Original Article

Low expression of citron kinase is associated with poor patient outcomes in hepatocellular carcinoma

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Background: Citron kinase (CIT) is a protein related to cytokinesis and is an important abscission regulator. However, the relationship between CIT and hepatocellular carcinoma (HCC) is unclear. The aim of this study was to investigate the expression CIT in HCC tissues, and explore the connection between this expression and clinicopathological characteristics of HCC.

Methods: Immunohistochemistry staining on 235 HCC tissues and 96 non-tumorous liver tissues controls was performed to examine the CIT protein expression. We then analyzed the correlation between protein expression and clinicopathological parameters via χ^2 tests, and we performed overall survival analyses via the Kaplan-Meier survival approach. Based on the online Oncomine Expression Array and UALCAN databases, we more broadly compared CIT mRNA expression between normal and HCC tissues. Finally, we compared CIT mRNA expression in these databases to protein expression in our study and explored potential sources for any observe differences.

Results: Compared to normal tissues, CIT expression was significantly lower in HCC tissues. Low CIT expression was found to be related to gender, tumor size, Edmondson Grade, Microvascular invasion, serum AFP levels and poor overall survival. Based on the online databases, CIT mRNA expression was found to be high in HCC tissues and decreased in normal tissues. We hypothesize that this unexpected result is due to a negative feedback loop whereby low protein CIT levels mediate increased CIT mRNA levels.

Conclusions: Lower CIT protein levels are associated with a poorer prognosis in HCC patients, and lower CIT protein levels may mediate a negative feedback loop leading to increased CIT mRNA levels.

Keywords: Citron kinase (CIT); hepatocellular carcinoma (HCC); immunohistochemistry

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common tumor type and the third leading cause of death related to cancer worldwide (1). Up to half of all HCC cases occur in China, and there were a total of 782,500 new liver cancer cases and 745,500 deaths worldwide in 2012, with 84.6% of liver cancer incidence and 86.3% of liver cancer deaths in the WHO Western Pacific region (WPRO) occurring

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in China (1-3). HCC is one of the most common forms of cancer in China and thus underscoring the urgent need for novel therapeutic treatment strategies for this deadly disease.

Citron kinase (CIT) is typed as an AGC (cAMP-dependent, cGMP-dependent and protein kinase C) protein kinase, and it is influenced by second messengers, including lipids such as PKC and cyclic AMP (4). The target proteins directly phosphorylated by CIT remain to be identified, although it is known to interact with proteins including KIF14 and TUBB3 (5,6). Known roles for CIT include a relationship with neurogenic cytokinesis, and this gene is known to be mutated in primary microcephaly, suggesting a key role for this gene in central nervous system development (7). A single nucleotide polymorphism in CIT has been found to be significantly related to schizophrenia, and the interaction between polymorphisms in CIT, NDEL1, and DISC1 is known to influence schizophrenia risk (8). CIK can also induce HIV-1 virion production by promoting Gag ubiquitination as well as improving viral release via the multivesicular bodies pathway (9). With respect to cancer, CIT appears to be related with the time to progression of ovarian cancer, and is also associated with therapeutic outcomes (10). CIT has been found to be overexpressed in human colon cancer tissues, wherein it may accelerate cancer cell growth via influencing the p53 signaling pathway (11). CIT protein is also overexpressed in breast cancer tissues, where it is associated with more aggressive forms of this disease (12). CIT depletion can mediate a failure of cytokinesis that may therefore valuable therapeutic efficacy as an anti-cancer strategy in cervical, breast, and colorectal cancer, and potentially in additional cancers (13).

Given the high incidence of HCC and the myriad roles of CIT, we were interested in exploring the role of CIT in HCC. We therefore investigated the expression of CIT in 235 HCC tissues and 96 non-tumorous liver tissues by immunohistochemistry staining to examine the correlations between CIT expression and clinicopathological parameters, as well as to compare this expression with overall patient survival rate. We found that CIT expression was associated with gender, tumor size, Edmondson Grade, Microvascular invasion, serum AFP level, and poor overall survival. We further reviewed available datasets in the Oncomine and UALCAN Expression Array databases to assess CIT mRNA expression. Unexpectedly, we found CIT mRNA expression to be higher in HCC tissues relative to normal liver tissue controls, leading us to speculate regarding the potential reasons for this discrepancy.

Methods

Patients and tissue samples

All the human tissues were acquired from HCC patients at Zhejiang Provincial People's Hospital (Hangzhou, China). This research was approved by the Ethics Committee of Zhejiang Provincial People's Hospital (Hangzhou, China). All the patients provided written informed consent.

A total of 235 paraffin-embedded HCC tissue samples and 96 non-tumorous liver tissue samples were acquired from April 2008 to September 2014. This patient cohort consisted 191 males and 44 females. Survival time was calculated based on the time between the date of surgery and the end of follow-up or date of death. All the tissues were used for a tissue microarray (TMA) analysis constructed by Shanghai Biochip Co., Ltd (Shanghai, China).

Immunohistochemical staining and evaluation

According to the manufacturer's instructions, immunohistochemical staining was conducted using the Histostain-Plus IHC Kit (cat.no.856143; Invetrogen, USA). We heated 5 μm sections from the TMAs at 70 ℃ for 2 hours, after which they were de-paraffinized, rehydrated, and boiled in TE buffer for 3 min to retrieve antigen. Next, the sections were blocked with 3% H_2O_2 for 15 min to inhibit endogenous peroxidase activity, and they were then incubated with 10% goat non-immune serum for 20 min to decrease background non-specific staining. After that, samples were probed with a rabbit anti-CIT polyclonal antibody (1:400; lot. no. GR48652-1; ab110897; Abcam, Cambridge, UK) at 4 ℃ overnight, followed by incubation with a biotin-labeled secondary antibody for 20 min at room temperature, and then with HRP-conjugated streptavidin for 20 min at room temperature. A DAB Kit (ZSGB-BIO, Beijing, China) was additionally used to enhance color development. Finally, the sections were counterstained with hematoxylin, dehydrated, cleared, and mounted.

Two independent pathologists reviewed and scored all samples based on the strength of staining and on the percent of positively stained cells. A four-tiered scoring system was used as followed: for staining, 0 = negative, 1 = weak, 2 = moderate, and 3 = strong; for cell staining positivity: 0 for no cell stained, 1 for 1–25% of cells stained, 2 for 26–50% of cell stained, 3 for more than 50% of cells stained. As all sections tended to exhibit >50% staining in both HCC tissues and non-tumorous liver tissues, scores for

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Table 1 Expression of Citron kinase (CIT) in hepatocellular carcinoma (HCC) and non-cancerous liver tissues

Samples	CIT expression		P
	Low	High	
Non-cancerous liver tissues	2	94	<0.001
HCC tissues	61	174	

the percent of positively stained cells were 3 for all samples. Scores for strength and percent of positively stained cells were multiplied together to yield an overall score. Scores <6 was indicative of low CIT expression, while scores ≥6 were indicative of high CIT expression.

Oncomine and UALCAN database analyses

A comprehensive analysis of extant datasets in the Oncomine Expression Array database (www.oncomine.org) was conducted to compare the mRNA expression of CIT between HCC and normal tissues, using the following search items: 'CIT', 'mRNA', 'Cancer *vs.* Normal Analysis' and 'Hepatocellular Carcinoma'. We identified five relevant datasets including Chen Liver (14), Roessler Liver, Roessler Liver 2 (15), Mas Liver (16), and Wurmbach Liver (17). An additional analysis based on the online UALCAN database analysis (ualcan.path.uab.edu) was also conducted as above, unsing the search items: 'Analysis', 'CIT', 'Liver Hepatocellular Carcinoma'.

Statistical analysis

Statistical analysis was fulfilled by using SPSS v13.0 (SPSS Inc., Chicago, IL). Chi-squared tests were used to assess the statistical significance of the relationship between CIT protein expression and clinicopathological parameters. We additionally used the Kaplan-Meier method to estimate survival curves, and the log-rank test was used for calculating differences between these curves. P<0.05 was the threshold of statistical significance.

Results

Expression of CIT in HCC and adjacent non-cancerous tissues

Immunostaining for CIT was evident in the cytoplasm and absent in the nuclei of both non-cancerous liver and HCC tissues. CIT was highly expressed in 94 of the 96 (97.91%) samples of adjacent non-cancerous liver tissues (*Table 1*). CIT expression was clearly decreased in HCC tissues, with low expression of CIT in 174 of the 235 (74.04%) HCC tissues (*Figures 1*,*2*). These decrease in CIT expression was significant (P<0.001).

Relationship between CIT expression and clinicopathologic parameters

The relation between the expression of CIT and clinical variables was explored, and the results are shown in *Table 2*. CIT expression was significantly associated with gender, tumor size, Edmondson Grade, microvascular invasion, and AFP. The expression of CIT was significantly decreased in tumor of females, large tumors, tumors with a high Edmondson Grade, tumors with evident microvascular invasion or those with a high AFP level. There was no significant relationship between CIT expression and other assessed clinicopathologic parameters. These parameters and lower CIT expression are thus associated with poorer patient outcomes.

Survival analysis

The 5-year cumulative survival rate of patients with low CIT expression was 33.3%, while that of patients with high CIT expression was 68.9% based on a Kaplan-Meier survival analysis. Patients with low CIT expression had a mean survival time of 26.706±7.563 months, which was significantly shorter than that of patients in the high CIT expression group (45.860±4.449, P<0.001). These data indicated that low expression of CIT is related with poor overall survival (*Figure 3*).

