

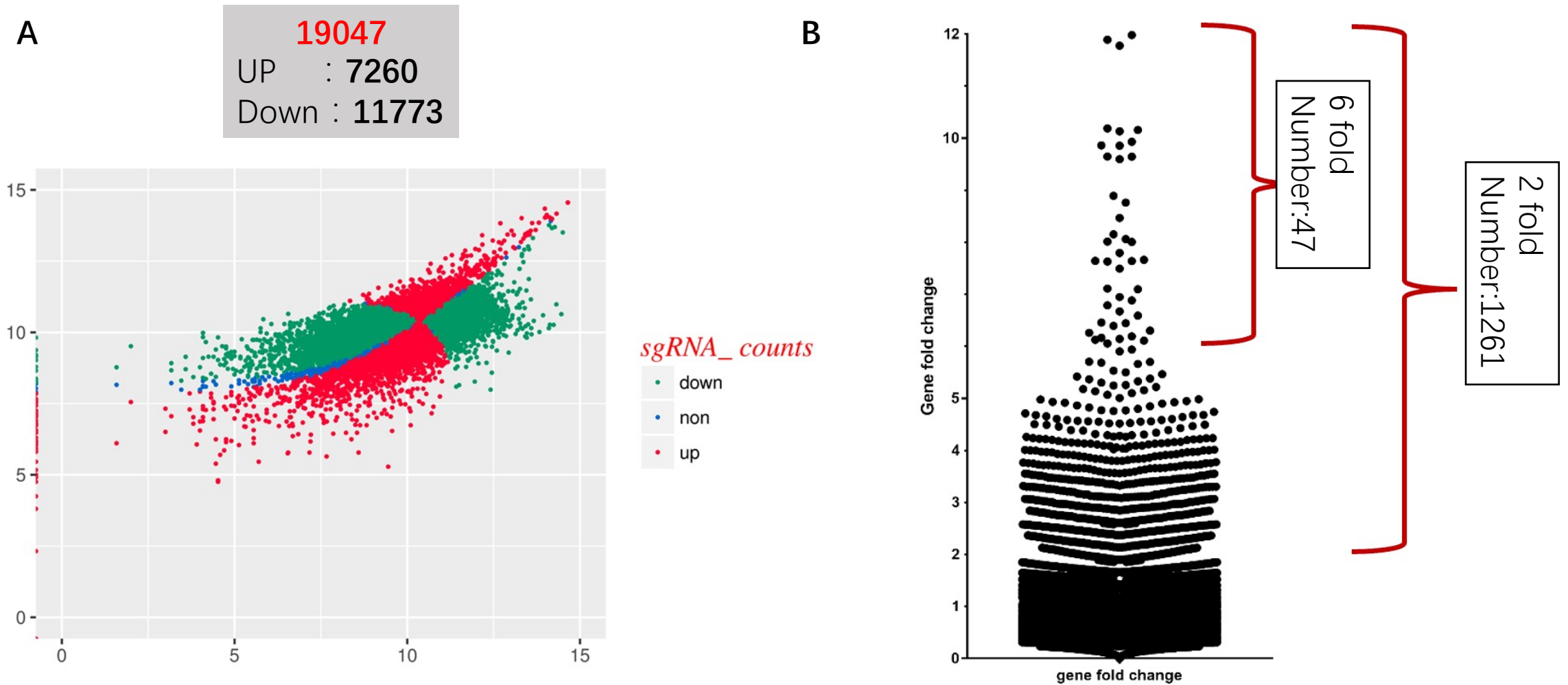


Figure S1. Results from CRISPR/Cas9 knockout library screening. A. 19047 sgRNA were found after high- throughput sequencing analysis; B. Scatter plot to indicate the numbers of sgRNAs with fold-change >2 or 6

