The American Journal of Human Genetics, Volume *105*

Supplemental Data

Systematic Functional Interrogation of Genes in GWAS Loci Identified *ATF1* as a Key Driver in Colorectal Cancer Modulated by a Promoter-Enhancer Interaction

Jianbo Tian, Jiang Chang, Jing Gong, Jiao Lou, Mingpeng Fu, Jiaoyuan Li, Juntao Ke, Ying Zhu, Yajie Gong, Yang Yang, Danyi Zou, Xiating Peng, Nan Yang, Shufang Mei, Xiaoyang Wang, Rong Zhong, Kailin Cai, and Xiaoping Miao

Supplemental Figures

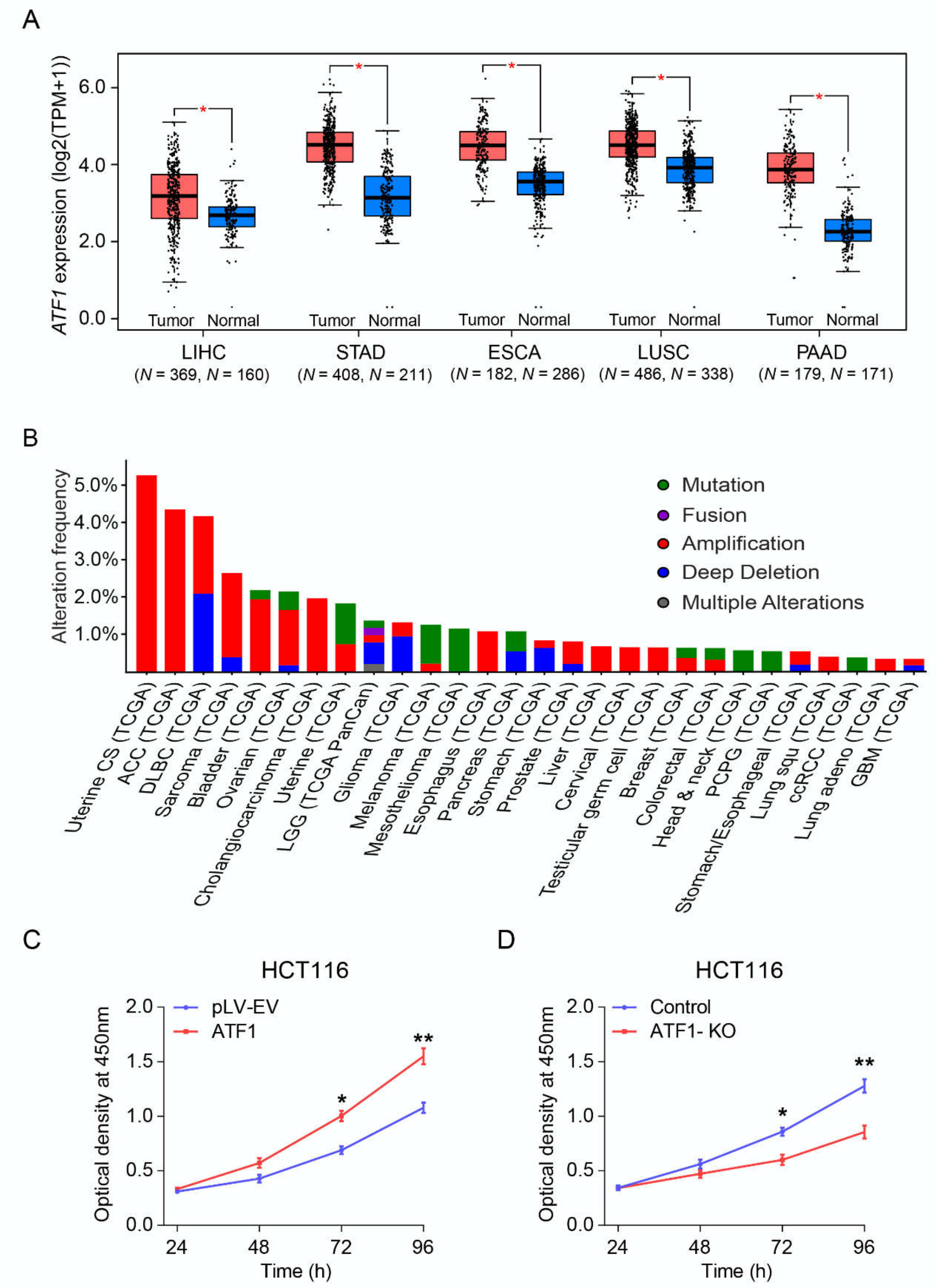

Figure S1. *ATF1* functions as an oncogene in CRC. A. *ATF1* is significantly higher in tumor tissues compared with normal tissues from the TCGA/GTEX databases in multiple cancers. Data were shown as the mean ± SD, and all $^{*}P < 0.05$ were calculated by a two-sided Student's *t*-test. LIHC, liver hepatocellular carcinoma (MIM: 114550); STAD, stomach adenocarcinoma (MIM: 175100); ESCA, esophageal carcinoma (MIM: 133239); LUSC, lung squamous cell carcinoma (MIM: 211980); PAAD, pancreatic adenocarcinoma

(MIM: 260350). **B.** Genomic alterations and aberrant expressions of *ATF1* across multiple cancer types. The data were displayed as a histogram from the “cBioPortal” database. **C, D.** *ATF1* overexpression using lentiviral transduction provokes cell proliferation (C), whereas *ATF1* knockout using CRISPR/Cas9 method inhibits cell proliferation in HCT116 cells (D). Data were shown as the mean ± s.e.m. from three repeated experiments and each with six replicates and all $^{*}P < 0.05$, $^{**}P < 0.01$ were calculated using a two-sided Student’s *t*-test.

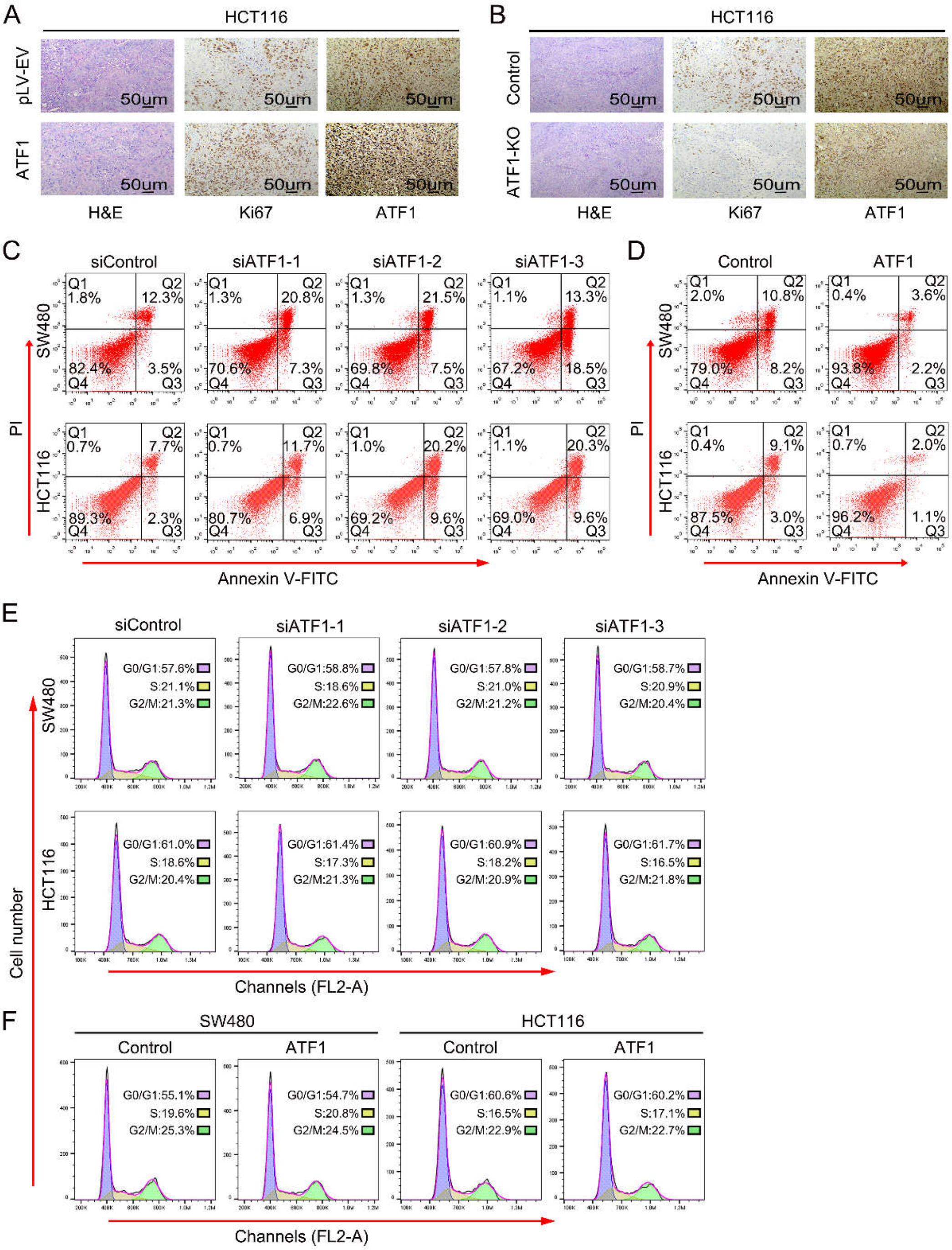

Figure S2. *ATF1* significantly inhibits cell apoptosis, rather than cell cycle. A-B. Immunohistochemical analysis of xenograft tumor of HCT16 cells treated with *ATF1* overexpression (A) or *ATF1* knockout (B) in nude mice. Images were a representative result from five replicates in each group. **C-F.** Effect of ATF1 overexpression (C, E) and ATF1 knockdown (D, F) on the apoptosis and cell-cycle process of SW480 and HCT116 cells, respectively. Flow cytometry images were a representative result from three repeated experiments and each with six replicates.