Analysis of CIT expression according to Oncomine and UALCAN databases

We next explored available datasets in the Oncomine database to compare CIT mRNA expression in HCC with normal tissues. What we found is that CIT mRNA

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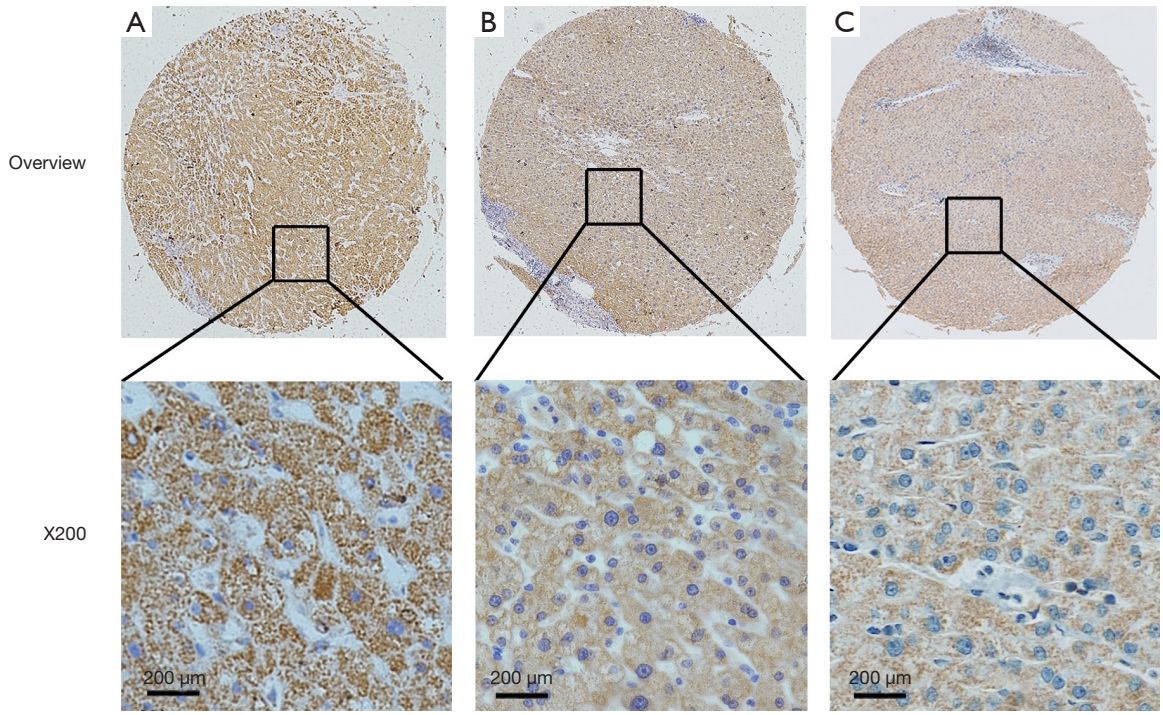

Figure 1 Immunohistochemical staining of Citron Kinase in non-cancerous liver tissues. (A) Cirrhosis tissues; (B) hyperplastic tissues; (C) inflammatory tissues.

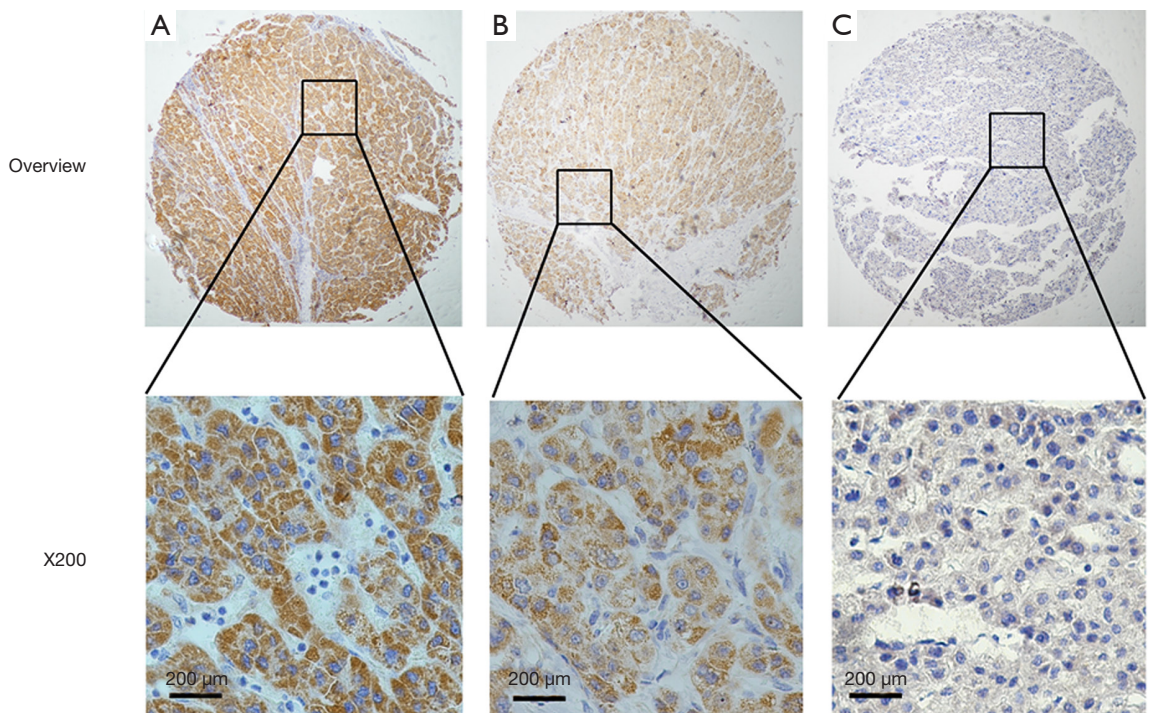

Figure 2 Immunohistochemical staining of Citron Kinase in hepatocellular carcinoma tissues. (A) Strong expression; (B) moderate expression; (C) negative expression.

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Table 2 Relationship between CIT expression and clinicopathologic parameters

Clinical parameters	All cases	CIT		P value
		Low	High	
Age (years)				0.240
<55	93	28	65	
≥55	142	33	109	
Gender				0.033
Male	191	44	147	
Female	44	17	27	
Size				0.017
<5	111	21	90	
≥5	119	39	80	
Tumour number				0.726
Single	193	51	142	
Multiple	42	10	32	
Edmondson grade				0.011
I+II	151	31	120	
III	84	30	54	
Metastasis				0.180
M0	212	52	160	
M1	18	7	11	
Microvascular invasion				0.015
Absence	85	17	68	
Presence	99	36	63	
HBs antigen				0.123
Negative	46	16	30	
Positive	186	44	142	
AFP				0.003
<50	96	10	86	
≥50	82	23	59	
Status				<0.001
Alive	75	13	62	
Dead	54	26	28	

expression was higher in HCC tissues relative to normal controls (*Figure 4*, all P<0.05, except P=0.980 between HCC and Mas Liver). Similarly, we found CIT mRNA expression to be higher in HCC tissues compared with normal tissues in the UALCAN Expression Array database (*Figure 5*, P<0.05). Survival analyses of these HCC patients showed that the patients with high CIT mRNA expression had significantly shorter survival times as compared with

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patients in the low CIT expression group based on the UALCAN database. These data thus demonstrate that high CIT mRNA expression was related to with poorer overall survival (*Figure 6*, P<0.05). These data highlight a discrepancy between these mRNA data and our protein level data, leading us to speculate that low CIT protein levels may mediate a feedback loop that results in a compensatory over-expression of the CIT mRNA.

Discussion

HCC is among the most common tumors in the world, and there is thus an urgent need to better understand and develop novel treatments for this disease. CIT is a multi-functional protein that is most highly expressed in fetal liver, with levels gradually decreasing after birth. Src and CIT are also downstream effectors of the Eph-induced signal transduction cascade, and Eph kinase activity control abscission (18). Indeed, CIT is known to be tightly linked with cytokinesis, a process which it controls using its coiled-coil domain, mediating the transition from constriction to abscission (19). Low level of TUBB3 in mitotic cells can be detrimental to their cytokinesis, and CIT can control TUBB3 phosphorylation to stabilize mid-body microtubules and cytokinesis (6). Two-pore channel 1 and $p27^{Kip1}$ (p27) also interact with CIT to regulate cytokinesis (20,21). We had found no evidence for CIT to play a role in other mitotic events besides cytokinesis, until a recent research reported that it is required for the orientation of the mitotic spindle during metaphase (22). Aurora B, ASPM and CIT control mid-body architecture and spindle positioning during cytokinesis, and are necessary to maintain proliferating cell division (22,23). Specific tyrosine residues in CIT are known to be phosphorylated, and it has been demonstrated that such tyrosine phosphorylation of CIT impairs cytokinesis (19). CIT is an important abscission regulator, using active RhoA and anillin to promote mid-body stability (24). In our research, we found CIT to be expressed at lower levels in HCC tissues and at higher levels in normal tissues. This result suggests that CIT may function as a tumor suppressor in HCC, and may thus be an ideal therapeutic target in this disease. We thus conclude that lower CIT levels are associated with poorer patient outcomes in HCC.

Interestingly, while we observed a decrease in CIT levels in HCC samples at the protein level, we observed the opposite finding when assessing CIT mRNA levels in normal and HCC tissues using the Oncomine and

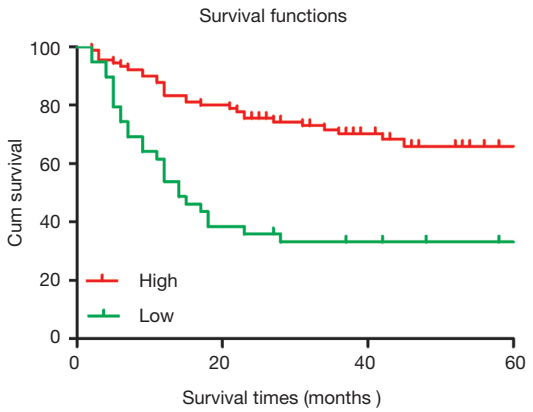

Figure 3 Kaplan-Meier survival curves of the hepatocellular carcinoma patients with high or low citron kinase expression.