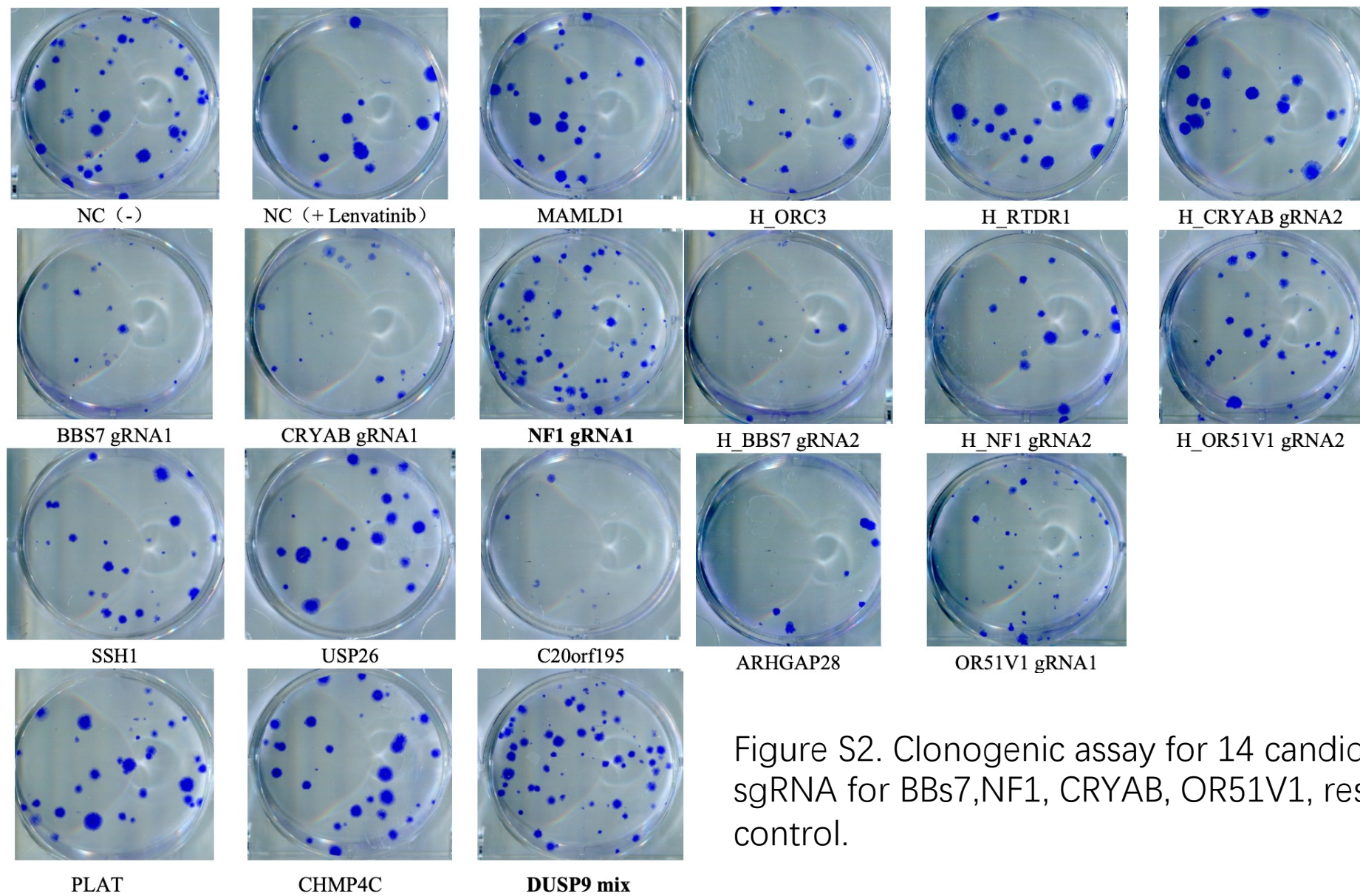
