

Supplementary Figure 1. Identification of the CpG islands of four promoter methylation-driven genes (PMDGs)

(A-D)The upstream 3kb DNA sequence of the promoter regions of four PMDGs including *DPP6*, *HIST1H4E*, *MTMR7*, and *ZFP281*s extracted from NCBI dataset. The CpG islands (blue segments) are confirmed if CGpercentage is more than 50%.

A

TTGCCTCGCTTAACCTTGATGCAGCTGGAGGCTTCCCAGTCAGCT
CAGTTCAAGACAGAAAAACCTGGCGCGCGCGCACACACACACCG
CTCCCCCTGGCGTCGCCGC CGGGGGCTGGCCCTGGCCCTAGGGACCA
GAAGCGGCGACCGCTGCACCCCGACCGCCTGGCTGGAGGAGGGCC
GGAGCGGGGGCGAGCCGCGCGCGTCCCCAGTGCGGCCCCCTGTG
CGTCGCCCGCGCTGTTGCTCGAGTGTGCTGGCGCGAGCTCGGT
GGACACAAGGCGAGTCAAGGGCTGCCCTCGCCCTCGCTAGCTGGC
**TGGCAGCCTCTCCCTCCCTGGCTCCTGGCTTTTGTAAAGCA
ACACCCACCCTCATCCAGGCTTTTCTTCCTTTATTGGTAGC
GGGCAAAAAGAGTTGATTGCTATTGGATCCCGTGAAGAACACAG
GGCAGGGTGC CGGAGGTGAGA **AAGTGAAGACCTGGAAGATTTT****

B

ATCTCATTTAGTTGTTAAATATGGCTAAATTCTCTTGGGAACGCA
AGACTTGCAAGAGATGACTCCATGGAGAGCGGACTCTGCCGGCGGA
ACTGGAGTCGTTGGTGA CGTCATCCCAGTCTGATCTGTAAGGGTAG
GGCCAGCAGGCAAGGACCAAAGTTCCCGTATGCGCGTTCAGCTTC
ATTAGGTCTCAAATTCCCGCATATAAGAATACCTCGTCGGCTTGT
TCAGATTTTGCGCTATTTCTGTTGGTGTGTTGGTCATGCTGGTC
CGCAGAAAGGCGGAAGGGACTGGTAAAGGAGGGCTAAGCGTCAC
CGTAAGGTCTCGAGA **TAACATCCAGGGCATTACCAAGCC**

C

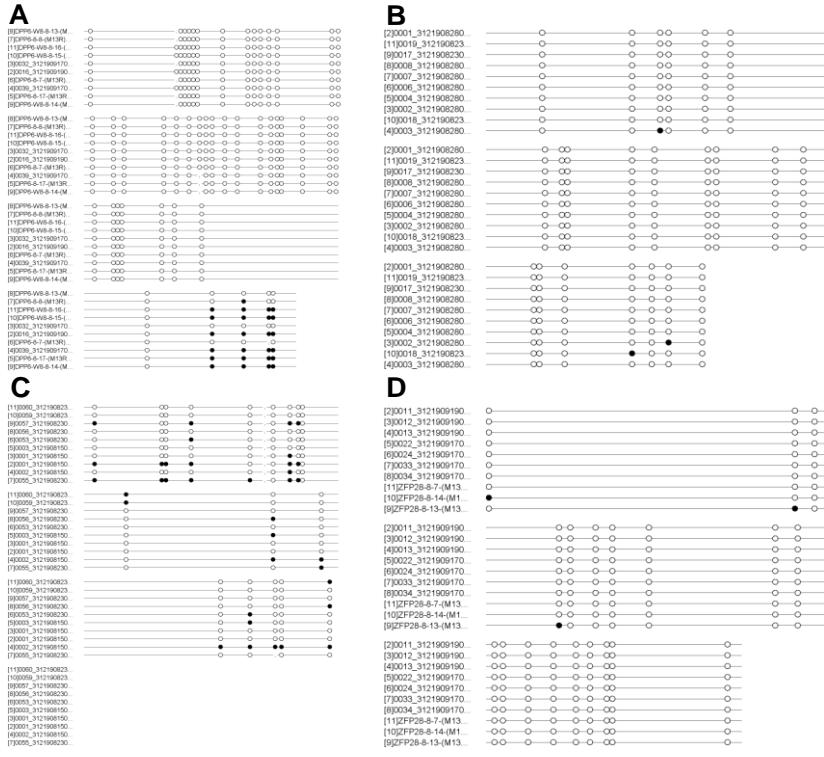
GGGAAAAGTGTCCCTGCAACAGTCAGTCAGTGCGCAGGTGGATGTGAGAT
GCCCTGACTTAAGAGCGCGCTTACCAAGGCCCTAACACTGCTGCTATT
ATTTCCACCGCACCCCGAGCGCTATGCGGCCGCCGGCTGGAGATGA
AACACACACATTGAGCTAACAGACCGTCCTGGGTCTAGGTGTGTG
GGCAGCCCTCTTCTGGCCACCCCTGAATCTAGCTATCCAGGAGAC
**GCCCTAGAGGAAGGCCAGGGGACGGTGTGGACAGGCTGTACTCCC
CATCTCTTCAGGAGGCCACACCCAAACAGGCCCTTTGTGTGTC
TGGGAGAACAGTGGCCGATAGTGTCTCGCCCGGCTGCCCTGTAAAG
AGAGAGCCAGCAGCCCTCGCCCGGCAACCCAG**