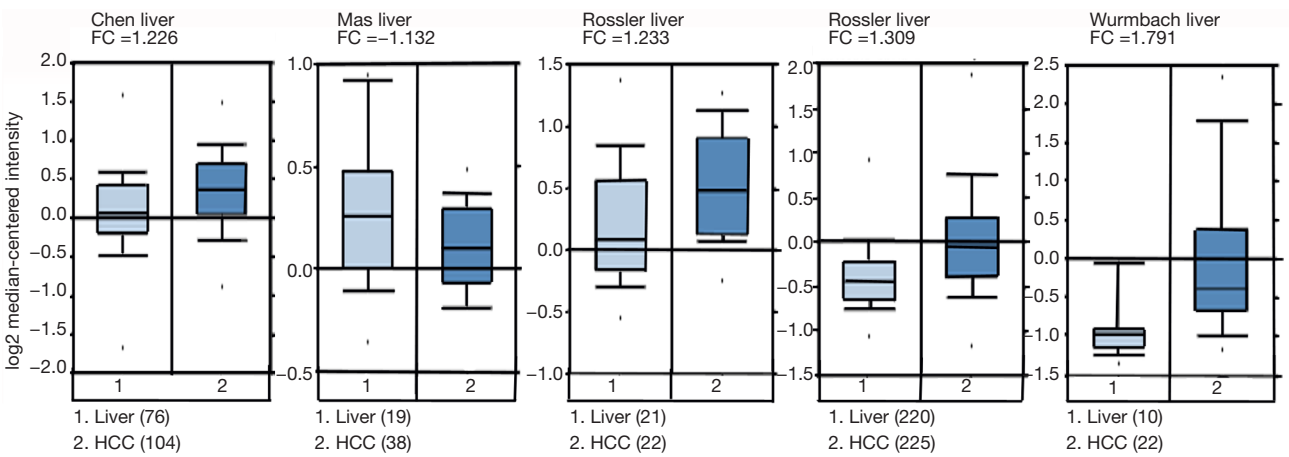

Figure 4 Expression of citron kinase in normal liver and hepatocellular carcinoma tissues according to Oncomine database.

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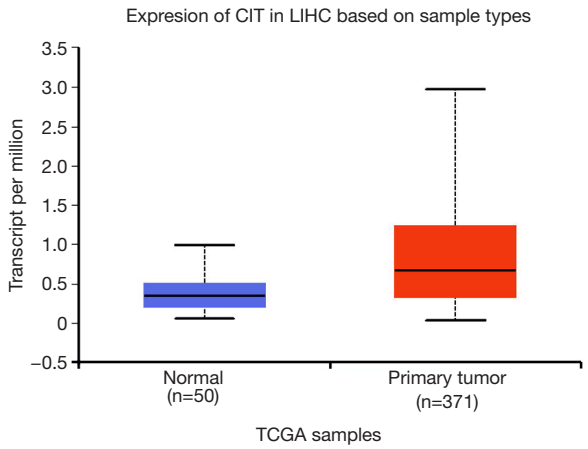

Figure 5 Expression of citron kinase in normal liver and hepatocellular carcinoma tissues based on UALCAN database.

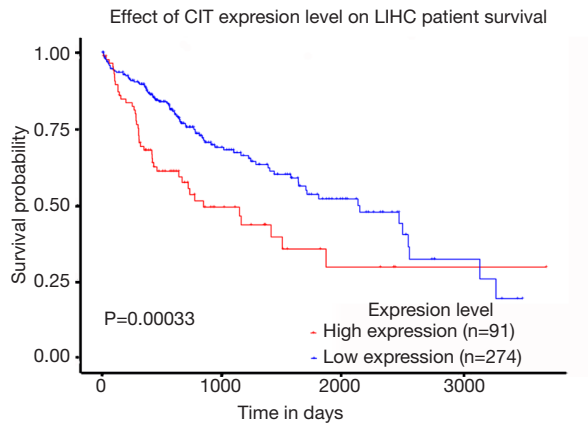

Figure 6 Survival curves of the hepatocellular carcinoma patients with high or low citron kinase expression based on UALCAN database.

UALCAN databases. Indeed, these results suggested that higher CIT expression was associated with poorer HCC prognosis, and a published article has also detected elevated CIT mRNA levels in HCC (25). These results are thus at odds with our protein level finding, which may be due to a difference in the readout being examined. Indeed, it may be that the decrease CIT protein levels which we observed in the present study initiated a feedback loop, resulting in increasing CIT mRNA expression in order to compensate for the decrease protein levels within cells, although further research will be needed to verify this finding.

In conclusion, we found that low CIT protein expression is associated with poorer outcomes in HCC patients. Low CIT expression was associated with gender, tumor size, Edmondson Grade, microvascular invasion, serum AFP level, and poor overall survival. Differences in the specific readout being examined may explain the discrepancies in the data between the present study and published databases.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.03.58). All authors reports grants from Zhejiang Province Bureau of Health, during the conduct of the study.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The research was allowed by Review Board of Hospital Ethics Committee, and the informed consent from every patient was obtained before we collected the data. Written informed consent was obtained from the patient to publish this paper.

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Supplementary

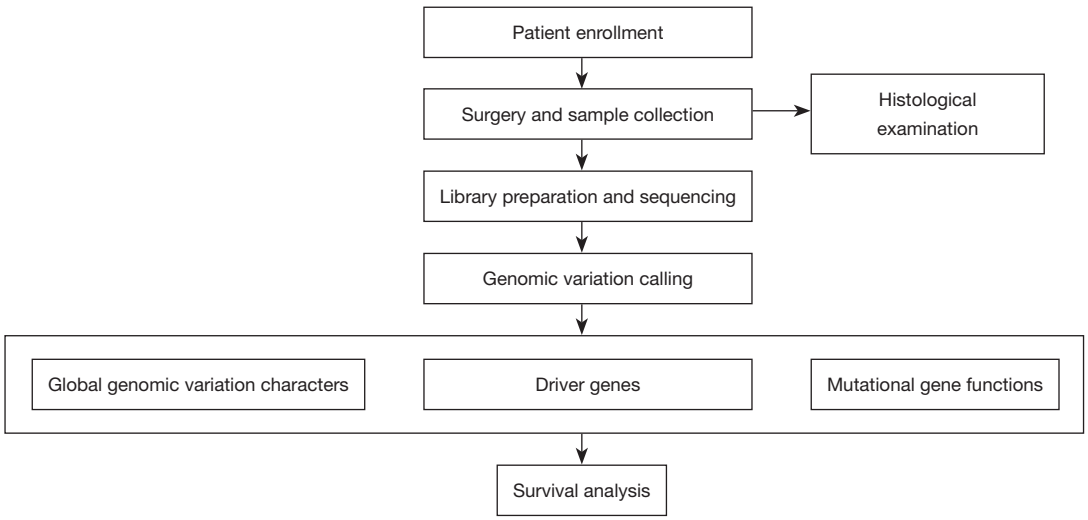

Figure S1 Workflow for this study.

Table S1 Clinical characteristics in each histological grade

Characteristics	Histological grade	
	Poor/moderate	Well
Age (mean ± SD)	54.9±15.0	60.7±12.5
Gender		
Male	358	44
Female	54	3
Stage		
I/II/III	375	43
IV	37	4
Drink		
Yes	50	7
No	362	40
Family		
Yes	92	5
No	320	42