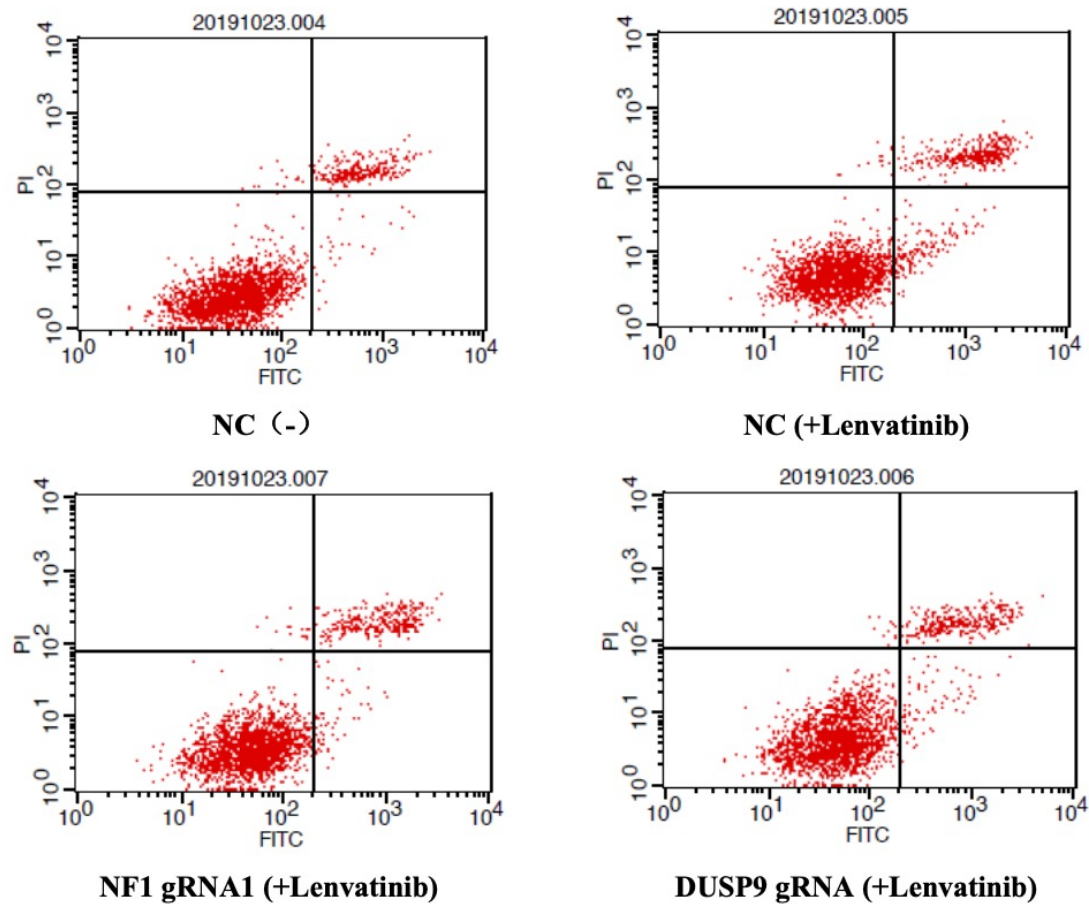