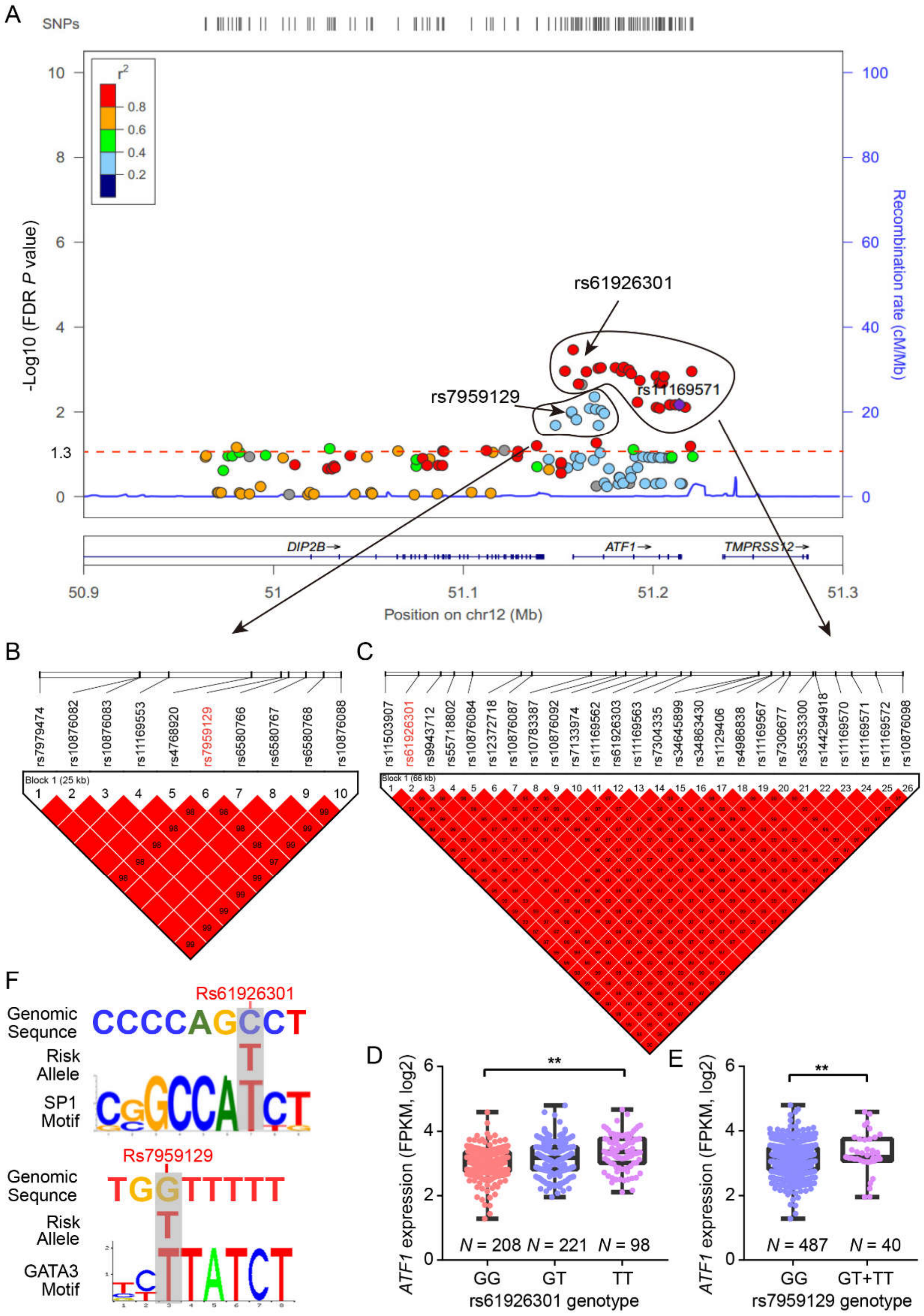

Figure S3. eQTL analysis between LD SNPs ($r^2 > 0.2$) of tagSNP rs11169571, which is located in the 12q13.12 region, and *ATF1* mRNA expression. A. Regional plots of eQTL results and recombination rates of rs11169571 LD SNPs ($r^2 \geq 0.2$) and *ATF1* expression. The eQTL *P* values (−log10 (FDR *P* values)) of the SNPs (y axis) are presented according to their chromosomal positions (x axis). The genetic recombination rates (cM/Mb) estimated using the 1000 Genomes June 2014 ASN samples are shown with a blue line. We annotated the SNPs within the interested region and these SNPs are shown as arrows. The r^2 values of these SNPs with the tag SNP rs11169571 are indicated by different colors. **B, C.** LD block plots ($r^2 \geq 0.8$) showing the r^2 value of SNPs having a significant eQTL with *ATF1* expression. For each plot, the r^2 values between variants were based on the 1000 Genomes June 2014 ASN samples. We selected the most potentially functional variant in each LD block ($r^2 \geq 0.8$), which have been labeled in red, for further population and experimental validation. **D, E.** eQTL results of rs61926301and rs7959129 genotypes with *ATF1* expression in the TCGA CRC cohort. Data were shown as the mean ± SD and $^{**}P < 0.01$ were calculated by linear regression analysis. **F.** The rs61926301[T] allele resides within a SP1 binding motif and the rs7959129[T] allele resides within a GATA3 binding motif.

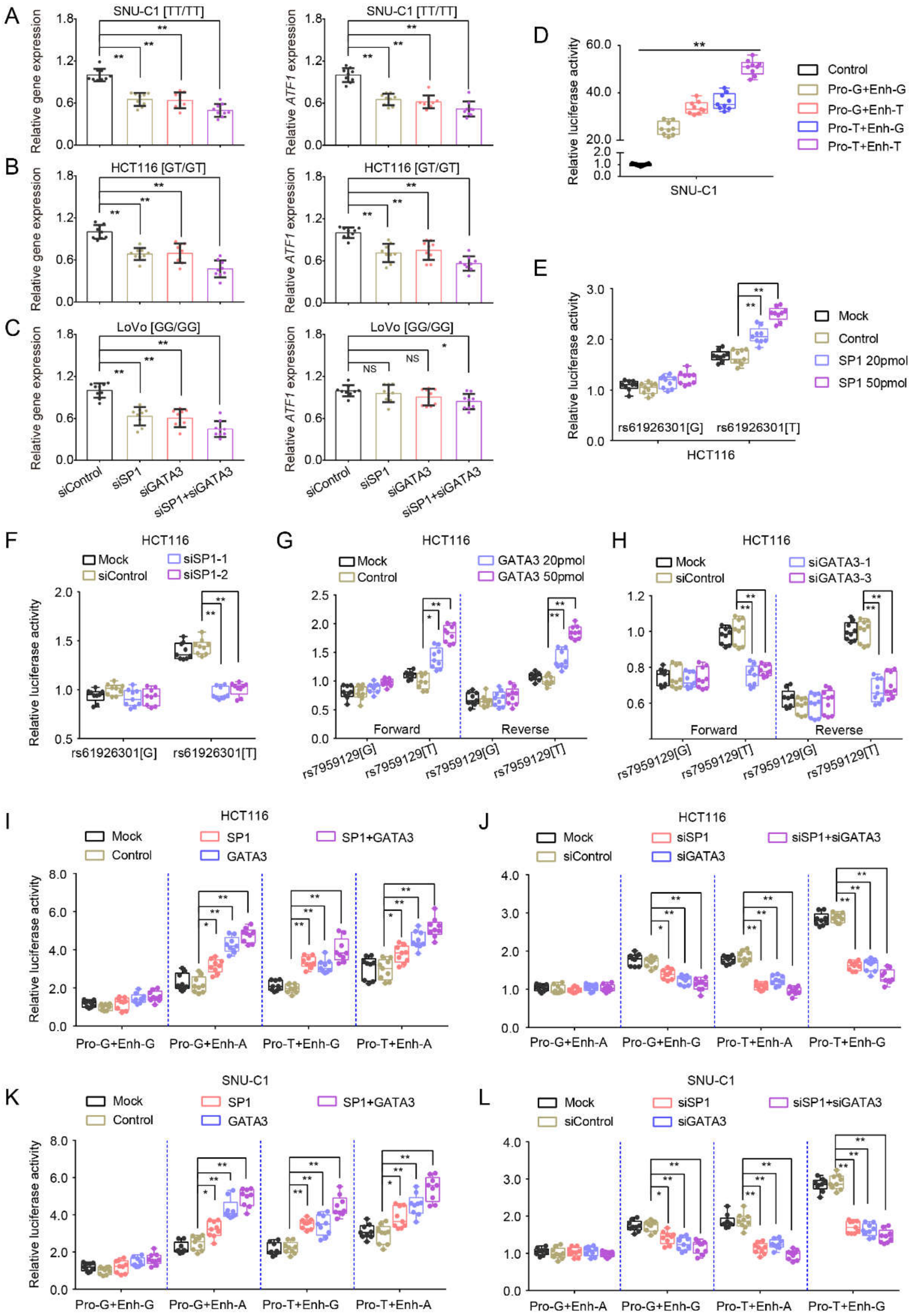

Figure S4. Risk alleles of rs61926301 and rs7959129 synergistically facilitate *ATF1* transcriptional activity mediated by TFs SP1 and GATA1. A-C. The expression of ATF1 when *SP1* or *GATA3* were knocked down in three CRC cell lines (SNU-C1 (A), HCT116 (B), LoVo (C)) with different genotypes of rs61926301 and rs7959129. **D.** Relative reporter gene activity of combined constructs containing both rs61926301 and rs7959129 in SNU-C1 cells. **E, F.** Effect of *SP1* overexpression or *SP1* knockdown on the relative luciferase activity of constructs containing the rs61926301[G] or rs61926301[T] allele in HCT116 cells. **G, H.** Effect of *GATA3* overexpression or *GATA3* knockdown on the luciferase activity of constructs containing the rs7959129[G] or rs7959129[T] allele in HCT116 cells. **I-L.** Effect of *SP1/GATA3* overexpression or *SP1/GATA3* knockdown on the luciferase activity of combined constructs containing both rs61926301 and rs12424860 in HCT116 and SNU-C1 cells, respectively. All experiments were performed in triplicate and each with three technical replicates. Data were shown as the mean ± SD and all *$P < 0.05$, **$P < 0.01$ were calculated by a two-sided Student's *t*-test.