ABCB1	CDKN2B	FGF12	LRP1B	PDCD1 (PD-1)	SMARCB1
ABL1	CDKN2C	FGF14	LRP2	PDCD1LG2	SMARCD1
ABL2	CEACAM3	FGF18	LTK	PDCD1LG2 (PD-L2)	SMO
ACVR1B	CEBPA	FGF19	LYN	PDGFB	SNCAIP
ACVR2A	CFTR	FGF2	LZTR1	PDGFRA	SND1
ADAM29	CHD2	FGF21	MACC1	PDGFRB	SOCS1
ADGRA2	CHD4	FGF23	MAF	PDK1	SOX10
AKT1	CHEK1	FGF3	MAGI2	PHF6	SOX2
AKT2	CHEK2	FGF4	MALAT1	PIK3C2B	SOX9
AKT3	CIC	FGF5	MAP2K1	PIK3C2G	SPEN
ALK	CLDN18	FGF6	MAP2K1 (MEK1)	PIK3C3	SPINK1
ALOX12B	COL1A1	FGF7	MAP2K2	PIK3CA	SPOP
AMER1	CRBN	FGF9	MAP2K2 (MEK2)	PIK3CB	SPTA1
APC	CREB3L1	FGFR1	MAP2K4	PIK3CD	SRC
APEX1	CREB3L2	FGFR2	MAP3K1	PIK3CG	SRGAP1
APOBEC3B	CREBBP	FGFR3	MAP3K13	PIK3R1	SRMS
AQP3	CRKL	FGFR4	MAP4K5	PIK3R2	SRSF2
AR	CRLF2	FGR	MAPK1	PIM1	SS18
ARAF	CSF1	FH	MCF2L	PKD2	SSX1
ARAP3	CSF1R	FLCN	MCL1	PKN1	STAG2
ARFRP1	CSF3R	FLI1	MDM2	PLA2G1B	STAT3
ARHGAP4	CSK	FLT1	MDM4	PLCG2	STAT4
ARHGAP6	CSNK1A1	FLT3	MECOM	PML	STAT6
ARHGDIA	CTCF	FLT4	MED12	PMS2	STK11
ARHGEF10	CTLA4	FOS	MEF2B	POLB	STK24
ARHGEF17	CTNNA1	FOXL2	MEN1	POLD1	SUFU
ARHGEF25	CTNNB1	FOXO1	MERTK	POLE	SUZ12
ARHGEF3	CUL3	FOXP1	MET	PPARG	SYK
ARID1A	CUL4A	FRS2	MGMT	PPP2R1A	TAF1
ARID1B	CXCR4	FUBP1	MITF	PPP2R2A	TBX3
ARID2	CYLD	FUS	MKNK1	PRDM1	TCF3
ASXL1	CYP17A1	FYN	MLH1	PREX2	TCF7L2
ATF1	CYP2D6	GABRA6	MPL	PRKACA	TEK
ATM	DAXX	GATA1	MR1	PRKAR1A	TERC
ATR	DDR1	GATA2	MRE11	PRKCI	TERT
ATRX	DDR2	GATA3	MS4A1	PRKDC	TET1
AURKA	DEF6	GATA4	MSH2	PRPF38B	TET2
AURKB	DICER1	GATA6	MSH3	PRSS1	TET3
AXIN1	DIS3	GID4	MSH6	PRSS8	TFE3
AXIN2	DLC1	GLI1	MST1R	PTCH1	TFEB
AXL	DNMT3A	GLI2	MTAP	PTEN	TGFBR1
B2M	DNMT3B	GLI3	MTG1	PTK2	TGFBR2
BAP1	DOT1L	GNA11	MTOR	PTK6	TIE1
BARD1	DPYD	GNA13	MUC16	PTPN11	TIPARP
BCL2	DYNLL1	GNAQ	MUTYH	PTPRO	TLX1
BCL2L1	ECT2	GNAS	MYB	QKI	TMPRSS2
BCL2L11 (BIM)	EED	GRIN2A	MYC	RAC1	TNFAIP3
BCL2L2	EGF	GRM3	MYCL	RAD17	TNFRSF14
BCL6	EGFR	GSK3B	MYCN	RAD21	TNFSF11
BCL7A	EMSY	GSTP1	MYD88	RAD50	TNFSF13B
BCOR	EP300	H2AFX	MYH11	RAD51	TNK2
BCORL1	EPCAM	H3F3A	MYOD1	RAD51B	TOP1
BCR	EPHA2	HCK	NAB2	RAD51C	TOP2A
BIRC3	EPHA3	HDAC1	NBN	RAD51D	TP53
BIRC5	EPHA5	HDAC9	NCOA2	RAD52	TP63
BLK	EPHA6	HGF	NCOR1	RAD54B	TPMT
BLM	EPHA7	HLA-A	NEK11	RAD54L	TRAF7
BMPR1A	EPHA8	HMGA2	NET1	RAF1	TRIO
BMX	EPHB1	HNF1A	NF1	RANBP2	TSC1
BRAF	EPHB4	HRAS	NF2	RARA	TSC2
BRCA1	ERBB2	HSD3B1	NFE2L2	RB1	TSHR
BRCA2	ERBB2 (HER2)	HSP90AA1	NFIB	RBM10	TSPAN1
BRD4	ERBB3	HTATIP2	NFKBIA	RECQL	TSPAN31
BRIP1	ERBB4	ID3	NKX2-1	RECQL4	TYK2
BTG1	ERCC1	IDH1	NOTCH1	REL	TYRO3
BTG2	ERCC4	IDH2	NOTCH2	RELA	U2AF1
BTK	ERCC5	IGF1R	NOTCH3	RELB	UGT1A1
CALR	ERG	IGF2	NOTCH4	RET	USP6
CAMTA1	ERRFI1	IKBKE	NPM1	REV3L	VEGFA
CARD11	ESR1	IKZF1	NR4A3	RHBDF2	VGLL3
CASP8	ESR1(ER)	IL7R	NRAS	RHOA	VHL
CBFB	ETV1	INHBA	NRG1	RICTOR	WEE1
CBL	ETV4	INPP4B	NRG3	RIT1	WEE2
CCND1	ETV5	IRF1	NSD1	RNF43	WISP3
CCND2	ETV6	IRF2	NSD2	ROCK1	WRN
CCND3	EWSR1	IRF4	NT5C2	ROCK2	WT1
CCNE1	EWSR1 (EWS)	IRS2	NTHL1	ROS1	XIAP
CD1A	EZH2	ITK	NTRK1	RPTOR	XPO1
CD1B	EZR	JAK1	NTRK2	RSPO2	XRCC2
CD1C	FAM135B	JAK2	NTRK3	RUNX1	XRCC3
CD1D	FAM46C	JAK3	NUP88	RUNX1T1	YAP1
CD1E	FANCA	JUN	NUP93	RXRA	YES1
CD22	FANCC	KAT6A	NUTM1	SDC4	YWHAE
CD274	FANCD2	KDM5A	OBSCN	SDHA	ZBTB2
CD274 (PD-L1)	FANCE	KDM5B	P2RY8	SDHB	ZNF217
CD36	FANCF	KDM5C	PAK1	SDHC	ZNF703
CD70	FANCG	KDM6A	PAK3	SDHD	ZNF750
CD74	FANCL	KDR	PALB2	SETBP1	ZRSR2
CD79A	FANCM	KEAP1	PARK2	SETD2	
CD79B	FARP1	KEL	PARP1	SF3B1	
CDC42	FAS	KIT	PARP2	SGK1	
CDC73	FAT1	KLHL6	PARP3	SIK1	
CDH1	FAT3	KMT2A	PARP4	SKP2	
CDK12	FAT4	KMT2C	PAX3	SLC34A2	
CDK4	FBXO31	KMT2D	PAX5	SLC6A2	
CDK6	FBXW7	KRAS	PAX7	SLIT2	
CDK8	FEN1	LCK	PBRM1	SMAD2	
CDKN1A	FEV	LIMK1	PBX1	SMAD3	
CDKN1B	FGF1	LMO1	PCA3	SMAD4	
CDKN2A	FGF10	LRP1	PDCD1	SMARCA4	

Figure S2 The gene list of the targeted sequencing.

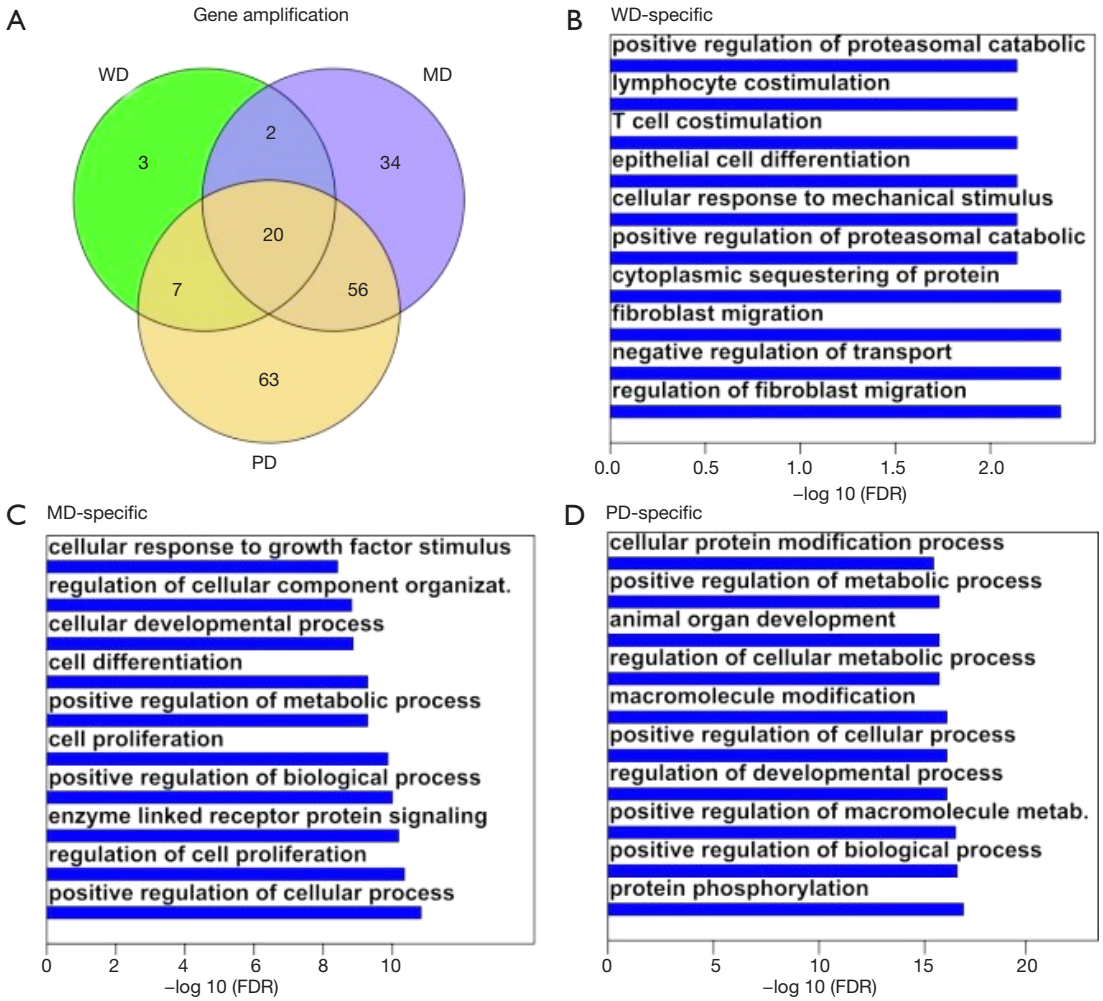

Figure S3 Gene amplification difference between different grades. (A) The gene amplification overlaps between three HGs for substitution/indel/truncation; (B) the enriched biological processes for well differentiated tumors; (C) the enriched biological processes for moderately differentiated tumors; (D) the enriched biological processes for poorly differentiated tumors. The length of the blue bar indicates the negative log transformed false discover rate (FDR). WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

