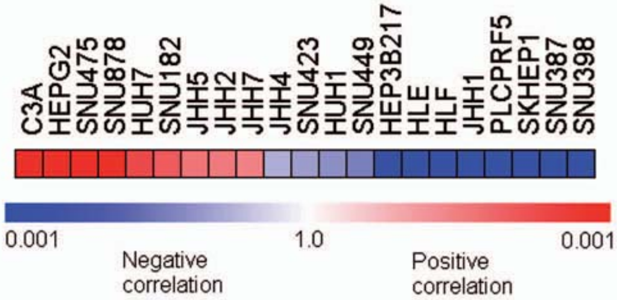
Supplementary Figure 4



Supplementary Figure 5

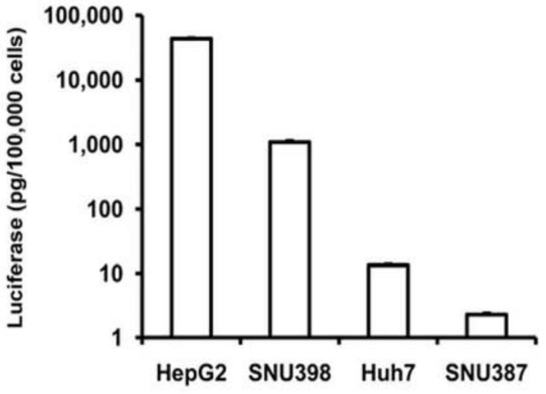


Hoshida's S1 signature enrichment p-value

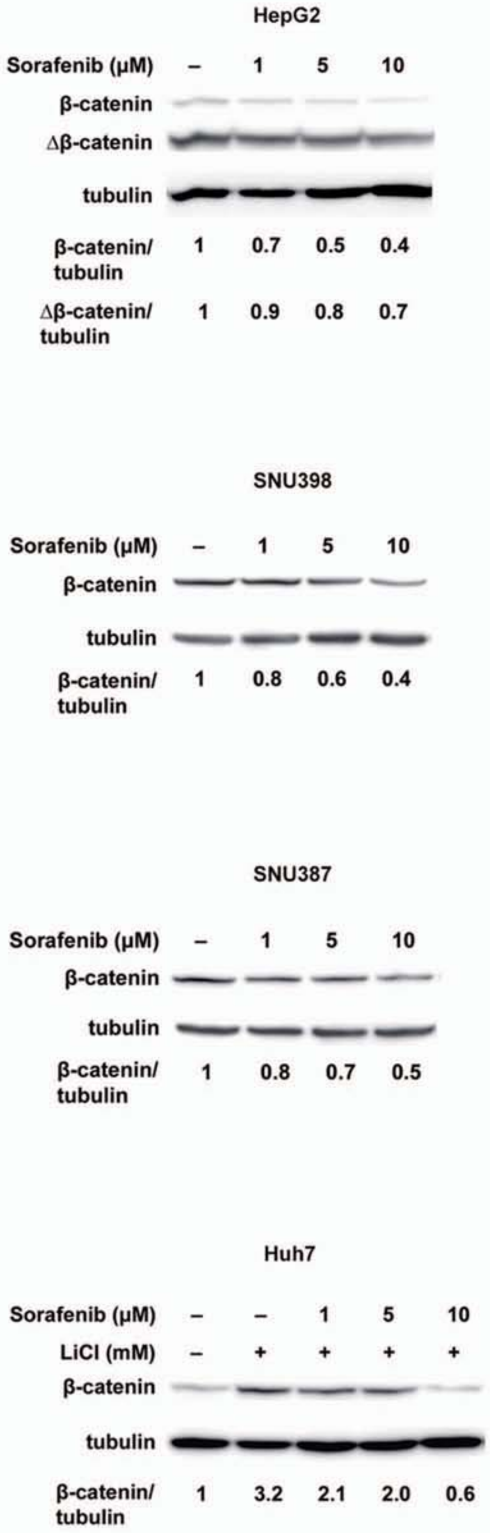


Chiang's CTNNB1 signature enrichment p-value

Supplementary Figure 6



Supplementary Figure 7



Supplementary Figure Legends

Supplementary Figure 1: **Differential Expression of Wnt-pathway mRNAs in the CTNNB1- and Wnt-TGFβ-classes in the training set** (A) Molecular classification, *CTNNB1*-mutation, and CTNNB1-immunohistochemistry (IHC) as reported by Chiang (1); prediction of Hoshida's (15) and Boyault's (16) molecular classes. (B) Heat map representing significantly (FDR<0.05) dysregulated Wnt-pathway-genes and liver-related Wnt-target-genes in CTNNB1- and Wnt-TGFβ-class compared to the remaining HCCs and normal livers. Gene names highlighted in red and green are related to Wnt-pathway activation and inhibition, respectively. Function of genes in black is unclear.