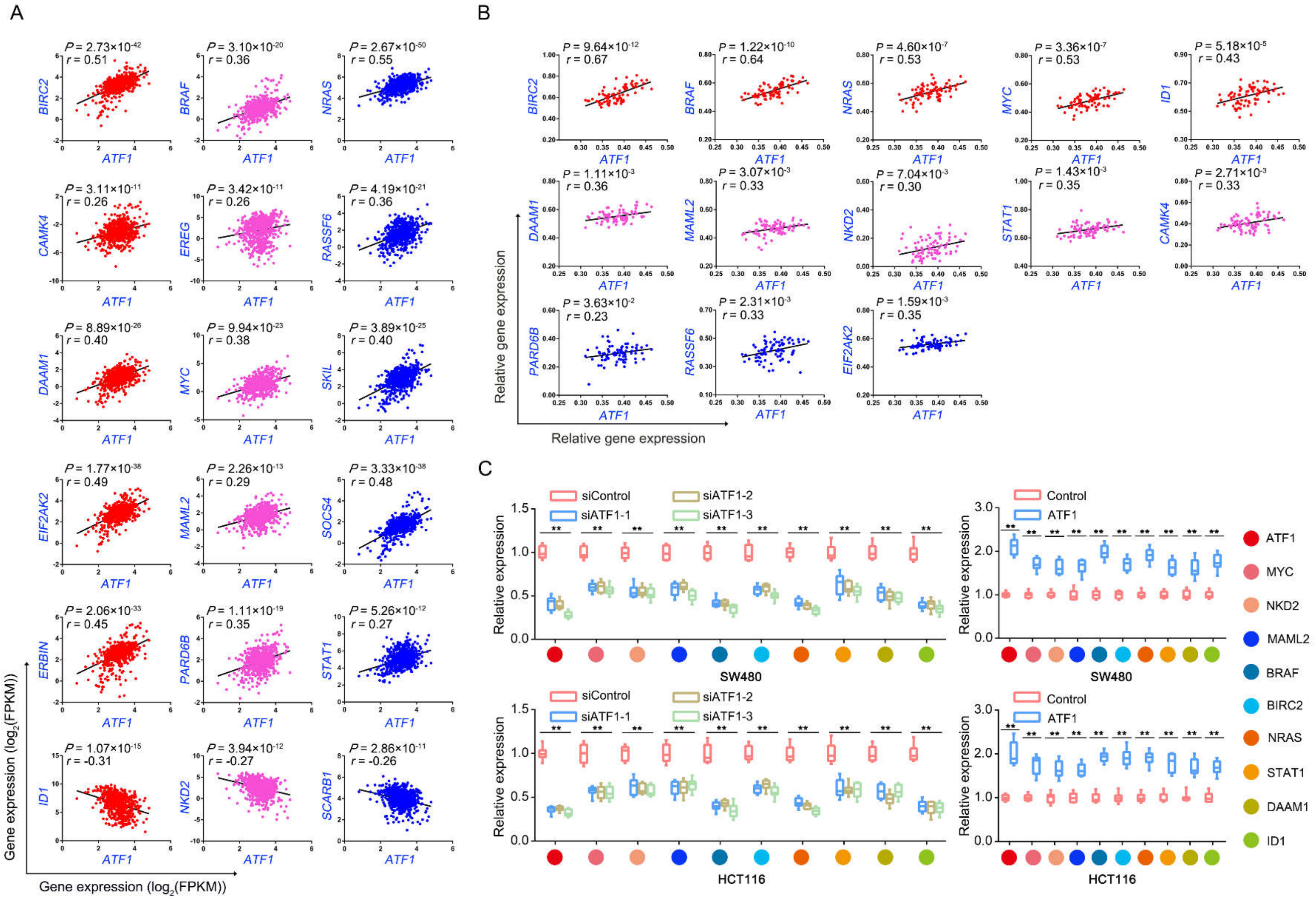
A
BIRC2 P = 2.73×10-42 r = 0.51
BRAF P = 3.10×10-20 r = 0.36
NRAS P = 2.67×10-50 r = 0.55
CAMK4 P = 3.11×10-11 r = 0.26
EREG P = 3.42×10-11 r = 0.26
RASSF6 P = 4.19×10-21 r = 0.36
DAAM1 P = 8.89×10-26 r = 0.40
MYC P = 9.94×10-23 r = 0.38
SKIL P = 3.89×10-25 r = 0.40
EIF2AK2 P = 1.77×10-38 r = 0.49
MAML2 P = 2.26×10-13 r = 0.29
SOCS4 P = 3.33×10-38 r = 0.48
ERBIN P = 2.06×10-33 r = 0.45
PARD6B P = 1.11×10-19 r = 0.35
STAT1 P = 5.26×10-12 r = 0.27
ID1 P = 1.07×10-15 r = -0.31
NKD2 P = 3.94×10-12 r = -0.27
SCARB1 P = 2.86×10-11 r = -0.26
ATF1
Gene expression (log2(FPKM))
Gene expression (log2(FPKM))
B
BIRC2 P = 9.64×10-12 r = 0.67
BRAF P = 1.22×10-10 r = 0.64
NRAS P = 4.60×10-7 r = 0.53
MYC P = 3.36×10-7 r = 0.53
ID1 P = 5.18×10-5 r = 0.43
DAAM1 P = 1.11×10-3 r = 0.36
MAML2 P = 3.07×10-3 r = 0.33
NKD2 P = 7.04×10-3 r = 0.30
STAT1 P = 1.43×10-3 r = 0.35
CAMK4 P = 2.71×10-3 r = 0.33
PARD6B P = 3.63×10-2 r = 0.23
RASSF6 P = 2.31×10-3 r = 0.33
EIF2AK2 P = 1.59×10-3 r = 0.35
ATF1
Relative gene expression
Relative gene expression
C
siControl
siATF1-1
siATF1-2
siATF1-3
Control
ATF1
Relative expression
**
SW480
HCT116
● ATF1
● MYC
● NKD2
● MAML2
● BRAF
● BIRC2
● NRAS
● STAT1
● DAAM1
● ID1

Figure S5. The correlation between *ATF1* expression and the genes in the top25 pathways of the pathway enrichment analyses in the three independent datasets, including TCGA CRC samples (A), our CRC tissues (B) and CRC cell lines (C). Gene expression data were normalized to FPKM (fragments per kilobase million) in TCGA samples or to *GAPDH* levels using qRT–PCR in both CRC tissues and CRC cell lines. In TCGA samples or our CRC tissues, all *P* values and *r* values were from Pearson's correlation analysis. In SW480 and HCT116 cells, data were shown as the mean ± SD from three repeated experiments and each with triplicates. All $^{*}P < 0.05$, $^{**}P < 0.01$ were calculated by a two-sided Student's *t*-test.

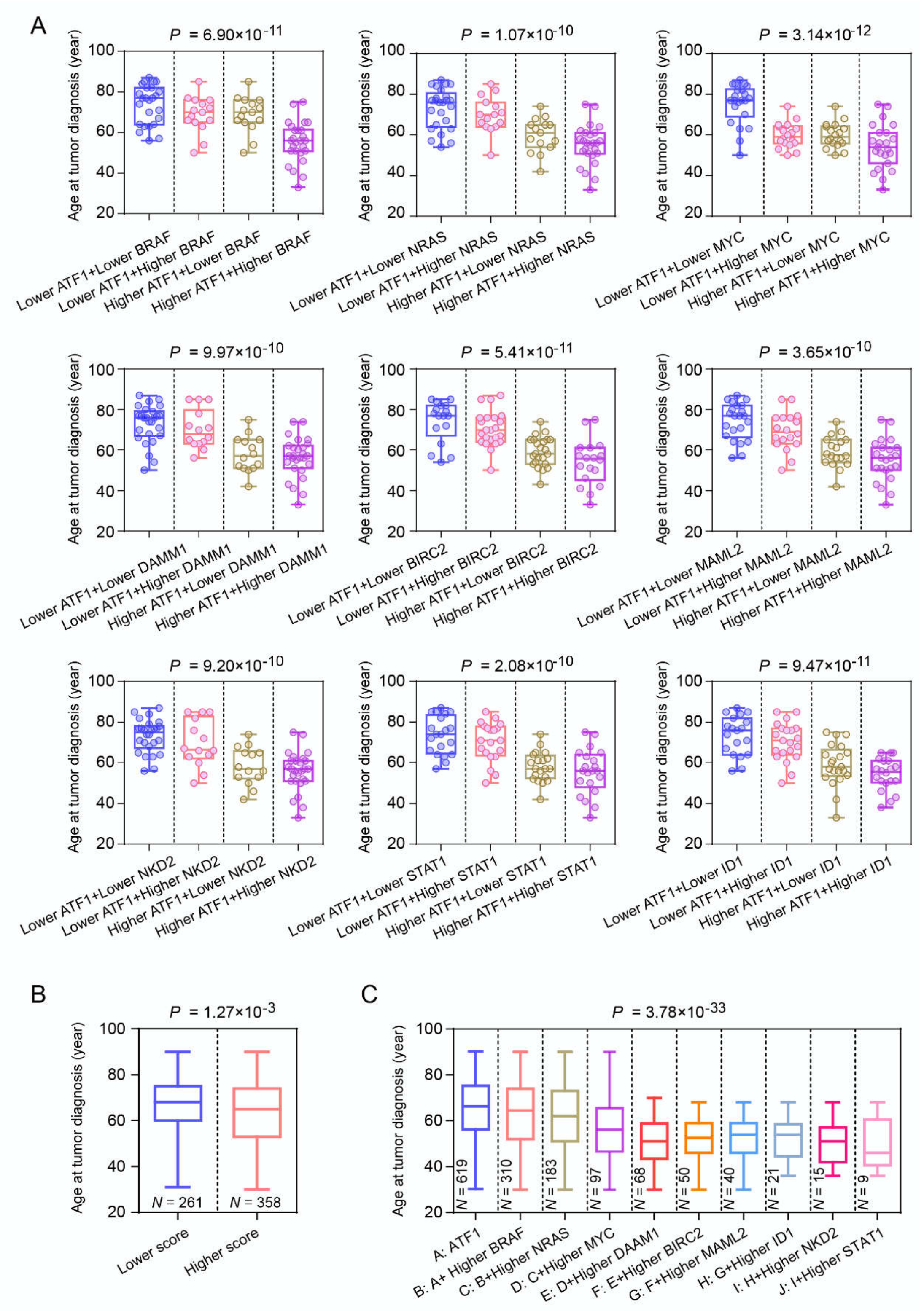

Figure S6. The association of age at CRC diagnosis with the synergy of *ATF1* and its target genes. A. The synergy of *ATF1* and its target genes significantly facilitates early-onset of CRC in our CRC patient sets. Data were shown as the mean ± SD and all *P* values were calculated by linear regression analysis. **B, C.** The association of age at CRC diagnosis with *ATF1* activity score (B) and with the synergy of *ATF1* and its target genes (C) in the TCGA CRC samples. *ATF1* activity scores were calculated based on the expression levels of *ATF1* and its target genes. Data were shown as the mean ± SD and all *P* values were calculated using linear regression analysis, while this in Figure S6B was calculated by a two-sided Student's *t*-test.