Figure S2. Clonogenic assay for 14 candidate genes. There are two sgRNA for BBs7,NF1, CRYAB, OR51V1, respectively. NC, Negative control.

A



B

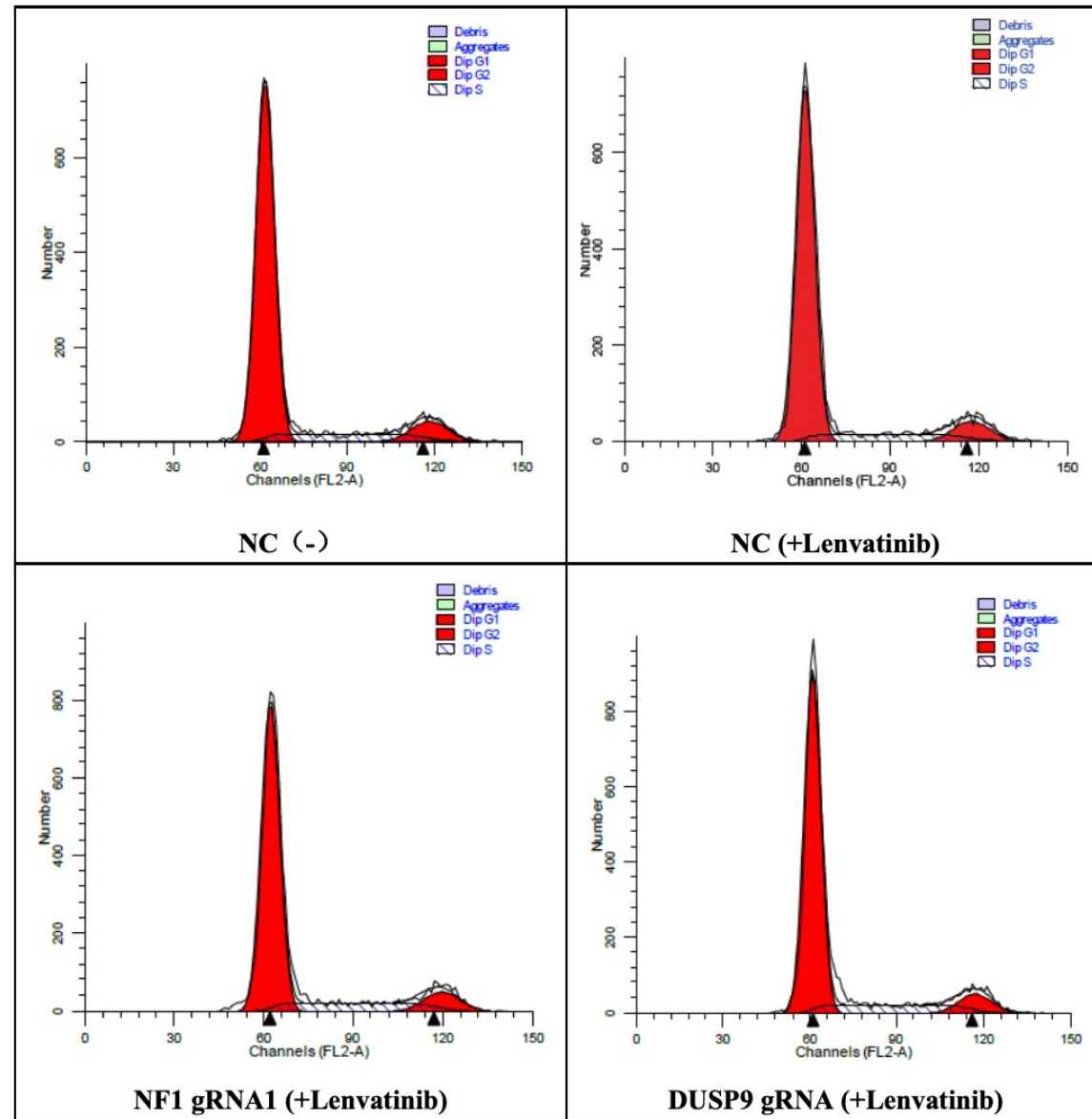


Figure S3. Cell apoptosis(A) and cycle(B) performed by flow citometry

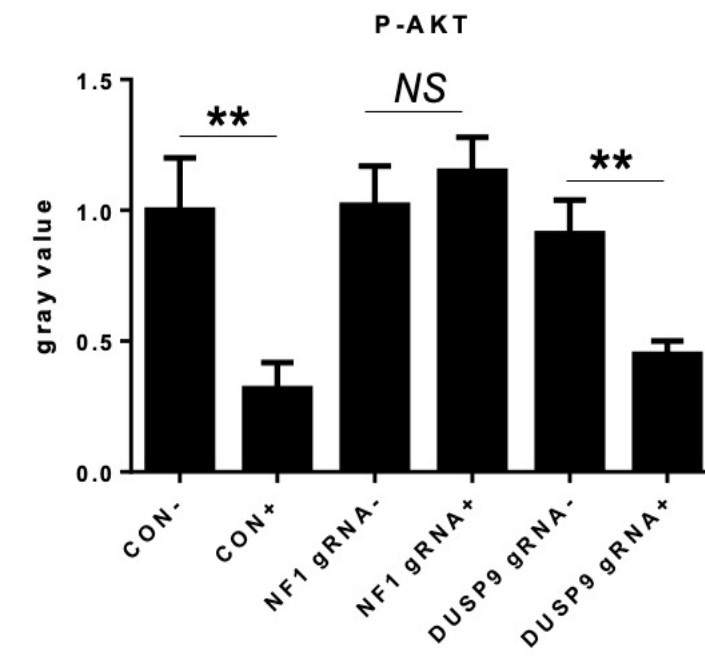
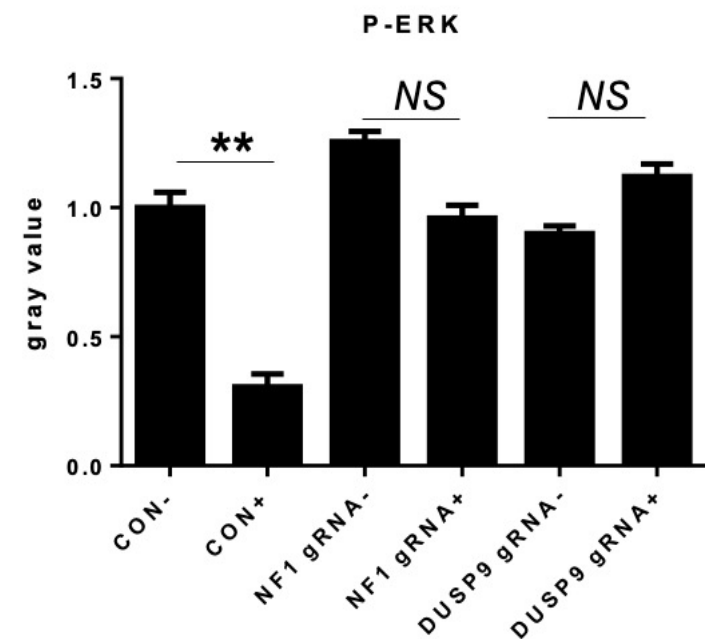