Supplementary Figure 2: **Differential Expression of Wnt-pathway-miRNAs in the CTNNB1- and Wnt-TGFβ-classes in the training set** (A) Molecular classification, as reported by Chiang (1), prediction of Hoshida's (15) molecular classes, and annotation of Toffanin's miRNA classes (17). (B) Heat map with differential expression of Wnt-related-miRNAs in CTNNB1- and Wnt-TGFβ-class compared to the remaining HCCs. MiRNAs highlighted in red and green are related to Wnt-pathway activation and inhibition, respectively. MiRNAs in black have no clear function reported.

Supplementary Figure 3: Validation of CTNNB1- and Wnt-TGFβ-specific Wnt-related mRNA profiles and mutation-status in 5 public HCC datasets CTNNB1-WntGenes-signature was significantly enriched in CTNNB1-class of datasets I, II, IV and V, while Wnt-TGFβ-WntGenes-signature was significantly enriched in Wnt-TGFβ-class of all datasets. Samples called by *CTNNB1*-mutation-signature were significantly correlated to CTNNB1-class in all datasets. All displayed cohorts are publicly available gene expression HCC datasets (Suppl. Table 1), Chiang's and Hoshida's class predicition as previuously published(15).

Supplementary Figure 4: Validation of the mutation signature in an independent cohort of HCC. A high overlap is observed between samples from HCC IV dataset captured by the CTNNB1-mutation-signature and samples known to be mutated for β-catenin. The displayed cohort is a publicly available gene expression HCC datasets (Suppl. Table 1) with CTNNB1 mutation annotation, Chiang's and Hoshida's class predicition as previuously published(15).

Supplementary Figure 5: Correlation of gene expression data from 21 different liver cancer cell lines with CTNNB1 and Wnt-TGFβ class signatures by GSEA (A) Chiang's CTNNB1-signature is significantly enriched in HepG2 cells, but not in SNU 387 and SNU389 cells. (B) Hoshida's Wnt-TGFβ-signature is significantly enriched in SNU387 cells, but not in SNU389, HepG2 and Huh7.

Supplementary Figure 6: Baseline luciferase levels in Wnt reporter liver cancer cells stably transduced with TCF/LEF luciferase reporter Mean inferred luciferase pg values of two independent experiments and standard error bars are represented (logarithmic scale in y-axis).

Supplementary Figure 7: Sorafenib decreases β-catenin protein levels in 4 liver cancer cell lines Decrease of total β-catenin protein levels in non-reporter HepG2, SNU398, SNU387, and LiCl-stimulated Huh7 cells.

Supplementary Methods

Immunocytofluorescence

Ice-cold methanol was used to fix (15 minutes) cells grown on poly-l-lysine coverslips (BD BioCoat, 354085). Cells were washed with PBS, permeabilized with 0.1% Triton X-100 in PBS for 5 minutes and blocking was performed in PBS-5%BSA for 1 hour at room temperature. Anti-β-catenin antibody (BD Transduction Laboratories) was diluted 1:500 in blocking solution, and added to cells for 1 hour at room temperature. Following PBS washes, goat anti-mouse Alexa Fluor-594 conjugated IgG secondary antibody (Molecular Probes, Invitrogen) was diluted 1:500 in blocking solution, and applied for 30 minutes at room temperature. Slides were washed in PBS and covered with Prolong Gold Antifade reagent with DAPI (Invitrogen).

Western blot

Proteins were extracted with RIPA buffer containing phosphatase- (78428, ThermoScientific, Maltham, MA) and protease-inhibitors (04693124001, Roche, Basel, Switzerland). Twenty-five μg of protein were loaded on 7.5% SDS gels and transferred to PVDF membranes. Membranes were BSA-blocked and hybridized at 4°C overnight with primary antibodies β-catenin 1:2000 (9582, Cell Signaling, Danvers, MA) and α-tubulin 1:15,000 (T-5168, Sigma-Aldrich, St. Louis, MO). HRP-conjugated secondary antibody was applied at room temperature for 1 hour. Blots were developed using RPN 2132 ECL plus solution (GE Healthcare) and imaged with FUJIfilm Laser Image Analyzer (GE Healthcare Life Sciences, Waukesha, WI).

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