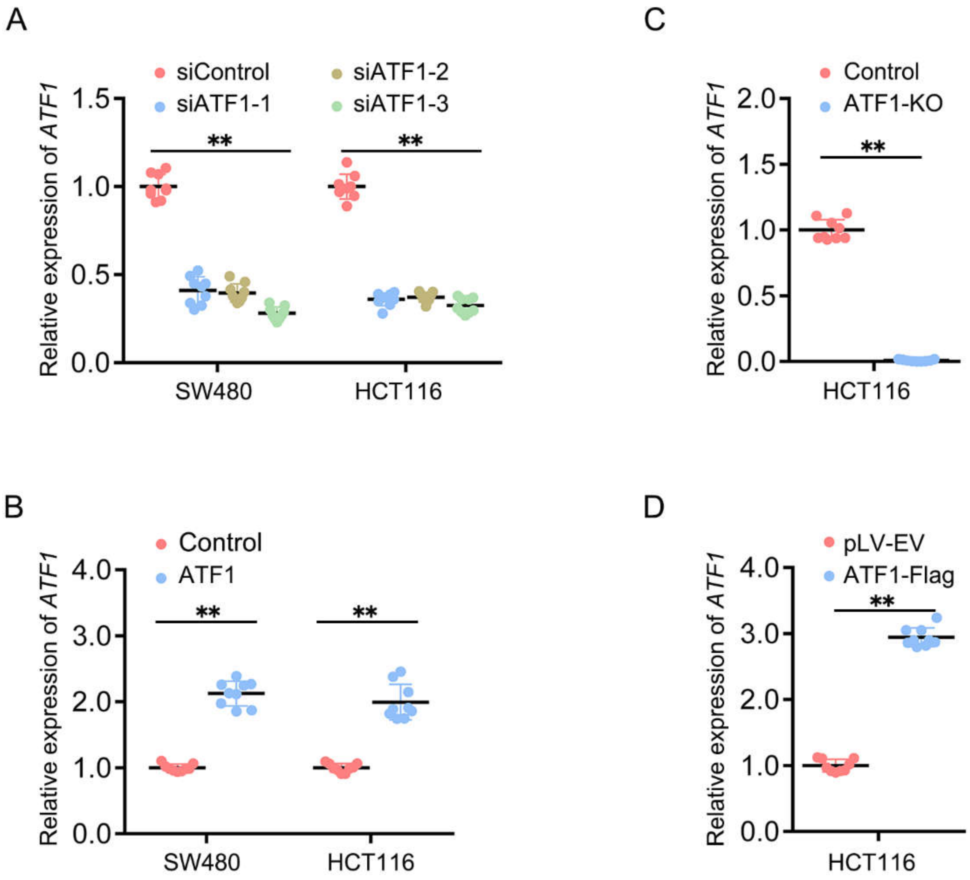

Figure S7. Determination of the transfection efficiency. A-D. Relative expression levels of *ATF1* were determined by qRT–PCR method in CRC SW480 and HCT116 cell lines transfected with siControl/siATF1 (A), pcDNA-control/pcDNA-ATF1 (B), ATF1 knockout by CRISPR/cas9 (C) and pLV-EV/ pLV-ATF1 by lentiviral transduction (D). Data were shown as the mean ± SD from three repeated experiments and each with three duplicates. All **P* < 0.05, ***P* < 0.01 compared with the controls by a two-sided Student's *t*-test.

Supplemental Tables

Table S1. A collection of tag SNPs in CRC GWAS loci of Asian population ($P \leq$ 1.00E-8)

ID	Locus	Tag SNP	Allele	Position (hg38)	Nearby gene	Location	*P* value
1	12p13.32	rs10774214	T/C	4259186	*CCND2*	Upstream	5.48E-10
2	5q31.1	rs647161	A/C	135163402	*C5ORF66*	Intron	3.77E-10
3	20p12.3	rs2423279	C/T	7831703	*HAO1*	Downstream	2.29E-07
4	10q26.12	rs1665650	T/C	116727589	*HSPA12A*	Intron	8.58E-07
5	10q22.3	rs704017	G/A	79059375	*ZMIZ1-AS1*	Intron 3	2.07E-08
6	10q25.2	rs11196172	A/G	112967084	*TCF7L2*	Intron 4	1.04E-12
7	11q12.2	rs174537	G/T	61785208	*MYRF*	Intron 24	9.22E-21
7	11q12.2	rs4246215	G/T	61796827	*FEN1*	3'UTR	7.65E-20
7	11q12.2	rs174550	T/C	61804006	*FADS1*	Intron 7	1.58E-19
7	11q12.2	rs1535	A/G	61830500	*FADS2*	Intron 1	8.21E-20
8	12p13.31	rs10849432	T/C	6276561	*CD9*	Intergenic	5.81E-10
9	17p13.3	rs12603526	C/T	897353	*NXN*	Intron 1	3.42E-08
10	19q13.2	rs1800469	G/A	41354391	*TGFB1*	Promoter	1.17E-08
10	19q13.2	rs2241714	C/T	41363487	*B9D2*	Exon 1	1.36E-08
11	18q21.1	rs7229639	G/A	48924606	*SMAD7*	Intron	2.93E-11
11	18q21.1	rs4939827	T/C	48927093	*SMAD7*	Intron 3	1.53E-08
12	1q41	rs6687758	G/A	221991606	*DUSP10*	Intergenic	8.99E-09
13	8q24.21	rs10505477	A/G	127395198	Unknown	Intergenic	3.43E-13
13	8q24.21	rs6983267	G/T	127401060	Unknown	Intergenic	4.85E-14
13	8q24.21	rs7014346	A/G	127412547	Unknown	Intergenic	1.96E-08
14	10p14	rs10795668	G/A	8659256	Unknown	Intergenic	4.91E-15
15	12q13.12	rs11169571	T/C	50819982	*ATF1*	3'UTR	1.65E-12

Table S2. Functional genomic screen based on high-throughput RNAi interrogation was used to identify genes essential for cell proliferation in CRC GWAS loci in Asian population in HCT116 and SW480 cells

Gene	HCT116				SW480			
	Fold change	†*P* value	Log2(Fold change)	Log10(*P* value)†	Fold change	†*P* value	Log2(Fold change)	Log10(*P* value)†
ATF1	0.405	9.67E-06	-1.304	5.014	0.550	3.71E-05	-0.862	4.430
PPP1R32	0.430	9.87E-06	-1.217	5.006	0.584	5.26E-04	-0.776	3.279
RPS19	0.544	1.55E-04	-0.879	3.810	0.899	1.03E-02	-0.153	1.987
LTBR	0.641	3.62E-04	-0.642	3.441	0.668	2.65E-03	-0.582	2.577
TFCP2	0.652	2.67E-04	-0.617	3.573	0.705	2.73E-04	-0.505	3.564
COPS7A	0.685	2.73E-04	-0.545	3.564	0.823	2.64E-02	-0.281	1.578
NOP2	0.686	8.45E-04	-0.544	3.073	0.822	3.62E-03	-0.283	2.441
MYC	0.689	2.27E-03	-0.538	2.643	0.691	3.94E-03	-0.534	2.404
GAPDH	0.719	2.32E-03	-0.476	2.635	0.850	1.77E-02	-0.235	1.752
CAMLG	0.723	7.54E-04	-0.467	3.123	0.844	5.05E-03	-0.245	2.297
CHD4	0.731	2.94E-03	-0.451	2.532	0.769	6.18E-03	-0.379	2.209
CCND2	0.736	7.55E-04	-0.443	3.122	0.917	4.70E-03	-0.125	2.328
DUSP10	0.753	1.24E-03	-0.409	2.905	0.811	5.67E-03	-0.302	2.247
SLC11A2	0.763	2.06E-03	-0.391	2.685	0.891	1.11E-03	-0.167	2.956
LETMD1	0.769	4.16E-04	-0.379	3.381	0.838	2.42E-03	-0.256	2.615
MYRF	0.773	4.80E-04	-0.371	3.319	0.841	2.73E-03	-0.250	2.564
FADS3	0.776	3.63E-04	-0.365	3.440	0.827	9.70E-03	-0.275	2.013
AKAP3	0.778	2.11E-03	-0.362	2.676	0.870	1.25E-02	-0.201	1.904
SMAGP	0.783	2.41E-04	-0.353	3.618	0.643	8.46E-04	-0.636	3.073
TMEM138	0.785	4.24E-04	-0.350	3.372	0.823	6.46E-03	-0.281	2.190
ZNF384	0.799	2.46E-04	-0.324	3.610	0.897	1.12E-02	-0.157	1.952
VWCE	0.802	2.09E-03	-0.318	2.681	0.872	1.06E-02	-0.197	1.973
INCENP	0.805	4.84E-03	-0.313	2.315	0.871	2.69E-02	-0.200	1.570
RAB3IL1	0.806	3.25E-04	-0.312	3.488	0.788	5.41E-05	-0.343	4.267
SDHAF2	0.810	1.59E-03	-0.305	2.800	0.851	4.09E-03	-0.233	2.388
CATSPER3	0.813	5.04E-03	-0.298	2.297	0.927	3.46E-02	-0.110	1.461
SEC24A	0.816	2.56E-03	-0.294	2.592	0.848	4.04E-03	-0.238	2.394
H2AFY	0.820	2.06E-03	-0.287	2.687	0.886	7.59E-03	-0.175	2.120
ENO4	0.823	5.36E-03	-0.281	2.271	0.872	3.45E-03	-0.197	2.462
ING4	0.825	2.03E-02	-0.277	1.692	1.459	6.35E-04	0.545	3.197
HSPA12A	0.826	1.38E-03	-0.276	2.860	0.888	4.48E-03	-0.171	2.349
DAZAP2	0.835	2.04E-03	-0.260	2.690	0.867	1.08E-03	-0.206	2.965
C5orf66	0.838	3.71E-03	-0.256	2.430	0.832	5.56E-03	-0.266	2.255
CEACAM6	0.852	1.07E-02	-0.231	1.969	0.577	1.02E-03	-0.793	2.992
CCDC172	0.866	7.56E-03	-0.208	2.121	0.864	3.46E-02	-0.210	1.461
NUTM2B-AS1	0.866	2.63E-02	-0.207	1.580	1.480	2.96E-04	0.566	3.529
PTMS	0.868	1.91E-02	-0.205	1.719	0.776	2.21E-05	-0.365	4.655
CYP2B6	0.870	3.89E-03	-0.201	2.410	0.865	1.72E-02	-0.209	1.765