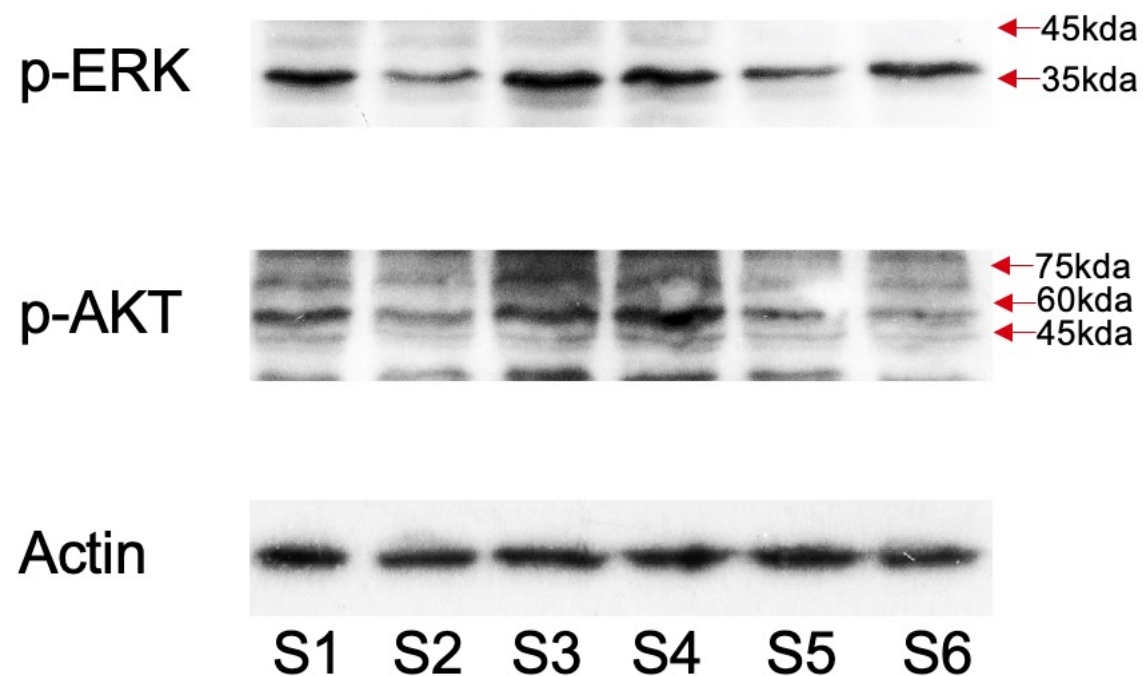


Figure S4. Expression of genes of interest in Huh7 cells was measured by Western blot.

S1: CON- S2 : CON+Lenvatinib

S3 : NF1 gRNA- S4 : NF gRNA+ Lenvatinib

S5 : Dusp9 gRNA- S6 : DUSP9+ Lenvatinib

Anti-p-ERK and p-AKT (1:2000). Goat anti-rabbit-HRP secondary antibody was applied at 1:3000.

