Supplementary Table 1 - Analysis of fitness interactions among previously known LINE-1 interactors (modify retrotransposition and/or physically bind LINE-1 proteins).

direction (LINE-1 vs. Luc.)	NAME	NOM p-val	FDR q-val	FWER p-val
downregulated	REACTOME_DNA_REPLICATION	0	0	0
downregulated	REACTOME_CELL_CYCLE_MITOTIC	0	0	0
downregulated	HALLMARK_E2F_TARGETS	0	0	0
downregulated	HALLMARK_G2M_CHECKPOINT	0	0	0
downregulated	REACTOME_MITOTIC_M_M_G1_PHASES	0	0	0
downregulated	REACTOME_CELL_CYCLE	0	0	0
downregulated	HALLMARK_MITOTIC_SPINDLE	0	0	0
downregulated	REACTOME_DNA_STRAND_ELONGATION	0	0	0
downregulated	REACTOME_MITOTIC_PROMETAPHASE	0	0	0
downregulated	REACTOME_G1_S_TRANSITION	0	0	0
downregulated	KEGG_DNA_REPLICATION	0	0	0
downregulated	REACTOME_S_PHASE	0	0	0
downregulated	REACTOME_SYNTHESIS_OF_DNA	0	0	0
downregulated	REACTOME_MITOTIC_G1_G1_S_PHASES	0	0	0
downregulated	REACTOME_CELL_CYCLE_CHECKPOINTS	0	0	0
downregulated	REACTOME_METABOLISM_OF_RNA	0	0	0
downregulated	REACTOME_G2_M_CHECKPOINTS	0	0	0
downregulated	REACTOME_ACTIVATION_OF_ATR_IN_RESPONSE_TO_REPLICATION_STRESS	0	0	0
downregulated	HALLMARK_MYC_TARGETS_V1	0	0	0
downregulated	REACTOME_MITOTIC_G2_G2_M_PHASES	0	0	0
downregulated	REACTOME_DNA_REPAIR	0	0	0
downregulated	REACTOME_ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX	0	0	0
downregulated	REACTOME_M_G1_TRANSITION	0	0	0
downregulated	KEGG_CELL_CYCLE	0	0	0
downregulated	REACTOME_METABOLISM_OF_MRNA	0	0	0
downregulated	REACTOME_INFLUENZA_LIFE_CYCLE	0	0	0
downregulated	REACTOME_TRANSLATION	0	0	0
downregulated	REACTOME_E2F_MEDIATED_REGULATION_OF_DNA_REPLICATION	0	0	0

Supplementary Table 1 - Analysis of fitness interactions among previously known LINE-1 interactors (modify retrotransposition and/or physically bind LINE-1 proteins).

downregulated	REACTOME_3_UTR_MEDIATED_TRANSLATIONAL_REGULATION	0	0	0
downregulated	REACTOME_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE	0	0	0
downregulated	REACTOME_EXTENSION_OF_TELOMERES	0	0	0
downregulated	REACTOME_MRNA_PROCESSING	0	0	0
downregulated	REACTOME_PROCESSING_OF_CAPPED_INTRON_CONTAINING_PRE_MRNA	0	0	0
downregulated	REACTOME_INFLUENZA_VIRAL_RNA_TRANSCRIPTION_AND_REPLICATION	0	0	0
downregulated	REACTOME_NONSENSE_MEDIATED_DECAY_ENHANCED_BY_THE_EXON_JUNCTION_COMPLEX	0	0	0
downregulated	KEGG_RIBOSOME	0	0	0
downregulated	REACTOME_PEPTIDE_CHAIN_ELONGATION	0	0	0
downregulated	KEGG_OOCYTE_MEIOSIS	0	0	0
downregulated	KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	0	0	0
downregulated	REACTOME_REGULATION_OF_MITOTIC_CELL_CYCLE	0	0	0
downregulated	HALLMARK_DNA_REPAIR	0	9.80E-05	0.002
downregulated	REACTOME_MRNA_SPLICING	0	9.57E-05	0.002
downregulated	REACTOME_FORMATION_OF_THE_TERNARY_COMPLEX_AND_SUBSEQUENTLY_THE_43S_COMPLEX	0	1.32E-04	0.003
downregulated	KEGG_SPLICEOSOME	0	1.73E-04	0.004
downregulated	REACTOME_ACTIVATION_OF_THE_MRNA_UPON_BINDING_OF_THE_CAP_BINDING_COMPLEX_AND_EIFS_AND_SUBSEQUENT_BINDING_TO_43S	0	1.69E-04	0.004
downregulated	REACTOME_METABOLISM_OF_NON_CODING_RNA	0	2.96E-04	0.007
downregulated	KEGG_PYRIMIDINE_METABOLISM	0.00440529	7.00E-04	0.017
upregulated	REACTOME_INTERFERON_ALPHA_BETA_SIGNALING	0	0	0
upregulated	REACTOME_INTERFERON_SIGNALING	0	0	0
upregulated	HALLMARK_INTERFERON_GAMMA_RESPONSE	0	0	0
upregulated	HALLMARK_INTERFERON_ALPHA_RESPONSE	0	0	0
upregulated	REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM	0	0	0
upregulated	HALLMARK_TNFA_SIGNALING_VIA_NFKB	0	0	0
upregulated	KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	0	0	0
upregulated	HALLMARK_INFLAMMATORY_RESPONSE	0	0	0