Table S2 The HG-specific biological processes

GOID	P values_adjusted	go_terms	Dataset	HG-specific
GO:0001525	1.264E-06	Angiogenesis	ZB	PD
GO:0036092	1.584E-05	Phosphatidylinositol-3-phosphate biosynthetic process	MSKCC	PD
GO:0006661	9.918E-05	Phosphatidylinositol biosynthetic process	MSKCC	PD
GO:0006650	0.0002442	Glycerophospholipid metabolic process	ZB	PD
GO:0036092	0.000248	Phosphatidylinositol-3-phosphate biosynthetic process	ZB	PD
GO:1902751	0.0002485	Positive regulation of cell cycle G2/M phase transition	ZB	PD
GO:0006650	0.0003463	Glycerophospholipid metabolic process	MSKCC	PD
GO:0006661	0.0007599	Phosphatidylinositol biosynthetic process	ZB	PD
GO:0006644	0.000767	Phospholipid metabolic process	ZB	PD
GO:0008584	0.0008151	Male gonad development	MSKCC	PD
GO:0046546	0.0008151	Development of primary male sexual characteristics	MSKCC	PD
GO:0006644	0.0010525	Phospholipid metabolic process	MSKCC	PD
GO:0046474	0.0010952	Glycerophospholipid biosynthetic process	MSKCC	PD
GO:0090218	0.0015026	Positive regulation of lipid kinase activity	MSKCC	PD
GO:0045017	0.0018219	Glycerolipid biosynthetic process	MSKCC	PD
GO:0019637	0.0019276	Organophosphate metabolic process	ZB	PD
GO:0007126	0.002289	Meiotic nuclear division	ZB	PD
GO:0008654	0.0023611	Phospholipid biosynthetic process	MSKCC	PD
GO:0043551	0.0026075	Regulation of phosphatidylinositol 3-kinase activity	MSKCC	PD
GO:1903046	0.0027839	Meiotic cell cycle process	ZB	PD
GO:1903727	0.0027864	Positive regulation of phospholipid metabolic process	MSKCC	PD
GO:0001525	0.0030352	Angiogenesis	MSKCC	PD
GO:0010518	0.0032304	Positive regulation of phospholipase activity	ZB	PD
GO:0030855	0.0040562	Epithelial cell differentiation	MSKCC	PD
GO:0035272	0.0042767	Exocrine system development	MSKCC	PD
GO:0043550	0.0042767	Regulation of lipid kinase activity	MSKCC	PD
GO:1902749	0.0046541	Regulation of cell cycle G2/M phase transition	MSKCC	PD
GO:0048146	0.0049414	Positive regulation of fibroblast proliferation	MSKCC	PD
GO:0033008	0.0050369	Positive regulation of mast cell activation involved in immune response	ZB	PD
GO:0043306	0.0050369	Positive regulation of mast cell degranulation	ZB	PD
GO:0046474	0.0050474	Glycerophospholipid biosynthetic process	ZB	PD
GO:0051321	0.0051928	Meiotic cell cycle	ZB	PD
GO:0043269	0.0052714	Regulation of ion transport	MSKCC	PD
GO:0014068	0.0059387	Positive regulation of phosphatidylinositol 3-kinase signaling	ZB	PD
GO:0033008	0.0062257	Positive regulation of mast cell activation involved in immune response	MSKCC	PD
GO:0043306	0.0062257	Positive regulation of mast cell degranulation	MSKCC	PD
GO:0033005	0.0066599	Positive regulation of mast cell activation	ZB	PD
GO:0045017	0.0071944	Glycerolipid biosynthetic process	ZB	PD
GO:0044839	0.0072853	Cell cycle G2/M phase transition	MSKCC	PD
GO:0014068	0.0073914	Positive regulation of phosphatidylinositol 3-kinase signaling	MSKCC	PD
GO:0002888	0.0080025	Positive regulation of myeloid leukocyte mediated immunity	ZB	PD
GO:0043302	0.0080025	Positive regulation of leukocyte degranulation	ZB	PD
GO:0033005	0.0082744	Positive regulation of mast cell activation	MSKCC	PD
GO:0008654	0.0087335	Phospholipid biosynthetic process	ZB	PD
GO:0034109	0.0088759	Homotypic cell-cell adhesion	ZB	PD
GO:0030855	0.0089828	Epithelial cell differentiation	ZB	PD
GO:1902751	0.0091779	Positive regulation of cell cycle G2/M phase transition	MSKCC	PD
GO:0006629	0.0093471	Lipid metabolic process	MSKCC	PD
GO:0008610	0.0100358	Lipid biosynthetic process	MSKCC	PD
GO:0002888	0.0100358	Positive regulation of myeloid leukocyte mediated immunity	MSKCC	PD
GO:0043302	0.0100358	Positive regulation of leukocyte degranulation	MSKCC	PD
GO:0034109	0.0114927	Homotypic cell-cell adhesion	MSKCC	PD
GO:0051656	0.0119185	Establishment of organelle localization	ZB	PD
GO:0043269	0.0125078	Regulation of ion transport	ZB	PD
GO:0060735	0.0129404	Regulation of eif2 alpha phosphorylation by dsRNA	ZB	PD
GO:0042102	0.0130323	Positive regulation of T cell proliferation	ZB	PD
GO:0030178	0.0141809	Negative regulation of Wnt signaling pathway	ZB	PD
GO:0006629	0.0150464	Lipid metabolic process	ZB	PD
GO:0051656	0.0165508	Establishment of organelle localization	MSKCC	PD
GO:0060735	0.0165508	Regulation of eif2 alpha phosphorylation by dsRNA	MSKCC	PD
GO:0007126	0.0170219	Meiotic nuclear division	MSKCC	PD
GO:0042102	0.0174305	Positive regulation of T cell proliferation	MSKCC	PD
GO:0090218	0.0181076	Positive regulation of lipid kinase activity	ZB	PD
GO:0032885	0.0187746	Regulation of polysaccharide biosynthetic process	ZB	PD
GO:0030178	0.0195602	Negative regulation of Wnt signaling pathway	MSKCC	PD
GO:1903046	0.0198476	Meiotic cell cycle process	MSKCC	PD
GO:0008610	0.020913	Lipid biosynthetic process	ZB	PD
GO:0032752	0.0213557	Positive regulation of interleukin-3 production	ZB	PD
GO:0042223	0.0213557	Interleukin-3 biosynthetic process	ZB	PD
GO:0043366	0.0213557	Beta selection	ZB	PD
GO:0045399	0.0213557	Regulation of interleukin-3 biosynthetic process	ZB	PD
GO:0045401	0.0213557	Positive regulation of interleukin-3 biosynthetic process	ZB	PD
GO:0007257	0.0216117	Activation of JUN kinase activity	ZB	PD
GO:0032881	0.0216117	Regulation of polysaccharide metabolic process	ZB	PD
GO:1902749	0.0218429	Regulation of cell cycle G2/M phase transition	ZB	PD
GO:0044839	0.0237717	Cell cycle G2/M phase transition	ZB	PD
GO:0033003	0.0243556	Regulation of mast cell activation	ZB	PD
GO:0043551	0.0243556	Regulation of phosphatidylinositol 3-kinase activity	ZB	PD
GO:1903727	0.0252945	Positive regulation of phospholipid metabolic process	ZB	PD
GO:0032885	0.0253146	Regulation of polysaccharide biosynthetic process	MSKCC	PD
GO:0009409	0.0262411	Response to cold	ZB	PD
GO:1903307	0.0262411	Positive regulation of regulated secretory pathway	ZB	PD
GO:0032752	0.0274151	Positive regulation of interleukin-3 production	MSKCC	PD
GO:0042223	0.0274151	Interleukin-3 biosynthetic process	MSKCC	PD
GO:0043366	0.0274151	Beta selection	MSKCC	PD
GO:0045399	0.0274151	Regulation of interleukin-3 biosynthetic process	MSKCC	PD
GO:0045401	0.0274151	Positive regulation of interleukin-3 biosynthetic process	MSKCC	PD
GO:0008584	0.0282742	Male gonad development	ZB	PD
GO:0046546	0.0282742	Development of primary male sexual characteristics	ZB	PD
GO:0002351	0.0282742	Serotonin production involved in inflammatory response	ZB	PD
GO:0002442	0.0282742	Serotonin secretion involved in inflammatory response	ZB	PD
GO:0002554	0.0282742	Serotonin secretion by platelet	ZB	PD
GO:0032252	0.0282742	Secretory granule localization	ZB	PD
GO:0032672	0.0282742	Regulation of interleukin-3 production	ZB	PD
GO:0045425	0.0282742	Positive regulation of granulocyte macrophage colony-stimulating factor biosynthetic process	ZB	PD
GO:0045588	0.0282742	Positive regulation of gamma-delta T cell differentiation	ZB	PD
GO:1901843	0.0282742	Positive regulation of high voltage-gated calcium channel activity	ZB	PD
GO:0007257	0.0285333	Activation of JUN kinase activity	MSKCC	PD
GO:0032881	0.0285333	Regulation of polysaccharide metabolic process	MSKCC	PD
GO:0042129	0.0307477	Regulation of T cell proliferation	ZB	PD
GO:0051321	0.0309104	Meiotic cell cycle	MSKCC	PD
GO:0035272	0.0318221	Exocrine system development	ZB	PD
GO:0043550	0.0318221	Regulation of lipid kinase activity	ZB	PD
GO:0033003	0.0322116	Regulation of mast cell activation	MSKCC	PD
GO:0048146	0.0343113	Positive regulation of fibroblast proliferation	ZB	PD