Table S1 The sequences used to construct the sgRNA-encoding plasmids

NO.	TargetSeq
NC	ACGGAGGCTAAGCGTCGCAA
H_ARHGAP28	AATGTTTCAGAAAACCAGATT
H_BBS7	TTGTGTAGCTCTGTGTCTTG
H_BBS7	AAGACACAGAGCTACACAAA
H_C20orf195	CAACTCATACTGCTCCGATG
H_CHMP4C	AAACAGCTCACTCAGATTGA
H_CRYAB	TTTCTAGATGCGCCTGGAGA
H_CRYAB	GTGGTGGATGGCGATGTCCA
H_DUSP9	TCTCAACGATGCCTATGACC
H_DUSP9	GTGTGGCACCCCTCCGAATCC
H_MAMLD1	ATCTTCTTCCTCCATCCACG
H_NF1	GTTGTGCTCAGTACTGACTT
H_NF1	AGTCAGTACTGAGCACAACA
H_OR51V1	CTTCTCCTCAATCTATGCCA
H_OR51V1	TAGTTACTATGCCCTGATGC
H_ORC3	TTTCTGCAAAAATCACATTC
H_PLAT	CTCCTCTTCTGAATCGGGCA
H_RTDR1	CAACCAGAACATCCGCAGCA
H_SSH1	ATTTAAGCCTGTGTCTGTCC
H_USP26	TCATGCATCATGAACGCCAC

NC, Negative control.

Table S2 The sgRNA oligo sequences for candidate genes

Plasmid's names	Primer Top	Primer Bottom
NC gRNA	caccgACGGAGGCTAAGCGTCGCAA	aaacTTGCGACGCTTAGCCTCCGTc
H_CRYAB gRNA	caccgTTTCTAGATGCGCCTGGAGA	aaacTCTCCAGGCGCATCTAGAAAc
H_ARHGAP28 gRNA	caccgAATGTTCAGAAAACCAGATT	aaacAATCTGGTTTTCTGAACATTc
H_BBS7 gRNA	caccgTTGTGTAGCTCTGTGTCTTG	aaacCAAGACACAGAGCTACACAAc
H_BBS7 gRNA2	caccgAAGACACAGAGCTACACAAA	aaacTTTGTGTAGCTCTGTGTCTTc
H_C20orf195 gRNA	caccgCAACTCATACTGCTCCGATG	aaacCATCGGAGCAGTATGAGTTGc
H_CHMP4C gRNA	caccgAAACAGCTCACTCAGATTGA	aaacTCAATCTGAGTGAGCTGTTTc
H_CRYAB gRNA2	caccGTGGTGATGGCGATGTCCA	aaacTGGACATCGCCATCCACCAC
H_DUSP9 gRNA	caccgTCTCAACGATGCCTATGACC	aaacGGTCATAGGCATCGTTGAGAc
H_DUSP9 gRNA2	caccGTGTGGCACCTCCGAATCC	aaacGGATTCGGAGGGTGCCACAC
H_MAMLD1 gRNA	caccgATCTTCTTCTCCATCCACG	aaacCGTGGATGGAGGAAGAAGATc
H_NF1 gRNA	caccGTTGTGCTCAGTACTGACTT	aaacAAGTCAGTACTGAGCACAAC
H_NF1 gRNA2	caccgAGTCAGTACTGAGCACAACA	aaacTGTTGTGCTCAGTACTGACTc
H_OR51V1 gRNA	caccgCTTCTCCTCAATCTATGCCA	aaacTGGCATAGATTGAGGAGAAGc
H_OR51V1 gRNA2	caccgTAGTTACTATGCCCTGATGC	aaacGCATCAGGGCATAGTAACTAc
H_ORC3 gRNA	caccgTTTCTGCAAAAATCACATTC	aaacGAATGTGATTTTTGCAGAAAc
H_PLAT gRNA	caccgCTCCTCTTCTGAATCGGGCA	aaacTGCCCGATTGAGAAGAGGAGc
H_RTDR1 gRNA	caccgCAACCAGAACATCCGAGCA	aaacTGCTGCGGATGTTCTGGTTGc
H_SSH1 gRNA	caccgATTTAAGCCTGTGTCTGTCC	aaacGGACAGACACAGGCTTAAATc
H_USP26 gRNA	caccgTCATGCATCATGAACGCCAC	aaacGTGGCGTTCATGATGCATGAc