D

TATTTGGAGGATGGGAGGCCCGTGTAGCCAGAGATAATGGGAGAAG
GTGAGGGGGCACCCAAAACAATCCACAAAGCTCTACATCCCCCTT
CTAGCCCCACACACATCACCCATCAGAGTGTCTCGGACTCCCGA
GGCCCCAAGATTGCTCTTCCCTCCCGTCCAGTGA CGCTCCCG
CAAGGAGCTGA CGCCAGGCCCCCTAGCACCTGTACAGGCCAGGAC
CTTTTACTCGGGCCCTGCGTCCACCCCTCGCCCAAGCCCCCCT
CACCGGTCTGCGCTGCGCCCTGCGCCACTCCCCAGAACGCTTGGG
GGTGGGTGTGAGTCAGAGCGGCCCTGTCTCCCG **CCACACCCAG
GCCAGCGTGGCCA**

Supplementary Figure 2. Selection of CpG islands for bisulfite sequencing polymerase chain reaction

CpG islands were selected closing to the probe location of HM450K BeadChip. The green segments represent the primerbindingsequence and the yellow segments mean the probe cites.(**A**) Sequence (yellow) of one probe (cg22620221) in the *DPP6* promoter. (**B**) Sequence (yellow) of six probes (cg02656667,cg07140158,cg16282993,cg16706631,cg17123534, and cg19595956) in the *HIST1H4E* promoter. (**C**) Sequence (yellow) of four probes (cg04792712,cg08231493,cg12296772, and cg15600488) in the *MTMR7* promoter. (**D**) Sequence (yellow) of four probes (cg03305181,cg12973930,cg25963041, and cg23850212) in the *ZFP28* promoter.



Supplementary Figure3. Evaluation of the promoter methylation status of four promoter methylation-driven genes

BiQ Analyzer is used to proceed the original sequencing data and to calculate the numbers of methylated CG sites.(A-D) The black dots represent the methylated CG sites in the promoters of *DPP6*, *HIST1H4E*, *MTMR7*, and *ZFP28*.