GO:0010897	0.0343113	Negative regulation of triglyceride catabolic process	ZB	PD
GO:0032632	0.0343113	Interleukin-3 production	ZB	PD
GO:0045423	0.0343113	Regulation of granulocyte macrophage colony-stimulating factor biosynthetic process	ZB	PD
GO:0060699	0.0343113	Regulation of endoribonuclease activity	ZB	PD
GO:0007405	0.0343407	Neuroblast proliferation	ZB	PD
GO:0009409	0.0344727	Response to cold	MSKCC	PD
GO:1903307	0.0344727	Positive regulation of regulated secretory pathway	MSKCC	PD
GO:0002351	0.0359801	Serotonin production involved in inflammatory response	MSKCC	PD
GO:0002442	0.0359801	Serotonin secretion involved in inflammatory response	MSKCC	PD
GO:0002554	0.0359801	Serotonin secretion by platelet	MSKCC	PD
GO:0032252	0.0359801	Secretory granule localization	MSKCC	PD
GO:0032672	0.0359801	Regulation of interleukin-3 production	MSKCC	PD
GO:0045425	0.0359801	Positive regulation of granulocyte macrophage colony-stimulating factor biosynthetic process	MSKCC	PD
GO:0045588	0.0359801	Positive regulation of gamma-delta T cell differentiation	MSKCC	PD
GO:1901843	0.0359801	Positive regulation of high voltage-gated calcium channel activity	MSKCC	PD
GO:0010518	0.040339	Positive regulation of phospholipase activity	MSKCC	PD
GO:0042129	0.0411271	Regulation of T cell proliferation	MSKCC	PD
GO:0010897	0.0437818	Negative regulation of triglyceride catabolic process	MSKCC	PD
GO:0032632	0.0437818	Interleukin-3 production	MSKCC	PD
GO:0045423	0.0437818	Regulation of granulocyte macrophage colony-stimulating factor biosynthetic process	MSKCC	PD
GO:0060699	0.0437818	Regulation of endoribonuclease activity	MSKCC	PD
GO:0007405	0.0450633	Neuroblast proliferation	MSKCC	PD
GO:0019637	0.045281	Organophosphate metabolic process	MSKCC	PD
GO:0042542	1.365E-07	Response to hydrogen peroxide	MSKCC	MD
GO:0014812	1.111E-06	Muscle cell migration	MSKCC	MD
GO:0042493	1.147E-06	Response to drug	MSKCC	MD
GO:1901652	1.569E-06	Response to peptide	ZB	MD
GO:0044092	1.981E-06	Negative regulation of molecular function	ZB	MD
GO:0043434	5.246E-06	Response to peptide hormone	ZB	MD
GO:0000302	1.172E-05	Response to reactive oxygen species	MSKCC	MD
GO:0034504	1.315E-05	Protein localization to nucleus	MSKCC	MD
GO:0033365	1.481E-05	Protein localization to organelle	MSKCC	MD
GO:0070301	2.532E-05	Cellular response to hydrogen peroxide	MSKCC	MD
GO:0009607	3.12E-05	Response to biotic stimulus	MSKCC	MD
GO:0034614	4.066E-05	Cellular response to reactive oxygen species	MSKCC	MD
GO:1904705	4.887E-05	Regulation of vascular smooth muscle cell proliferation	MSKCC	MD
GO:1990874	4.887E-05	Vascular smooth muscle cell proliferation	MSKCC	MD
GO:0003279	6.629E-05	Cardiac septum development	MSKCC	MD
GO:0051707	6.996E-05	Response to other organism	MSKCC	MD
GO:0043207	7.068E-05	Response to external biotic stimulus	MSKCC	MD
GO:1901652	7.61E-05	Response to peptide	MSKCC	MD
GO:0051223	9.568E-05	Regulation of protein transport	MSKCC	MD
GO:0060411	0.0001143	Cardiac septum morphogenesis	MSKCC	MD
GO:0014909	0.0001298	Smooth muscle cell migration	MSKCC	MD
GO:0032496	0.0001321	Response to lipopolysaccharide	MSKCC	MD
GO:0045682	0.0001383	Regulation of epidermis development	MSKCC	MD
GO:0006273	0.0001448	Lagging strand elongation	MSKCC	MD
GO:0043434	0.0001755	Response to peptide hormone	MSKCC	MD
GO:0002237	0.0001807	Response to molecule of bacterial origin	MSKCC	MD
GO:0003179	0.000188	Heart valve morphogenesis	MSKCC	MD
GO:0050864	0.0002231	Regulation of B cell activation	MSKCC	MD
GO:0003170	0.0002759	Heart valve development	MSKCC	MD
GO:0051570	0.0003745	Regulation of histone H3-K9 methylation	ZB	MD
GO:0044092	0.0004357	Negative regulation of molecular function	MSKCC	MD
GO:0042100	0.0004756	B cell proliferation	MSKCC	MD
GO:0000302	0.0005009	Response to reactive oxygen species	ZB	MD
GO:1904019	0.0005234	Epithelial cell apoptotic process	MSKCC	MD
GO:0006266	0.0005342	DNA ligation	ZB	MD
GO:0034614	0.00056	Cellular response to reactive oxygen species	ZB	MD
GO:2001242	0.0005685	Regulation of intrinsic apoptotic signaling pathway	MSKCC	MD
GO:0046879	0.0006353	Hormone secretion	MSKCC	MD
GO:0006271	0.0006777	DNA strand elongation involved in DNA replication	MSKCC	MD
GO:0003205	0.0007089	Cardiac chamber development	MSKCC	MD
GO:0003007	0.0007878	Heart morphogenesis	MSKCC	MD
GO:0009914	0.0008096	Hormone transport	MSKCC	MD
GO:0034504	0.0008947	Protein localization to nucleus	ZB	MD
GO:0051567	0.000944	Histone H3-K9 methylation	ZB	MD
GO:0030888	0.001	Regulation of B cell proliferation	MSKCC	MD
GO:0032611	0.001	Interleukin-1 beta production	MSKCC	MD
GO:0033157	0.001093	Regulation of intracellular protein transport	ZB	MD
GO:1902042	0.001286	Negative regulation of extrinsic apoptotic signaling pathway via death domain receptors	ZB	MD
GO:0050852	0.0012901	T cell receptor signaling pathway	MSKCC	MD
GO:0006266	0.0012907	DNA ligation	MSKCC	MD
GO:0032845	0.0013576	Negative regulation of homeostatic process	MSKCC	MD
GO:0003281	0.0014821	Ventricular septum development	MSKCC	MD
GO:0033143	0.0014821	Regulation of intracellular steroid hormone receptor signaling pathway	MSKCC	MD
GO:0022616	0.001571	DNA strand elongation	MSKCC	MD
GO:0071887	0.0016635	Leukocyte apoptotic process	ZB	MD
GO:1904035	0.0017433	Regulation of epithelial cell apoptotic process	MSKCC	MD
GO:0032612	0.0019145	Interleukin-1 production	MSKCC	MD
GO:0097306	0.0019363	Cellular response to alcohol	ZB	MD
GO:0034968	0.0021658	Histone lysine methylation	ZB	MD
GO:0061647	0.002279	Histone H3-K9 modification	ZB	MD
GO:0033146	0.002285	Regulation of intracellular estrogen receptor signaling pathway	MSKCC	MD
GO:0022408	0.0023527	Negative regulation of cell-cell adhesion	MSKCC	MD
GO:0033157	0.0023985	Regulation of intracellular protein transport	MSKCC	MD
GO:0051223	0.0024086	Regulation of protein transport	ZB	MD
GO:0032446	0.0024086	Protein modification by small protein conjugation	ZB	MD
GO:0051573	0.0028681	Negative regulation of histone H3-K9 methylation	ZB	MD
GO:0018022	0.0028725	Peptidyl-lysine methylation	ZB	MD
GO:0046824	0.0028725	Positive regulation of nucleocytoplasmic transport	ZB	MD
GO:0031648	0.0030756	Protein destabilization	MSKCC	MD
GO:0009636	0.0032692	Response to toxic substance	ZB	MD
GO:0006261	0.0033055	DNA-dependent DNA replication	MSKCC	MD
GO:0006273	0.0033374	Lagging strand elongation	ZB	MD
GO:0002223	0.0035118	Stimulatory C-type lectin receptor signaling pathway	ZB	MD
GO:0002220	0.0036986	Innate immune response activating cell surface receptor signaling pathway	ZB	MD
GO:0051103	0.0038896	DNA ligation involved in DNA repair	ZB	MD
GO:0003007	0.0040602	Heart morphogenesis	ZB	MD
GO:0016571	0.0042866	Histone methylation	ZB	MD
GO:0097306	0.0044943	Cellular response to alcohol	MSKCC	MD
GO:0031060	0.0045733	Regulation of histone methylation	ZB	MD
GO:0023061	0.0047426	Signal release	MSKCC	MD
GO:0051573	0.0047426	Negative regulation of histone H3-K9 methylation	MSKCC	MD
GO:0001666	0.0047462	Response to hypoxia	MSKCC	MD
GO:0006284	0.0050431	Base-excision repair	MSKCC	MD
GO:0018205	0.0051017	Peptidyl-lysine modification	ZB	MD
GO:0036293	0.0053204	Response to decreased oxygen levels	MSKCC	MD
GO:0061647	0.0053204	Histone H3-K9 modification	MSKCC	MD
GO:0006261	0.0055276	DNA-dependent DNA replication	ZB	MD
GO:2001020	0.0055567	Regulation of response to DNA damage stimulus	MSKCC	MD
GO:0032446	0.0057176	Protein modification by small protein conjugation	MSKCC	MD
GO:0014909	0.0058867	Smooth muscle cell migration	ZB	MD
GO:0070664	0.0058867	Negative regulation of leukocyte proliferation	ZB	MD