There are two sgRNA for BBs7,NF1, CRYAB, OR51V1, respectively

Table S3 shRNA sequences for NF1 and DUSP9

Name	sequences 5'to 3'
Primer-NC-T	gatctGTTCTCCGAACGTGTACGTTTCAAGAGAACGTGA CACGTTTCGGAGAATTTTTTc
Primer-NC-B	aattgAAAAAATTCTCCGAACGTGTACGTTCTCTTGAAA CGTGACACGTTTCGGAGAAc
H_NF1-shRNA1-T	gatccGCCAACCTTAACCTTTCTAATCTCGAGATTAGAAA GGTTAAGGTTGGCTTTTTT
H_NF1-shRNA1-B	aattAAAAAAGCCAACCTTAACCTTTCTAATCTCGAGATT AGAAAGGTTAAGGTTGGCg
H_NF1-shRNA2-T	gatccGCTGGCAGTTTCAAACGTAATCTCGAGATTACGTT TGAAACTGCCAGCTTTTTT
H_NF1-shRNA2-B	aattAAAAAAGCTGGCAGTTTCAAACGTAATCTCGAGATT ACGTTTGAAACTGCCAGCg
H_dusp9-shRNA1-T	gatccGCATCCGCTACATCCTCAATGCTCGAGCATTGAGG ATGTAGCGGATGCTTTTTT
H_dusp9-shRNA1-B	aattAAAAAAGCATCCGCTACATCCTCAATGCTCGAGCAT TGAGGATGTAGCGGATGCg
H_dusp9-shRNA2-T	gatccGGCCATTGAGTTCATTGATGACTCGAGTCATCAAT GAACTCAATGGCCTTTTTT
H_dusp9-shRNA2-B	aattAAAAAAGGCCATTGAGTTCATTGATGACTCGAGTCA TCAATGAACTCAATGGCCg
H_dusp9-shRNA3-T	gatccGATCCTGCCCAACCTCTATCTCTCGAGAGATAGAG GTTGGGCAGGATCTTTTTT
H_dusp9-shRNA3-B	aattAAAAAAGATCCTGCCCAACCTCTATCTCTCGAGAGA TAGAGGTTGGGCAGGATCg

T: Top; B: Bottom

Table S4. The top 10 for BP and CC in Go analysis

ONTOLOGY	ID	Description	pvalue	p.adjust	qvalue
BP	GO:0060541	respiratory system development	6.9541E-07	0.00306249	0.00277695
BP	GO:0048880	sensory system development	1.3248E-06	0.00306249	0.00277695
		regulation of mononuclear cell			
BP	GO:0032944	proliferation	1.9248E-06	0.00306249	0.00277695
		cell-cell adhesion via plasma-			
BP	GO:0098742	membrane adhesion molecules	2.4122E-06	0.00306249	0.00277695
		regulation of lymphocyte			
BP	GO:0050670	proliferation	2.883E-06	0.00306249	0.00277695
BP	GO:0150063	visual system development	3.8831E-06	0.00306249	0.00277695
BP	GO:0031341	regulation of cell killing	4.0764E-06	0.00306249	0.00277695
		regulation of leukocyte			
BP	GO:0070663	proliferation	4.2167E-06	0.00306249	0.00277695
		positive regulation of			
BP	GO:0032946	mononuclear cell proliferation	4.2772E-06	0.00306249	0.00277695
		homophilic cell adhesion via			
		plasma membrane adhesion			
BP	GO:0007156	molecules	5.2341E-06	0.00317256	0.00287675
CC	GO:0030667	secretory granule membrane	5.6659E-05	0.03571522	0.03277385
		collagen-containing extracellular			
CC	GO:0062023	matrix	9.3201E-05	0.03571522	0.03277385
CC	GO:0005788	endoplasmic reticulum lumen	0.00015371	0.03571522	0.03277385
CC	GO:0031093	platelet alpha granule lumen	0.00026204	0.03571522	0.03277385
CC	GO:0031091	platelet alpha granule	0.00026468	0.03571522	0.03277385
CC	GO:0016323	basolateral plasma membrane	0.00031489	0.03571522	0.03277385
CC	GO:0016605	PML body	0.00032384	0.03571522	0.03277385
CC	GO:0045177	apical part of cell	0.00044774	0.04320684	0.03964849
CC	GO:0005667	transcription factor complex	0.00098637	0.08274313	0.07592872
CC	GO:1990907	beta-catenin-TCF complex	0.00111362	0.08274313	0.07592872