EXOSC5	0.878	5.34E-03	-0.188	2.273	0.811	4.60E-04	-0.301	3.337
DDB1	0.885	4.22E-02	-0.176	1.374	1.274	3.63E-03	0.350	2.440
NCAPD2	0.889	2.38E-03	-0.170	2.623	0.856	7.51E-03	-0.224	2.124
DIP2B	0.903	1.03E-01	-0.147	0.986	0.989	3.05E-01	-0.017	0.515
PNLIP	0.906	6.56E-01	-0.143	0.183	0.893	2.13E-02	-0.163	1.671
TMEM258	0.910	4.54E-03	-0.136	2.343	1.039	6.44E-02	0.055	1.191
PIANP	0.911	3.96E-02	-0.135	1.403	0.936	3.47E-02	-0.095	1.460
CYB561A3	0.913	9.45E-03	-0.132	2.025	0.913	6.82E-02	-0.131	1.166
CPSF7	0.914	1.27E-02	-0.130	1.896	0.959	1.36E-01	-0.061	0.868
FAM186A	0.916	1.69E-01	-0.126	0.772	0.962	2.33E-01	-0.056	0.633
ACRBP	0.917	7.31E-03	-0.125	2.136	1.028	2.91E-01	0.040	0.536
PCBD2	0.930	4.58E-02	-0.104	1.339	0.860	1.75E-02	-0.218	1.756
CEACAM21	0.931	5.17E-02	-0.103	1.286	0.894	4.91E-04	-0.161	3.309
CCAT1	0.935	1.73E-01	-0.097	0.763	0.829	3.45E-04	-0.271	3.462
CSRNP2	0.947	2.69E-01	-0.079	0.571	0.984	2.74E-01	-0.023	0.562
NDUFA9	0.952	2.05E-01	-0.071	0.687	0.895	1.39E-02	-0.160	1.856
DMRTC2	0.953	2.60E-01	-0.069	0.586	0.943	6.47E-02	-0.085	1.189
SFTPA2	0.958	1.13E-01	-0.063	0.948	0.935	5.88E-02	-0.097	1.231
POU6F1	0.959	5.63E-01	-0.061	0.250	0.957	3.74E-01	-0.064	0.427
BEST1	0.961	2.15E-01	-0.058	0.667	1.009	7.41E-01	0.013	0.130
PPIF	0.966	2.74E-01	-0.050	0.562	1.016	2.48E-01	0.024	0.606
FADS1	0.973	1.59E-01	-0.040	0.800	0.954	6.71E-02	-0.068	1.173
HIGD1C	0.974	2.95E-01	-0.038	0.530	0.985	1.14E-01	-0.022	0.943
GALNT8	0.978	5.74E-01	-0.032	0.241	0.903	6.26E-02	-0.147	1.204
KCNK18	0.979	8.26E-01	-0.030	0.083	0.965	3.05E-01	-0.052	0.516
ATP5SL	0.983	5.66E-01	-0.025	0.247	0.989	7.18E-01	-0.016	0.144
EIF5AL1	0.986	5.79E-01	-0.021	0.237	0.945	1.02E-01	-0.081	0.990
NEUROG1	0.987	6.27E-01	-0.018	0.203	1.009	7.86E-01	0.013	0.105
TMPRSS12	0.989	6.42E-01	-0.016	0.193	0.996	4.35E-01	-0.006	0.361
FGF6	0.989	7.32E-01	-0.015	0.135	0.940	4.66E-02	-0.090	1.332
CEACAM3	0.991	8.27E-01	-0.012	0.082	0.974	2.21E-01	-0.038	0.656
VWF	1.001	9.38E-01	0.002	0.028	1.025	2.30E-01	0.036	0.639
LRRC10B	1.001	9.70E-01	0.002	0.013	1.023	2.21E-01	0.033	0.656
FADS2	1.012	5.20E-01	0.017	0.284	1.212	6.94E-03	0.277	2.159
GEMIN4	1.012	5.83E-01	0.018	0.234	0.906	3.08E-02	-0.142	1.511
SCGB2A2	1.015	5.64E-01	0.021	0.248	1.007	6.06E-01	0.010	0.218
SMAD7	1.017	6.62E-01	0.024	0.179	0.880	4.30E-03	-0.185	2.366
DAK	1.017	4.87E-01	0.024	0.313	0.998	9.42E-01	-0.003	0.026
ZCCHC24	1.017	5.49E-01	0.024	0.261	1.055	3.68E-02	0.078	1.434
CCDC97	1.017	6.37E-01	0.024	0.196	0.941	9.36E-02	-0.088	1.029
C12orf4	1.017	6.81E-01	0.025	0.167	1.016	6.59E-01	0.023	0.181
C10orf82	1.023	2.82E-01	0.033	0.550	0.896	4.12E-03	-0.158	2.385
VPS53	1.025	4.24E-01	0.035	0.373	0.986	7.43E-02	-0.020	1.129
SCNN1A	1.027	4.48E-01	0.039	0.349	0.950	8.97E-02	-0.074	1.047

CEACAM5	1.028	2.18E-01	0.039	0.661	1.014	6.07E-01	0.020	0.217
FEN1	1.028	1.76E-01	0.040	0.755	1.081	5.67E-02	0.113	1.246
DDX46	1.029	2.75E-01	0.041	0.561	0.964	2.37E-01	-0.053	0.624
TXNDC15	1.029	3.00E-01	0.041	0.523	1.176	1.31E-03	0.234	2.883
LPAR5	1.031	5.43E-01	0.044	0.265	1.067	4.78E-02	0.094	1.321
CEACAM4	1.033	3.20E-01	0.047	0.495	0.933	7.16E-02	-0.100	1.145
ZMIZ1	1.037	1.67E-01	0.053	0.778	1.016	2.07E-01	0.023	0.683
B9D2	1.042	1.53E-01	0.059	0.815	0.927	6.82E-02	-0.109	1.166
CYP2A13	1.045	3.32E-01	0.063	0.479	0.911	5.31E-02	-0.134	1.275
PNLIPRP2	1.046	1.68E-01	0.064	0.774	0.905	4.01E-02	-0.143	1.396
DYM	1.047	2.40E-01	0.066	0.620	1.198	1.37E-03	0.260	2.864
SCGB2A1	1.051	8.06E-02	0.072	1.094	0.962	1.28E-01	-0.055	0.891
SCGB1D2	1.052	4.43E-02	0.073	1.354	0.997	8.20E-01	-0.004	0.086
TAPBPL	1.054	2.01E-01	0.075	0.697	0.881	3.99E-02	-0.183	1.399
PNLIPRP1	1.054	8.09E-02	0.076	1.092	1.009	6.81E-01	0.013	0.167
B3GNT8	1.060	1.32E-01	0.084	0.880	1.040	1.57E-01	0.057	0.803
C12orf5	1.063	2.04E-01	0.088	0.691	0.987	5.25E-01	-0.018	0.280
SYT7	1.063	4.61E-02	0.088	1.336	0.969	5.44E-02	-0.045	1.265
ABR	1.066	1.38E-01	0.092	0.861	1.075	1.38E-01	0.105	0.861
PARP11	1.067	6.32E-02	0.094	1.200	0.973	2.34E-01	-0.040	0.631
TMEM91	1.070	1.25E-01	0.097	0.904	0.900	4.79E-02	-0.151	1.319
MLF2	1.073	4.51E-02	0.101	1.346	1.168	9.33E-03	0.224	2.030
CYP2A7	1.074	6.05E-02	0.103	1.218	0.824	8.95E-04	-0.279	3.048
VAMP1	1.076	9.11E-02	0.105	1.041	1.142	2.36E-02	0.191	1.627
VTI1A	1.077	6.62E-02	0.106	1.179	1.254	2.95E-02	0.327	1.530
CEACAM7	1.077	1.06E-01	0.107	0.973	1.037	1.69E-01	0.052	0.772
SCGB1D1	1.079	2.58E-02	0.110	1.588	1.029	3.02E-01	0.041	0.520
C5orf24	1.080	3.02E-02	0.111	1.519	0.933	1.51E-02	-0.100	1.820
VAX1	1.088	3.99E-01	0.122	0.400	0.976	1.06E-01	-0.034	0.975
IFFO1	1.090	3.16E-02	0.125	1.501	1.042	3.17E-01	0.059	0.498
BCKDHA	1.091	5.00E-03	0.126	2.301	0.830	1.45E-02	-0.269	1.839
CTIF	1.094	1.10E-01	0.129	0.959	1.067	5.33E-02	0.094	1.274
TCF7L2	1.094	1.40E-02	0.130	1.855	0.747	2.33E-03	-0.421	2.632
YWHAE	1.096	1.92E-02	0.132	1.716	1.100	5.93E-02	0.137	1.227
DYRK4	1.098	1.75E-02	0.135	1.758	0.938	4.92E-02	-0.093	1.308
GFRA1	1.098	2.14E-02	0.136	1.670	0.979	3.54E-01	-0.030	0.451
AXL	1.099	1.89E-02	0.136	1.724	1.172	3.72E-03	0.229	2.429
C19orf69	1.121	6.38E-03	0.165	2.195	1.162	2.50E-02	0.216	1.603
PLEKHG6	1.121	3.12E-03	0.165	2.506	1.200	6.93E-03	0.263	2.159
HAO1	1.127	8.12E-03	0.172	2.090	1.177	3.79E-03	0.236	2.421
CYP2F1	1.127	1.40E-02	0.173	1.853	1.198	1.99E-02	0.261	1.701
CXCL14	1.131	3.01E-02	0.178	1.521	1.572	1.38E-04	0.653	3.862
TIMM22	1.132	3.67E-02	0.179	1.435	1.456	9.53E-04	0.542	3.021
METTL7A	1.134	7.73E-03	0.182	2.112	1.232	1.99E-03	0.302	2.701