GO:0090316	0.0059508	Positive regulation of intracellular protein transport	MSKCC	MD
GO:0032651	0.0061433	Regulation of interleukin-1 beta production	MSKCC	MD
GO:0006304	0.0062479	DNA modification	MSKCC	MD
GO:0051103	0.0062941	DNA ligation involved in DNA repair	MSKCC	MD
GO:0030520	0.0064205	Intracellular estrogen receptor signaling pathway	MSKCC	MD
GO:0042093	0.0064205	T-helper cell differentiation	MSKCC	MD
GO:0045936	0.0065605	Negative regulation of phosphate metabolic process	ZB	MD
GO:0010563	0.0066057	Negative regulation of phosphorus metabolic process	ZB	MD
GO:0045604	0.0067768	Regulation of epidermal cell differentiation	MSKCC	MD
GO:0031061	0.0067822	Negative regulation of histone methylation	ZB	MD
GO:0034968	0.0067993	Histone lysine methylation	MSKCC	MD
GO:0002294	0.0071277	CD4-positive, alpha-beta T cell differentiation involved in immune response	MSKCC	MD
GO:0002287	0.0074349	alpha-beta T cell activation involved in immune response	MSKCC	MD
GO:0002293	0.0074349	alpha-beta T cell differentiation involved in immune response	MSKCC	MD
GO:0031663	0.0074349	Lipopolysaccharide-mediated signaling pathway	MSKCC	MD
GO:0038034	0.0077505	Signal transduction in absence of ligand	ZB	MD
GO:0097192	0.0077505	Extrinsic apoptotic signaling pathway in absence of ligand	ZB	MD
GO:0034284	0.0078981	Response to monosaccharide	MSKCC	MD
GO:0006271	0.0081662	DNA strand elongation involved in DNA replication	ZB	MD
GO:0046660	0.0082366	Female sex differentiation	MSKCC	MD
GO:0014812	0.008241	Muscle cell migration	ZB	MD
GO:0003283	0.0088126	Atrial septum development	ZB	MD
GO:0023019	0.0088126	Signal transduction involved in regulation of gene expression	ZB	MD
GO:0007259	0.0089793	JAK-STAT cascade	ZB	MD
GO:0097696	0.0089793	STAT cascade	ZB	MD
GO:0018022	0.0091089	Peptidyl-lysine methylation	MSKCC	MD
GO:0046824	0.0091089	Positive regulation of nucleocytoplasmic transport	MSKCC	MD
GO:0001541	0.0092698	Ovarian follicle development	MSKCC	MD
GO:0070301	0.0095041	Cellular response to hydrogen peroxide	ZB	MD
GO:0002292	0.0096977	T cell differentiation involved in immune response	MSKCC	MD
GO:1903533	0.0097929	Regulation of protein targeting	ZB	MD
GO:0006479	0.0099192	Protein methylation	ZB	MD
GO:0008213	0.0099192	Protein alkylation	ZB	MD
GO:0050852	0.0099192	T cell receptor signaling pathway	ZB	MD
GO:0032845	0.0101971	Negative regulation of homeostatic process	ZB	MD
GO:0031060	0.0104978	Regulation of histone methylation	MSKCC	MD
GO:0032652	0.0104978	Regulation of interleukin-1 production	MSKCC	MD
GO:0008625	0.0108141	Extrinsic apoptotic signaling pathway via death domain receptors	ZB	MD
GO:0032496	0.0108141	Response to lipopolysaccharide	ZB	MD
GO:0009743	0.0108748	Response to carbohydrate	MSKCC	MD
GO:0001947	0.0108748	Heart looping	MSKCC	MD
GO:0048678	0.0108748	Response to axon injury	MSKCC	MD
GO:0072091	0.0108748	Regulation of stem cell proliferation	MSKCC	MD
GO:1903533	0.0110206	Regulation of protein targeting	MSKCC	MD
GO:0002223	0.0110206	Stimulatory C-type lectin receptor signaling pathway	MSKCC	MD
GO:0031061	0.0110206	Negative regulation of histone methylation	MSKCC	MD
GO:0043367	0.0112179	CD4-positive, alpha-beta T cell differentiation	MSKCC	MD
GO:0002220	0.0115502	Innate immune response activating cell surface receptor signaling pathway	MSKCC	MD
GO:1904705	0.0117161	Regulation of vascular smooth muscle cell proliferation	ZB	MD
GO:1990874	0.0117161	Vascular smooth muscle cell proliferation	ZB	MD
GO:0042100	0.0117593	B cell proliferation	ZB	MD
GO:1904019	0.0124536	Epithelial cell apoptotic process	ZB	MD
GO:0006471	0.0125445	Protein ADP-ribosylation	ZB	MD
GO:0002237	0.0127762	Response to molecule of bacterial origin	ZB	MD
GO:0061371	0.0130477	Determination of heart left/right asymmetry	MSKCC	MD
GO:0016571	0.0132027	Histone methylation	MSKCC	MD
GO:0022616	0.0132769	DNA strand elongation	ZB	MD
GO:0008585	0.0132769	Female gonad development	ZB	MD
GO:0003143	0.0134719	Embryonic heart tube morphogenesis	MSKCC	MD
GO:0008589	0.0134719	Regulation of smoothened signaling pathway	MSKCC	MD
GO:0035710	0.0134719	CD4-positive, alpha-beta T cell activation	MSKCC	MD
GO:0070664	0.0134719	Negative regulation of leukocyte proliferation	MSKCC	MD
GO:0071301	0.0136096	Cellular response to vitamin B1	ZB	MD
GO:0090347	0.0136096	Regulation of cellular organohalogen metabolic process	ZB	MD
GO:0090348	0.0136096	Regulation of cellular organofluorine metabolic process	ZB	MD
GO:0090349	0.0136096	Negative regulation of cellular organohalogen metabolic process	ZB	MD
GO:0090350	0.0136096	Negative regulation of cellular organofluorine metabolic process	ZB	MD
GO:1904404	0.0136096	Response to formaldehyde	ZB	MD
GO:0003279	0.0136766	Cardiac septum development	ZB	MD
GO:0046545	0.0139992	Development of primary female sexual characteristics	ZB	MD
GO:0009743	0.0140538	Response to carbohydrate	ZB	MD
GO:0043086	0.0143878	Negative regulation of catalytic activity	ZB	MD
GO:0003283	0.0143938	Atrial septum development	MSKCC	MD
GO:0023019	0.0143938	Signal transduction involved in regulation of gene expression	MSKCC	MD
GO:0007389	0.015078	Pattern specification process	MSKCC	MD
GO:0006304	0.0153019	DNA modification	ZB	MD
GO:0051100	0.0154442	Negative regulation of binding	MSKCC	MD
GO:0045936	0.0155204	Negative regulation of phosphate metabolic process	MSKCC	MD
GO:0051570	0.015525	Regulation of histone H3-K9 methylation	MSKCC	MD
GO:0010563	0.01554	Negative regulation of phosphorus metabolic process	MSKCC	MD
GO:0046634	0.0155981	Regulation of alpha-beta T cell activation	MSKCC	MD
GO:0071301	0.0155981	Cellular response to vitamin B1	MSKCC	MD
GO:0090347	0.0155981	Regulation of cellular organohalogen metabolic process	MSKCC	MD
GO:0090348	0.0155981	Regulation of cellular organofluorine metabolic process	MSKCC	MD
GO:0090349	0.0155981	Negative regulation of cellular organohalogen metabolic process	MSKCC	MD
GO:0090350	0.0155981	Negative regulation of cellular organofluorine metabolic process	MSKCC	MD
GO:1904404	0.0155981	Response to formaldehyde	MSKCC	MD
GO:0033146	0.0159353	Regulation of intracellular estrogen receptor signaling pathway	ZB	MD
GO:0051051	0.0167241	Negative regulation of transport	MSKCC	MD
GO:0038034	0.0167508	Signal transduction in absence of ligand	MSKCC	MD
GO:0097192	0.0167508	Extrinsic apoptotic signaling pathway in absence of ligand	MSKCC	MD
GO:0046660	0.0191336	Female sex differentiation	ZB	MD
GO:0031648	0.01952	Protein destabilization	ZB	MD
GO:0006471	0.0196997	Protein ADP-ribosylation	MSKCC	MD
GO:0043086	0.0202833	Negative regulation of catalytic activity	MSKCC	MD
GO:0003179	0.0203264	Heart valve morphogenesis	ZB	MD
GO:0003230	0.0203264	Cardiac atrium development	ZB	MD
GO:0033365	0.0219486	Protein localization to organelle	ZB	MD
GO:0042542	0.0231473	Response to hydrogen peroxide	ZB	MD
GO:0010868	0.0231473	Negative regulation of triglyceride biosynthetic process	ZB	MD
GO:0071460	0.0231473	Cellular response to cell-matrix adhesion	ZB	MD
GO:0090345	0.0231473	Cellular organohalogen metabolic process	ZB	MD
GO:0090346	0.0231473	Cellular organofluorine metabolic process	ZB	MD
GO:0050864	0.0232449	Regulation of B cell activation	ZB	MD
GO:0044262	0.0234314	Cellular carbohydrate metabolic process	MSKCC	MD
GO:0003170	0.0234325	Heart valve development	ZB	MD
GO:0008625	0.0238195	Extrinsic apoptotic signaling pathway via death domain receptors	MSKCC	MD
GO:0043029	0.0244019	T cell homeostasis	ZB	MD