Supplementary Table 1 Identification of 50 promoter methylation-driven genes

Gene	Normal ^a	Tumor ^b	P ^c	Fold change ^d	Hazard Ratio ^e	P of survival ^f	R value ^g	P of correlation ^h
<i>FMN2</i>	0.069	0.371	<0.001	5.37	-0.26	0.013	-0.43	<0.001
<i>PCSK2</i>	0.049	0.222	<0.001	4.52	-0.21	0.045	-0.20	<0.001
<i>ZFP28</i>	0.086	0.342	<0.001	3.99	-0.28	0.001	-0.73	<0.001
<i>SRRM4</i>	0.088	0.325	<0.001	3.70	0.60	0.015	-0.29	<0.001
<i>HMX2</i>	0.098	0.338	<0.001	3.44	0.58	0.011	-0.21	<0.001
<i>RADIL</i>	0.069	0.237	<0.001	3.43	-0.26	0.012	-0.43	<0.001
<i>NEU1</i>	0.057	0.189	<0.001	3.30	-0.16	0.046	-0.65	<0.001
<i>ZNF569</i>	0.054	0.169	<0.001	3.11	-0.20	0.048	-0.67	<0.001
<i>ELMO1</i>	0.126	0.388	<0.001	3.09	-0.32	0.006	-0.65	<0.001
<i>ZNF879</i>	0.060	0.185	<0.001	3.07	-0.33	0.016	-0.68	<0.001
<i>FSD1</i>	0.085	0.261	<0.001	3.05	-0.21	0.049	-0.25	<0.001
<i>RIMS1</i>	0.111	0.326	<0.001	2.93	-0.23	0.016	-0.23	<0.001
<i>PRKAR2B</i>	0.030	0.087	<0.001	2.85	-0.18	0.019	-0.20	<0.001
<i>C8orf48</i>	0.093	0.256	<0.001	2.75	-0.17	0.043	-0.47	<0.001
<i>ZNF71</i>	0.085	0.234	<0.001	2.74	-0.29	0.012	-0.70	<0.001
<i>ZNF471</i>	0.158	0.428	<0.001	2.70	-0.23	0.033	-0.66	<0.001
<i>ZNF671</i>	0.078	0.209	<0.001	2.69	-0.42	0.001	-0.49	<0.001
<i>ZNF781</i>	0.149	0.395	<0.001	2.65	-0.24	0.030	-0.55	<0.001
<i>ZNF470</i>	0.104	0.272	<0.001	2.61	-0.23	0.030	-0.67	<0.001
<i>SCAND3</i>	0.088	0.223	<0.001	2.55	-0.19	0.038	-0.57	<0.001
<i>KIF19</i>	0.179	0.454	<0.001	2.54	-0.38	0.015	-0.42	<0.001
<i>ALX3</i>	0.068	0.171	<0.001	2.51	-0.34	0.001	-0.20	<0.001
<i>KCNK12</i>	0.162	0.406	<0.001	2.51	-0.23	0.043	-0.31	<0.001
<i>SLCO4C1</i>	0.107	0.265	<0.001	2.48	-0.18	0.038	-0.49	<0.001
<i>KIAA1529</i>	0.045	0.109	<0.001	2.42	-0.58	0.002	-0.45	<0.001
<i>STXBP5L</i>	0.104	0.249	<0.001	2.39	-0.18	0.040	-0.22	<0.001
<i>WASF3</i>	0.088	0.209	<0.001	2.36	-0.23	0.004	-0.41	<0.001
<i>DYNLRB2</i>	0.046	0.108	<0.001	2.36	-0.24	0.005	-0.44	<0.001
<i>CLDN3</i>	0.053	0.123	<0.001	2.33	-0.16	0.004	-0.32	<0.001
<i>FBLL1</i>	0.116	0.265	<0.001	2.29	-0.32	0.015	-0.28	<0.001
<i>RGS22</i>	0.179	0.410	<0.001	2.29	-0.20	0.024	-0.40	<0.001
<i>C1orf70</i>	0.146	0.332	<0.001	2.28	-0.27	0.024	-0.25	<0.001
<i>DBC1</i>	0.223	0.507	<0.001	2.27	-0.19	0.027	-0.37	<0.001
<i>HIST1H4E</i>	0.107	0.240	<0.001	2.25	-0.14	0.022	-0.29	<0.001
<i>CCDC3</i>	0.082	0.185	<0.001	2.24	-0.26	0.020	-0.27	<0.001
<i>VASH1</i>	0.038	0.086	<0.001	2.24	-0.31	0.004	-0.16	<0.001
<i>MPPED1</i>	0.101	0.225	<0.001	2.23	0.60	0.017	-0.19	<0.001
<i>ADCY5</i>	0.147	0.325	<0.001	2.22	-0.15	0.013	-0.31	<0.001
<i>MTMR7</i>	0.247	0.545	<0.001	2.21	-0.31	0.014	-0.50	<0.001
<i>RLTPR</i>	0.042	0.092	<0.001	2.17	-0.39	0.007	-0.18	<0.001
<i>ALK</i>	0.056	0.122	<0.001	2.17	-0.20	0.019	-0.29	<0.001
<i>LOC642597</i>	0.171	0.370	<0.001	2.16	-0.24	0.034	-0.24	<0.001
<i>HOXB4</i>	0.154	0.333	<0.001	2.16	-0.15	0.050	-0.41	<0.001
<i>ZNF625</i>	0.078	0.167	<0.001	2.15	-0.32	0.045	-0.56	<0.001
<i>TRPC6</i>	0.187	0.395	<0.001	2.11	-0.07	0.034	-0.53	<0.001

<i>LINGO3</i>	0.083	0.175	<0.001	2.10	0.56	0.006	-0.18	<0.001
<i>GRM6</i>	0.258	0.536	<0.001	2.08	-0.23	0.025	-0.35	<0.001
<i>DPP6</i>	0.244	0.502	<0.001	2.06	-0.20	0.028	-0.55	<0.001
<i>EFHA2</i>	0.064	0.130	<0.001	2.04	-0.22	0.040	-0.57	<0.001
<i>RTP4</i>	0.306	0.109	<0.001	0.36	0.26	0.003	-0.44	<0.001

^aThe average β-value of the genetic promoter in normal tissues (GSE49149).

^bThe average β-value of the genetic promoter in tumor tissues (GSE49149).

^cP value of t-test of β-value between normal and tumor tissues (GSE49149).

^dFold change of β-value (tumor versus normal tissues, GSE49149).

^eHazard ratio of univariate Cox regression analyses according to mRNA expression (high- versus low-level groups based on median value, PDAC cohort of TCGA).

^fP value of univariate Cox regression analyses (PDAC cohort of TCGA).

^gCorrelation coefficient between β-value and mRNA expression (PDAC cohort of TCGA).

^hP value of the correlation between β-value and mRNA expression (PDAC cohort of TCGA).