TNFRSF1A	1.137	8.32E-04	0.186	3.080	1.287	2.12E-03	0.364	2.673
CD27	1.151	6.38E-03	0.203	2.195	1.188	4.13E-03	0.248	2.385
RAD51AP1	1.152	5.77E-03	0.204	2.239	1.216	4.82E-03	0.282	2.317
KIAA1598	1.152	1.94E-03	0.204	2.712	1.145	8.76E-03	0.196	2.058
CYP2S1	1.155	1.38E-02	0.208	1.861	1.156	9.17E-03	0.209	2.038
HNRNPUL1	1.155	9.62E-03	0.208	2.017	1.197	9.19E-03	0.260	2.037
TGFB1	1.157	7.89E-03	0.211	2.103	1.185	6.65E-03	0.245	2.177
POU5F1B	1.159	1.04E-02	0.213	1.985	1.220	7.10E-03	0.287	2.149
TIFAB	1.162	3.56E-03	0.217	2.448	1.187	2.53E-02	0.247	1.597
GLOD4	1.163	2.59E-02	0.218	1.587	1.479	1.99E-04	0.564	3.700
PITX1	1.173	3.31E-03	0.230	2.481	1.144	1.02E-02	0.194	1.992
TMX4	1.186	1.73E-03	0.246	2.762	1.112	3.36E-02	0.153	1.473
SCGB1D4	1.188	1.93E-02	0.249	1.715	1.113	1.72E-02	0.154	1.765
DAGLA	1.192	6.27E-03	0.254	2.203	1.215	3.49E-02	0.281	1.457
RNMTL1	1.193	2.96E-03	0.254	2.528	1.213	1.17E-02	0.278	1.931
LYPD4	1.194	4.13E-05	0.256	4.384	1.179	1.01E-03	0.238	2.995
ANO2	1.196	2.10E-04	0.258	3.679	1.249	2.22E-03	0.320	2.654
FGF23	1.226	5.23E-03	0.294	2.281	1.206	2.03E-02	0.271	1.692
LARP4	1.234	1.01E-03	0.304	2.994	1.126	1.33E-02	0.171	1.875
TUSC5	1.240	5.64E-03	0.311	2.249	0.821	7.84E-04	-0.285	3.106
LAG3	1.247	5.13E-03	0.318	2.290	1.211	1.14E-02	0.276	1.942
FTH1	1.273	5.83E-03	0.349	2.235	1.207	2.24E-02	0.271	1.650
CD9	1.278	4.93E-03	0.354	2.307	1.157	1.73E-02	0.210	1.762
NXN	1.313	3.28E-03	0.393	2.485	1.260	1.29E-02	0.333	1.890
TMEM216	1.318	3.56E-03	0.399	2.448	1.204	9.12E-03	0.267	2.040
PLCB1	1.323	2.55E-03	0.404	2.593	1.223	1.12E-02	0.290	1.952
FAM57A	1.327	1.57E-03	0.408	2.805	1.126	2.86E-02	0.172	1.544
BIN2	1.339	1.46E-03	0.422	2.837	1.156	3.78E-02	0.210	1.422
MRPL51	1.367	1.49E-03	0.451	2.828	1.328	2.99E-04	0.409	3.525
DCANP1	1.526	6.19E-04	0.610	3.208	1.178	1.04E-03	0.236	2.983
PNLIPRP3	1.583	6.15E-04	0.663	3.211	1.411	9.70E-04	0.496	3.013

[†] All *P* values were calculated by a two-sided Student's *t*-test

Table S3. Summary of characteristics of individuals in the two stage case-control studies

	Discovery phase			Replication phase			Combined study		
	Cases	Controls	*P*[†]	Cases	Controls	*P*[†]	Cases	Controls	*P*[†]
	N (%)	*N* (%)		*N* (%)	*N* (%)		*N* (%)	*N* (%)	
Total	1,524	1,522		4,689	8,866		6,213	10,388	
Gender			0.498			0.631			0.429
Male	923 (60.56)	940 (61.76)		2,879 (61.40)	5,481 (61.82)		3,802 (61.19)	6,421 (61.81)	
Female	601 (39.44)	582 (38.24)		1,810 (38.60)	3,385 (38.18)		2,411 (38.81)	3,967 (38.19)	
Age (mean ± SD)	58.84±11.86	60.48±10.11	<0.001	59.73±12.06	61.33±11.57	<0.001	59.51±12.02	61.20±11.37	<0.001
Age group (year)			0.041			0.937			0.201
≤50	327 (21.46)	281 (18.46)		708 (15.10)	1,321 (14.90)		1,035 (16.66)	1,602 (15.42)	
51-60	420 (27.56)	433 (28.45)		1,263 (26.94)	2,396 (27.02)		1,683 (27.09)	2,829 (27.23)	
61-70	484 (31.76)	542 (35.61)		1,602 (34.17)	3,001 (33.85)		2,086 (33.57)	3,543 (34.11)	
≥71	293 (19.23)	266 (17.48)		1,116 (23.80)	2,148 (24.23)		1,409 (22.68)	2,414 (23.24)	
Smoking status			1.32×10^{-10}			0.011			6.57×10^{-4}
No	1042 (68.37)	1197 (78.65)		2,834 (60.44)	5,556 (62.67)		3,876 (62.39)	6,753 (65.01)	
Yes	482 (31.63)	325 (21.35)		1,855 (39.56)	3,310 (37.33)		2,337 (37.61)	3,635 (34.99)	
Drinking status			0.725			0.159			0.092
No	1133 (74.34)	1123 (73.78)		3,414 (72.81)	6,354 (71.67)		4,547 (73.19)	7,477 (71.98)	
Yes	391 (25.66)	399 (26.22)		1,275 (27.19)	2,512 (28.33)		1,666 (26.81)	2,911 (28.02)	

SD, standard deviation.

[†] All *P* values were calculated by a two sided Student's *t* test for age or the Pearson's χ^2 test for gender, age group, smoking status, and drinking status.

Table S4. Interaction analysis between *ATF1* promoter-rs61926301 and enhancer-rs7959129 in the risk of CRC

Stage	Interaction analysis		Stratified analysis	Enhancer rs7959129								
				GG			GT			TT		
	$^{\dagger}P_{multiplicative}$	$^{\ddagger}P_{additive}$	Promoter rs61926301	Cases/ Controls	OR(95%CI)	$P^{\dagger}$	Cases/ Controls	OR(95%CI)	$P^{\dagger}$	Cases/ Controls	OR(95%CI)	$P^{\dagger}$
Discovery phase	8.20×10^{-7}	1.04×10^{-3}	GG	176/331	1.00 (Reference)		259/212	2.21 (1.70-2.89)	2.76×10^{-9}	102/97	1.92 (1.37-2.70)	1.55×10^{-4}
			GT	268/264	1.83 (1.42-2.36)	2.62×10^{-6}	396/357	2.02 (1.59-2.56)	6.03×10^{-9}	122/90	2.41 (1.73-3.37)	2.54×10^{-7}
			TT	51/28	3.30 (2.00-5.46)	3.03×10^{-6}	92/85	1.93 (1.35-2.75)	2.76×10^{-4}	34/16	3.63 (1.94-6.79)	5.43×10^{-5}
Replication phase	3.47×10^{-15}	1.12×10^{-4}	GG	768/1,579	1.00 (Reference)		1,025/2,116	0.98 (0.87-1.10)	6.94×10^{-1}	340/694	1.03 (0.88-1.21)	6.68×10^{-1}
			GT	749/1,678	0.92 (0.81-1.04)	1.68×10^{-1}	941/1,448	1.34 (1.19-1.51)	1.72×10^{-6}	313/441	1.47 (1.24-1.75)	7.54×10^{-6}
			TT	169/326	1.06 (0.87-1.31)	5.56×10^{-1}	242/401	1.25 (1.04-1.50)	1.73×10^{-2}	142/183	1.64 (1.29-2.08)	5.37×10^{-5}
Combined study	1.20×10^{-22}	6.50×10^{-3}	GG	944/1,910	1.00 (Reference)		1,284/2,328	1.09 (0.98-1.21)	1.15×10^{-1}	442/791	1.15 (1.00-1.32)	5.72×10^{-2}
			GT	1,017/1,942	1.06 (0.95-1.18)	3.11×10^{-1}	1,337/1,805	1.49 (1.34-1.66)	1.52×10^{-13}	435/531	1.65 (1.42-1.91)	6.70×10^{-11}
			TT	220/354	1.25 (1.04-1.51)	1.71×10^{-2}	334/486	1.39 (1.18-1.63)	6.65×10^{-5}	176/199	1.77 (1.42-2.21)	3.16×10^{-7}

Abbereviation: Odds ratios (ORs), Confidence intervals (CIs).

$^{\dagger}P$ values were calculated by unconditional logistic regression model after adjusting for gender, age group, smoking status and drinking status.

$^{\ddagger}P$ values in additive interaction model were calculated by the bootstrapping test of goodness-of-fit.

Table S5. Combined ChIP-seq and RNA-seq data reveals 278 genes directly regulated by *ATF1*

Gene	*ATF1* group (mean, FPKM)	Control group (mean, FPKM)	log2 (Fold change)	[†]FDR *P* value
CD109	1.287	0.225	2.516	7.00E-03
CREB5	1.746	0.423	2.045	7.00E-03
AKT3	3.802	0.930	2.031	7.00E-03
PRL	7.786	2.003	1.959	7.00E-03
BICC1	17.579	6.617	1.410	7.00E-03
RASSF6	6.748	2.557	1.400	7.00E-03
PTGS2	70.011	27.313	1.358	7.00E-03
HAS2	3.193	1.283	1.316	7.00E-03
LCA5	4.648	2.107	1.141	7.00E-03
KIAA1217	5.928	2.745	1.111	7.00E-03
GDF15	37.642	17.489	1.106	7.00E-03
SLC25A12	24.984	11.829	1.079	7.00E-03
SYNE1	4.393	2.135	1.041	7.00E-03
ACTL8	5.405	2.698	1.002	7.00E-03
ZNF521	26.537	13.291	0.998	7.00E-03
DCDC2	3.038	1.547	0.974	7.00E-03
RASEF	5.283	2.751	0.941	7.00E-03
SPOCK1	6.954	3.623	0.941	7.00E-03
CXCL3	150.491	81.539	0.884	7.00E-03
CIITA	6.110	3.323	0.879	7.00E-03
CNTNAP2	3.056	1.674	0.868	7.00E-03
F3	68.306	37.659	0.859	7.00E-03
ZC3H12C	8.654	4.811	0.847	7.00E-03
CENPE	8.373	4.684	0.838	7.00E-03
SH3BGRL2	13.933	8.019	0.797	7.00E-03
GAB2	7.538	4.376	0.785	7.00E-03
RAET1L	7.078	4.158	0.767	7.00E-03
DKK1	325.257	191.410	0.765	7.00E-03
SEMA3C	11.060	6.575	0.750	7.00E-03
SLCO4C1	18.283	11.040	0.728	7.00E-03
PROX1	2.497	1.521	0.716	7.00E-03
MYC	109.984	67.049	0.714	7.00E-03
PDK4	2.148	1.319	0.703	7.00E-03
ZNF449	2.949	1.827	0.691	7.00E-03
PHIP	19.732	12.300	0.682	7.00E-03
FRK	4.418	2.790	0.663	7.00E-03
PSD3	4.998	3.168	0.658	7.00E-03
FUT1	5.727	3.640	0.654	7.00E-03
REL	9.195	5.852	0.652	7.00E-03
HINT3	21.340	13.636	0.646	7.00E-03