GO:0046825	0.0252439	Regulation of protein export from nucleus	ZB	MD
GO:0018205	0.0254654	Peptidyl-lysine modification	MSKCC	MD
GO:0090316	0.0255328	Positive regulation of intracellular protein transport	ZB	MD
GO:0022408	0.0260472	Negative regulation of cell-cell adhesion	ZB	MD
GO:0006284	0.0260472	Base-excision repair	ZB	MD
GO:0010883	0.0260472	Regulation of lipid storage	ZB	MD
GO:0007259	0.0262577	JAK-STAT cascade	MSKCC	MD
GO:0097696	0.0262577	STAT cascade	MSKCC	MD
GO:0051567	0.0262577	Histone H3-K9 methylation	MSKCC	MD
GO:0010868	0.0262577	Negative regulation of triglyceride biosynthetic process	MSKCC	MD
GO:0071460	0.0262577	Cellular response to cell-matrix adhesion	MSKCC	MD
GO:0090345	0.0262577	Cellular organohalogen metabolic process	MSKCC	MD
GO:0090346	0.0262577	Cellular organofluorine metabolic process	MSKCC	MD
GO:0044262	0.0265122	Cellular carbohydrate metabolic process	ZB	MD
GO:0042493	0.0271005	Response to drug	ZB	MD
GO:0006479	0.0275738	Protein methylation	MSKCC	MD
GO:0008213	0.0275738	Protein alkylation	MSKCC	MD
GO:0008585	0.0277022	Female gonad development	MSKCC	MD
GO:0051100	0.029382	Negative regulation of binding	ZB	MD
GO:0032651	0.0295013	Regulation of interleukin-1 beta production	ZB	MD
GO:0043525	0.0295013	Positive regulation of neuron apoptotic process	ZB	MD
GO:0051055	0.0295013	Negative regulation of lipid biosynthetic process	ZB	MD
GO:0007389	0.0295013	Pattern specification process	ZB	MD
GO:0023061	0.0295013	Signal release	ZB	MD
GO:0030520	0.0295013	Intracellular estrogen receptor signaling pathway	ZB	MD
GO:0042093	0.0295013	T-helper cell differentiation	ZB	MD
GO:0009822	0.0295013	Alkaloid catabolic process	ZB	MD
GO:0010266	0.0295013	Response to vitamin B1	ZB	MD
GO:0033076	0.0295013	Isoquinoline alkaloid metabolic process	ZB	MD
GO:0071494	0.0295013	Cellular response to UV-C	ZB	MD
GO:0098760	0.0295013	Response to interleukin-7	ZB	MD
GO:0098761	0.0295013	Cellular response to interleukin-7	ZB	MD
GO:1990785	0.0295013	Response to water-immersion restraint stress	ZB	MD
GO:0071887	0.029714	Leukocyte apoptotic process	MSKCC	MD
GO:0045604	0.0298719	Regulation of epidermal cell differentiation	ZB	MD
GO:0046545	0.0305378	Development of primary female sexual characteristics	MSKCC	MD
GO:1902042	0.0306947	Negative regulation of extrinsic apoptotic signaling pathway via death domain receptors	MSKCC	MD
GO:0002294	0.0309829	CD4-positive, alpha-beta T cell differentiation involved in immune response	ZB	MD
GO:0002287	0.0320739	alpha-beta T cell activation involved in immune response	ZB	MD
GO:0002293	0.0320739	alpha-beta T cell differentiation involved in immune response	ZB	MD
GO:0031663	0.0320739	Lipopolysaccharide-mediated signaling pathway	ZB	MD
GO:0003230	0.0321242	Cardiac atrium development	MSKCC	MD
GO:2001242	0.0323501	Regulation of intrinsic apoptotic signaling pathway	ZB	MD
GO:0051051	0.0324454	Negative regulation of transport	ZB	MD
GO:0051707	0.0338559	Response to other organism	ZB	MD
GO:0043207	0.033997	Response to external biotic stimulus	ZB	MD
GO:0009822	0.0354738	Alkaloid catabolic process	MSKCC	MD
GO:0010266	0.0354738	Response to vitamin B1	MSKCC	MD
GO:0033076	0.0354738	Isoquinoline alkaloid metabolic process	MSKCC	MD
GO:0071494	0.0354738	Cellular response to UV-C	MSKCC	MD
GO:0098760	0.0354738	Response to interleukin-7	MSKCC	MD
GO:0098761	0.0354738	Cellular response to interleukin-7	MSKCC	MD
GO:1990785	0.0354738	Response to water-immersion restraint stress	MSKCC	MD
GO:0003205	0.0358613	Cardiac chamber development	ZB	MD
GO:0001541	0.0363016	Ovarian follicle development	ZB	MD
GO:0007089	0.0363016	Traversing start control point of mitotic cell cycle	ZB	MD
GO:0010989	0.0363016	Negative regulation of low-density lipoprotein particle clearance	ZB	MD
GO:0014042	0.0363016	Positive regulation of neuron maturation	ZB	MD
GO:0035799	0.0363016	Ureter maturation	ZB	MD
GO:0042997	0.0363016	Negative regulation of Golgi to plasma membrane protein transport	ZB	MD
GO:0070427	0.0363016	Nucleotide-binding oligomerization domain containing 1 signaling pathway	ZB	MD
GO:2000048	0.0363016	Negative regulation of cell-cell adhesion mediated by cadherin	ZB	MD
GO:0046879	0.0364954	Hormone secretion	ZB	MD
GO:0002292	0.0371894	T cell differentiation involved in immune response	ZB	MD
GO:0030888	0.0371894	Regulation of B cell proliferation	ZB	MD
GO:0032611	0.0371894	Interleukin-1 beta production	ZB	MD
GO:0043029	0.0386747	T cell homeostasis	MSKCC	MD
GO:0032652	0.0392552	Regulation of interleukin-1 production	ZB	MD
GO:2001020	0.039929	Regulation of response to DNA damage stimulus	ZB	MD
GO:0046825	0.0400926	Regulation of protein export from nucleus	MSKCC	MD
GO:0001947	0.040316	Heart looping	ZB	MD
GO:0048678	0.040316	Response to axon injury	ZB	MD
GO:0072091	0.040316	Regulation of stem cell proliferation	ZB	MD
GO:0009914	0.0407189	Hormone transport	ZB	MD
GO:0009607	0.0410816	Response to biotic stimulus	ZB	MD
GO:0043367	0.0414048	CD4-positive, alpha-beta T cell differentiation	ZB	MD
GO:0010883	0.0416577	Regulation of lipid storage	MSKCC	MD
GO:0007089	0.0432135	Traversing start control point of mitotic cell cycle	MSKCC	MD
GO:0010989	0.0432135	Negative regulation of low-density lipoprotein particle clearance	MSKCC	MD
GO:0014042	0.0432135	Positive regulation of neuron maturation	MSKCC	MD
GO:0035799	0.0432135	Ureter maturation	MSKCC	MD
GO:0042997	0.0432135	Negative regulation of Golgi to plasma membrane protein transport	MSKCC	MD
GO:0070427	0.0432135	Nucleotide-binding oligomerization domain containing 1 signaling pathway	MSKCC	MD
GO:2000048	0.0432135	Negative regulation of cell-cell adhesion mediated by cadherin	MSKCC	MD
GO:0003281	0.0437357	Ventricular septum development	ZB	MD
GO:0033143	0.0437357	Regulation of intracellular steroid hormone receptor signaling pathway	ZB	MD
GO:0060411	0.0437357	Cardiac septum morphogenesis	ZB	MD
GO:0061371	0.0447239	Determination of heart left/right asymmetry	ZB	MD
GO:0009636	0.0455879	Response to toxic substance	MSKCC	MD
GO:0003143	0.0456721	Embryonic heart tube morphogenesis	ZB	MD
GO:0008589	0.0456721	Regulation of smoothened signaling pathway	ZB	MD
GO:0035710	0.0456721	CD4-positive, alpha-beta T cell activation	ZB	MD
GO:0001666	0.0462698	Response to hypoxia	ZB	MD
GO:0043525	0.0463606	Positive regulation of neuron apoptotic process	MSKCC	MD
GO:0051055	0.0463606	Negative regulation of lipid biosynthetic process	MSKCC	MD
GO:0045682	0.0465784	Regulation of epidermis development	ZB	MD
GO:1904035	0.0465784	Regulation of epithelial cell apoptotic process	ZB	MD
GO:0034284	0.0473956	Response to monosaccharide	ZB	MD
GO:0032612	0.0473956	Interleukin-1 production	ZB	MD
GO:0036293	0.047653	Response to decreased oxygen levels	ZB	MD
GO:0046634	0.0493719	Regulation of alpha-beta T cell activation	ZB	MD
GO:1905005	0.0303648	Regulation of epithelial to mesenchymal transition involved in endocardial cushion formation	ZB	WD
GO:0003198	0.0462411	Epithelial to mesenchymal transition involved in endocardial cushion formation	ZB	WD
GO:0034110	0.0498585	Regulation of homotypic cell-cell adhesion	ZB	WD
GO:1905005	0.027475	Regulation of epithelial to mesenchymal transition involved in endocardial cushion formation	MSKCC	WD
GO:0003198	0.0414965	Epithelial to mesenchymal transition involved in endocardial cushion formation	MSKCC	WD
GO:0034110	0.0441837	Regulation of homotypic cell-cell adhesion	MSKCC	WD

Note: dataset, our dataset was named ZB. PD, poor differentiated; MD, moderate differentiated; WD, well differentiated.