TGFB2	72.996	47.146	0.631	7.00E-03
CXCL2	76.247	49.700	0.617	7.00E-03
BRAF	18.331	12.013	0.610	7.00E-03
SMC2	11.188	7.436	0.589	7.00E-03
MBOAT2	3.250	2.160	0.589	7.00E-03
RNF152	3.751	2.496	0.588	7.00E-03
ASPM	20.746	13.858	0.582	7.00E-03
WNT5A	99.937	67.020	0.576	7.00E-03
KIAA1462	4.315	2.896	0.575	7.00E-03
PTBP3	40.559	27.353	0.568	7.00E-03
ZNF22	6.955	4.701	0.565	7.00E-03
MAML2	3.427	2.333	0.555	7.00E-03
CCDC186	12.488	8.524	0.551	7.00E-03
CAMK4	4.585	3.134	0.549	7.00E-03
B3GNT5	11.133	7.626	0.546	7.00E-03
ERBIN	29.438	20.168	0.546	7.00E-03
CLIC4	85.985	59.089	0.541	7.00E-03
RHOBTB3	22.501	15.639	0.525	7.00E-03
STAT5B	6.404	4.454	0.524	7.00E-03
MITF	25.248	17.567	0.523	7.00E-03
CEP97	5.859	4.090	0.518	7.00E-03
PELI2	6.283	4.388	0.518	7.00E-03
E2F7	10.037	7.047	0.510	7.00E-03
MAL2	70.978	49.922	0.508	7.00E-03
TMEM170B	8.774	6.175	0.507	7.00E-03
ENPP4	9.626	6.783	0.505	7.00E-03
CKAP2L	13.652	9.641	0.502	7.00E-03
ASNS	303.795	215.047	0.498	7.00E-03
MSANTD4	9.075	6.427	0.498	7.00E-03
AHR	125.593	89.013	0.497	7.00E-03
ETV6	16.196	11.488	0.496	7.00E-03
TMEM65	5.951	4.225	0.494	7.00E-03
CLDN1	19.789	14.051	0.494	7.00E-03
DGKH	5.263	3.750	0.489	7.00E-03
PARD6B	5.140	3.663	0.489	7.00E-03
ZBTB20	17.028	12.139	0.488	7.00E-03
CDT1	19.724	14.068	0.487	7.00E-03
FERMT2	24.395	17.407	0.487	7.00E-03
BCAT1	34.530	24.709	0.483	7.00E-03
NRAS	120.921	87.365	0.469	7.00E-03
RAP2A	20.428	14.783	0.467	7.00E-03
PDZD8	22.310	16.153	0.466	7.00E-03
RAB3B	13.733	9.949	0.465	7.00E-03
ADAM9	33.698	24.416	0.465	7.00E-03

DEK	78.536	57.287	0.455	7.00E-03
ETNK1	22.034	16.082	0.454	7.00E-03
PANK3	29.460	21.504	0.454	7.00E-03
GTF2A1	22.513	16.457	0.452	7.00E-03
SMC3	51.860	37.972	0.450	7.00E-03
EPRS	122.227	90.342	0.436	7.00E-03
CDS1	11.019	8.161	0.433	7.00E-03
FSTL1	28.477	21.127	0.431	7.00E-03
GRPEL2	25.764	19.183	0.426	7.00E-03
TOP2A	119.019	88.799	0.423	7.00E-03
RSL24D1	109.620	81.952	0.420	7.00E-03
KIF5B	87.814	67.327	0.383	7.00E-03
TBC1D4	38.053	50.390	-0.405	7.00E-03
TRIM25	34.226	46.751	-0.450	7.00E-03
JUN	15.031	20.535	-0.450	7.00E-03
MT1E	111.418	152.265	-0.451	7.00E-03
SFN	43.617	59.892	-0.457	7.00E-03
ID1	175.712	126.499	0.474	7.00E-03
KIFAP3	11.918	16.680	-0.485	7.00E-03
NAA35	17.266	24.414	-0.500	7.00E-03
S100A6	787.828	1121.770	-0.510	7.00E-03
BSN	0.778	1.114	-0.518	7.00E-03
MALL	10.150	14.699	-0.534	7.00E-03
RIMKLA	1.978	2.882	-0.543	7.00E-03
TNFSF9	10.035	14.630	-0.544	7.00E-03
IER5L	13.756	20.082	-0.546	7.00E-03
KREMEN1	11.670	17.060	-0.548	7.00E-03
PODXL2	8.280	12.115	-0.549	7.00E-03
SUMO3	28.278	41.545	-0.555	7.00E-03
LGALS3BP	97.715	143.798	-0.557	7.00E-03
DUSP1	4.750	7.006	-0.561	7.00E-03
FRMD8	12.265	18.149	-0.565	7.00E-03
HPDL	6.217	9.206	-0.566	7.00E-03
NMU	33.107	49.132	-0.570	7.00E-03
HS6ST1	26.581	39.715	-0.579	7.00E-03
EIF2AK2	17.183	25.679	-0.580	7.00E-03
HES1	21.764	32.714	-0.588	7.00E-03
FOXF2	4.448	6.717	-0.595	7.00E-03
UBL5	154.829	234.840	-0.601	7.00E-03
CCDC85B	17.571	26.759	-0.607	7.00E-03
GMPR	13.984	21.391	-0.613	7.00E-03
JAG1	13.907	21.281	-0.614	7.00E-03
LSS	13.238	20.322	-0.618	7.00E-03
ADRB1	2.892	4.468	-0.628	7.00E-03

EN1	13.370	20.673	-0.629	7.00E-03
IFIH1	10.303	15.932	-0.629	7.00E-03
HMOX1	9.469	14.901	-0.654	7.00E-03
ATG3	53.849	84.988	-0.658	7.00E-03
PARP14	16.904	27.016	-0.676	7.00E-03
UBE2L6	41.388	66.239	-0.678	7.00E-03
CEBPD	2.794	4.533	-0.698	7.00E-03
SLCO4A1	11.278	18.566	-0.719	7.00E-03
IGFBP6	13.973	23.053	-0.722	7.00E-03
PFKFB4	6.369	10.642	-0.741	7.00E-03
ARL15	9.199	15.424	-0.746	7.00E-03
SNX18	24.422	41.026	-0.748	7.00E-03
MT2A	221.908	375.026	-0.757	7.00E-03
SLC7A8	19.585	33.177	-0.760	7.00E-03
PCSK9	12.356	21.014	-0.766	7.00E-03
ETS2	20.118	34.221	-0.766	7.00E-03
NMNAT2	2.537	4.350	-0.778	7.00E-03
PRKCDBP	5.054	8.818	-0.803	7.00E-03
IGFL1	39.094	68.716	-0.814	7.00E-03
KIZ	42.567	76.271	-0.841	7.00E-03
FZD1	3.826	6.991	-0.870	7.00E-03
BAMBI	9.741	18.288	-0.909	7.00E-03
USP18	7.370	14.134	-0.939	7.00E-03
MAOA	3.828	7.344	-0.940	7.00E-03
LAP3	9.531	18.412	-0.950	7.00E-03
LIPA	33.875	65.513	-0.952	7.00E-03
IFIT5	11.451	22.208	-0.956	7.00E-03
S100A4	26.006	50.667	-0.962	7.00E-03
ADAR	40.904	79.859	-0.965	7.00E-03
CYP2J2	13.551	26.460	-0.965	7.00E-03
S100A16	22.499	44.396	-0.981	7.00E-03
KRT19	64.781	128.813	-0.992	7.00E-03
PRRX1	2.774	5.519	-0.993	7.00E-03
SOX5	1.101	2.193	-0.994	7.00E-03
PRSS35	1.292	2.594	-1.005	7.00E-03
RARRES3	5.570	11.585	-1.057	7.00E-03
CHST2	2.598	5.443	-1.067	7.00E-03
HELZ2	4.899	10.331	-1.076	7.00E-03
RUNX1	5.122	10.952	-1.096	7.00E-03
OSR1	19.148	41.288	-1.108	7.00E-03
CDYL2	4.755	10.708	-1.171	7.00E-03
CECR6	1.073	2.432	-1.180	7.00E-03
PLSCR1	7.855	18.212	-1.213	7.00E-03
DHRS2	5.877	14.678	-1.321	7.00E-03

EYA1	1.822	4.592	-1.334	7.00E-03
ZC3HAV1	5.336	13.598	-1.350	7.00E-03
APCDD1	16.471	45.795	-1.475	7.00E-03
PTPRZ1	0.500	1.433	-1.520	7.00E-03
TNS4	0.370	1.072	-1.533	7.00E-03
OAS3	22.496	73.706	-1.712	7.00E-03
EPSTI1	1.286	4.280	-1.735	7.00E-03
KRT75	0.489	1.653	-1.758	7.00E-03
HERC6	1.308	4.655	-1.832	7.00E-03
FOS	2.653	9.522	-1.844	7.00E-03
ISG15	83.998	373.081	-2.151	7.00E-03
EGR1	8.065	35.947	-2.156	7.00E-03
MX2	2.294	11.546	-2.332	7.00E-03
IFI27	5.262	30.442	-2.532	7.00E-03
IFI6	22.090	151.523	-2.778	7.00E-03
NR4A1	0.763	5.660	-2.892	7.00E-03
KRT85	0.330	4.143	-3.649	7.00E-03
KRT5	0.244	5.401	-4.468	7.00E-03
SEMA7A	3.626	1.680	1.110	1.31E-02
DST	7.369	3.954	0.898	1.31E-02
NCOA7	9.304	5.019	0.890	1.31E-02
RYR2	1.442	0.843	0.774	1.31E-02
SOCS4	12.688	8.283	0.615	1.31E-02
ACER3	6.857	4.599	0.576	1.31E-02
IFRD1	59.288	40.963	0.533	1.31E-02
TMEM56	6.590	4.569	0.528	1.31E-02
FAM84B	11.590	8.547	0.439	1.31E-02
HAUS6	14.790	10.927	0.437	1.31E-02
NHLRC2	17.774	13.390	0.409	1.31E-02
HIST1H3H	135.623	179.308	-0.403	1.31E-02
BHLHE40	17.048	22.947	-0.429	1.31E-02
HIST3H2A	76.402	105.096	-0.460	1.31E-02
NKD2	19.684	12.689	0.633	1.31E-02
CCDC80	2.334	3.666	-0.652	1.31E-02
SSH3	4.696	7.835	-0.739	1.31E-02
PARP12	9.259	16.895	-0.868	1.31E-02
MX1	1.175	8.449	-2.847	1.31E-02
HPGD	7.041	2.984	1.238	1.88E-02
DAAM1	4.622	2.609	0.825	1.88E-02
CEP135	5.827	3.722	0.647	1.88E-02
VAMP4	2.743	1.794	0.613	1.88E-02
VASH2	5.951	3.930	0.599	1.88E-02
MOB3B	1.982	1.337	0.568	1.88E-02
DEPDC1	18.030	12.562	0.521	1.88E-02

KIF21B	6.753	4.721	0.516	1.88E-02
CCDC50	32.738	23.351	0.487	1.88E-02
FBXO30	4.403	3.250	0.438	1.88E-02
KLF2	9.194	13.498	-0.554	1.88E-02
HNRNPR	38.523	14.716	1.388	2.39E-02
SESTD1	3.635	2.496	0.542	2.39E-02
RFX3	15.288	11.228	0.445	2.39E-02
OGFRL1	4.671	3.496	0.418	2.39E-02
MB21D2	30.141	39.006	-0.372	2.39E-02
EREG	18.032	23.770	-0.399	2.39E-02
ID3	120.762	162.900	-0.432	2.39E-02
SRM	46.920	64.162	-0.452	2.39E-02
SERPINE2	26.300	38.295	-0.542	2.39E-02
COL15A1	1.683	2.474	-0.556	2.39E-02
ATL3	1.530	2.285	-0.579	2.39E-02
MT1X	0.895	9.978	-3.479	2.39E-02
LDLRAP1	11.054	7.523	0.555	2.92E-02
ARRDC4	3.704	2.618	0.501	2.92E-02
ZNF121	17.915	13.476	0.411	2.92E-02
PODXL	32.906	43.772	-0.412	2.92E-02
HK2	23.751	31.763	-0.419	2.92E-02
STAT1	22.198	7.059	1.653	2.92E-02
GLI3	0.809	3.377	-2.061	2.92E-02
POLI	3.158	1.902	0.731	3.38E-02
EGF	2.189	1.336	0.712	3.38E-02
SEPSECS	4.463	2.973	0.586	3.38E-02
CEP78	7.073	4.750	0.574	3.38E-02
TTC39B	2.857	1.997	0.517	3.38E-02
LYST	2.771	1.943	0.512	3.38E-02
MAN2A1	17.008	12.074	0.494	3.38E-02
BIRC2	25.435	18.948	0.425	3.38E-02
UTRN	7.998	5.980	0.419	3.38E-02
PPM1H	9.956	7.480	0.413	3.38E-02
PRSS23	14.378	20.758	-0.530	3.38E-02
SCARB1	11.561	16.820	-0.541	3.38E-02
FBL	63.745	105.223	-0.723	3.38E-02
HR	2.650	4.498	-0.763	3.38E-02
HSPH1	9.618	4.181	1.202	3.84E-02
B3GALT1	1.258	0.731	0.783	3.84E-02
SKIL	6.720	4.481	0.585	3.84E-02
SYK	7.024	5.094	0.464	3.84E-02
ZDHHC21	3.520	2.593	0.441	3.84E-02
AK3	30.412	22.490	0.435	3.84E-02
SMC5	14.192	10.698	0.408	3.84E-02

F2RL1	26.066	19.829	0.395	3.84E-02
SMIM3	11.199	15.060	-0.427	3.84E-02
ATP1B1	129.092	175.732	-0.445	3.84E-02
NTN4	4.769	3.036	0.652	4.27E-02
ARHGAP29	8.803	6.144	0.519	4.27E-02
ATAD2	35.590	26.955	0.401	4.27E-02
QSER1	22.115	17.109	0.370	4.27E-02
SLC46A3	4.907	7.043	-0.521	4.27E-02
RTN4R	3.232	6.154	-0.929	4.27E-02
EGR4	0.512	1.366	-1.415	4.27E-02
UGGT2	7.961	5.505	0.532	4.69E-02
KIF20B	16.152	11.717	0.463	4.69E-02
OTUD3	6.783	5.033	0.430	4.69E-02
PIM3	43.498	56.453	-0.376	4.69E-02
TRIB1	16.969	22.505	-0.407	4.69E-02
B4GALNT4	16.973	22.612	-0.414	4.69E-02
SLC25A28	5.908	10.257	-0.796	4.69E-02
CYP11A1	1.414	3.772	-1.416	4.69E-02

Abbreviations: FPKM (fragments per kilobase million)

[†] *P* values were calculated by a two-sided Student's *t*-test

Table S6. Probes or primers sequence used in the study

Electrophoretic mobility shift assay (5'-3')		
rs61926301-G	Forward	CCCCGCCCCCAGGCTTGTGTAGATC
	Reverse	GATCTACACAAGCCTGGGGGCGGGG
rs61926301-T	Forward	CCCCGCCCCCAGTCTTGTGTAGATC
	Reverse	GATCTACACAAGACTGGGGGCGGGG
rs7959129-G	Forward	TTGATATGTGTGGTTTTTTTTTGAT
	Reverse	ATCAAAAAAAAACCACACATATCAA
rs7959129-T	Forward	TTGATATGTGTGTTTTTTTTTTGAT
	Reverse	ATCAAAAAAAAAACACACATATCAA
qRT-PCR (5'-3')		
GAPDH	Forward	CCTCCCGCTTCGCTCTCT
	Reverse	TGGCGACGCAAAAGAAGAT
ATF1	Forward	GTCTACAGAAAGTCTCCTAACACT
	Reverse	TGTGGCAGAGAAGTAGCTGAAG
BIRC2	Forward	AATGGAAGATAGCACGAT
	Reverse	TCTGAGACAGGCACCC
BRAF	Forward	CACTTGGTAGACGGGACT
	Reverse	AAGGCTTGTAACTGCTGA
NRAS	Forward	AAACAAGCCCACGAAC
	Reverse	CAATCCCATACAACCCT
CAMK4	Forward	GGTTGTGCCTATGGACC
	Reverse	AATGTAGTCAGCCGTTTCT
EREG	Forward	GGGAGGAGGATGGAGA
	Reverse	TGTTATTGACACTTGAGCC
RASS	Forward	GGCAAACTAATTGTTGA
	Reverse	ACATAGGAATCTGGGTC
DAAM	Forward	TCACCCAGAAATCACG
	Reverse	GTCCAGTTCATCCACCA
MYC	Forward	AGTTTCATCTGCGACCCG
	Reverse	GCTGCCGCTGTCTTTGC
SKIL	Forward	GAGGCAAGTAAGTCCATA
	Reverse	GCATCTAAACGGCTACA
EIF2AK2	Forward	GGAAAGCGAACAAGGA
	Reverse	ATGATGCCATCCCGTA
MAML2	Forward	CCCCAGTCCAAGTCCTA
	Reverse	TTGCTGTTTCTGCTCCA
SOCS4	Forward	AAATCAGATGAATGGGTAAG
	Reverse	AAAGCATTGTCGGTGG
ERBIN	Forward	GACCGACTTATTCCTGC
	Reverse	GAGTTCTTCCCGCTGA
PARD6B	Forward	GGATGGCTCCAGTGTC
	Reverse	TGATGAGGTTACGGCTA
STAT1	Forward	GCTTCTTGGTCCTAACG

	Reverse	TCGCTCCTTGCTGATG
ID1	Forward	CTACGACATGAACGGCTGTTACTC
	Reverse	GCTCCAACTGAAGGTCCCTGAT
NKD2	Forward	CGTTCACGCTCTATGACTTTGAC
	Reverse	GCCAGTTCACCCTCCATCC
SCARB1	Forward	CCCATCCTCACTTCCTCAA
	Reverse	TGCCTGCGACAGATTTCA
SP1	Forward	CACTCTCACACCCATTGCCT
	Reverse	CTTCCTCTCCACCTGCTGTG
GATA3	Forward	GTCCTGTGCGAACTGTCAGA
	Reverse	CGAGCTGTTCTTGGGGAAGT
Chromosome conformation capture (3C) assay (5'-3')		
P1-E1~E16	Forward	GCCATAGCCTACCCCAAACGCAC
P1-E1	Reverse	AGGAAGCACACTTTTTCAAATAA
P1-E2	Reverse	TAACGGGACCCTATCTCTAAGAAAA
P1-E3	Reverse	ACTCCTGGTATCAAGCCATCCTCCT
P1-E4	Reverse	AAATTAAATGAGATAGGGAGCCATG
P1-E5	Reverse	AAATCAGAGCTGGGCGTGGTGGTTC
P1-E6	Reverse	AAAATTGGCCGGGCACGGTGGCTCA
P1-E7	Reverse	TACTTTTGGCCAGACACGGTGGCTC
P1-E8	Reverse	TTCTCCGACCCAAAGGGCCAAAAAT
P1-E9	Reverse	AAATCAGCCTGGCACGGTGGCTCAG
P1-E10	Reverse	TAAGTTGGCCGGGCACAGTGGCTCA
P1-E11	Reverse	TATTTTTAGTAGAAATGGGGTTTTG
P1-E12	Reverse	TATTGTCTAAAATGTTACTTGCTGA
P1-E13	Reverse	GTACCGTGGAATTTACTATCTTTTT
P1-E14	Reverse	ATTTGTTTGTTTGTTTTTTGAGACA
P1-E15	Reverse	TTGGCAGGCTGGGCACAGTGGCTCA
P1-E16	Reverse	TGGTTGGTTCTTGGCTGGAGGCTGC
GAPDH	Forward	ACAGTCCATGCCATCACTGCC
GAPDH	Reverse	GCCTGCTTCACCACCTTCTTG
Chromatin immunoprecipitation qPCR (ChIP-qPCR) assay (5'-3')		
DNA fragment spanning rs61926301	Forward	GTGCTCAGTTTTGCCCCCCTCC
	Reverse	TGTCCTAAGCTACCGTTTCCTC
DNA fragment spanning rs7959129	Forward	TGTTACTTGCTGATTATAGTGGCTT
	Reverse	GACCCTGTTTCAGAAAAGTAAGATA
siRNAs		
siGATA3	siRNA1	CCAAGAACAGCTCGTTTAA
	siRNA2	CCTGTGGGCTCTACTACAA
	siRNA3	GAGAAAGAGTGCCTCAAGT
siSP1	siRNA1	ATCACTCCATGGATGAAATGA
	siRNA2	AAGCGCTTCATGAGGAGTG
	siRNA3	GCCAATAGCTACTCAACTA
siATF1	siRNA1	CGAACTACACCTTCAGCTA

	siRNA2	CCACAAGAGTACCACGTCA
	siRNA3	GTACAACTATTCTTCAGTA
sgRNAs used in CRISPR/Cas9		
ATF1	sgRNA1	CCAGCAATCAGGTGGTCGTACAA
	sgRNA2	GTTTACCATCTAGCTGCATCAGG
	sgRNA3	CCTCTCAGACAACTAAGACAGAT