Supplementary Table 1 - Analysis of fitness interactions among previously known LINE-1 interactors (modify retrotransposition and/or physically bind LINE-1 proteins).

upregulated	KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS	0	0	0
upregulated	REACTOME_INTERFERON_GAMMA_SIGNALING	0	7.50E-05	0.001
upregulated	REACTOME_RNA_POL_I_PROMOTER_OPENING	0	2.81E-04	0.004
upregulated	HALLMARK_KRAS_SIGNALING_UP	0	2.58E-04	0.004
upregulated	KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	0	3.57E-04	0.006
upregulated	REACTOME_IMMUNE_SYSTEM	0	3.85E-04	0.007
upregulated	REACTOME_AMYLOIDS	0	4.13E-04	0.008
upregulated	REACTOME_RNA_POL_I_TRANSCRIPTION	0	3.87E-04	0.008
upregulated	REACTOME_CLASS_A1_RHODOPSIN_LIKE_RECEPTORS	0.00125786	3.65E-04	0.008
upregulated	HALLMARK_IL6_JAK_STAT3_SIGNALING	0	3.89E-04	0.009
upregulated	HALLMARK_P53_PATHWAY	0	5.69E-04	0.014
upregulated	HALLMARK_COMPLEMENT	0.00116279	6.52E-04	0.017
upregulated	KEGG_LEISHMANIA_INFECTION	0	6.58E-04	0.018
upregulated	REACTOME_RNA_POL_I_RNA_POL_III_AND_MITOCHONDRIAL_TRANSCRIPTION	0	0.00101581	0.028
upregulated	HALLMARK_APOPTOSIS	0	0.00120769	0.034

Supplementary Table 4 - Overrepresentation analysis results for GO terms among the 1,390 significant growth interactions using the Webgestalt program.

category	geneset	description	link	P	FDR	OverlapGene_UserID
Biological_Process	GO:0006397	mRNA processing	http://amigo.geneontology.org/amigo/term/GO:0006397	3.01E-13	2.29E-10	ISY1-RAB43;PDCD7;RBM7;BCAS2;ADAR;PPIH;KHDRBS1;AHCYL1;SRSF10;PAPOLA;WBP4;LEO1;U2AF1L4;SNW1;KDM1A;SF3B3;TFIP11;FUS;KIAA1429;PRPF31;PABPC1;AKAP8L;GPKOW;HTATSF1;DCPS;GTF2H1;HNRNPA1;HNRNPA2B1;NOVA1;CRNKL1;CDC40;CWC15;CDK12;PLRG1;PNN;PRMT7;RBM28;PSPC1;ZCCHC8;RBM22;CCAR1;PTBP1;PHRF1;METTL14;SUGP1;BARD1;SCAF1;RBBP6;PAPD5;SRSF6;TRA2B;RBM15;SNRPB;SNRPC;SNRPE;SRPK2;SUPT6H;SLBP;SNRNP25;SLTM;PABPC1L;TSEN2;PABPN1;SF3A2;RBM10;WDR83;DHX16;KHSRP;SRSF9;RNGTT;YTHDC1;ZRANB2;WTAP;TGS1;AQR;DHX38;DDX46;CDC5L;PAN2;RBM8A;THOC1
Biological_Process	GO:0018205	peptidyl-lysine modification	http://amigo.geneontology.org/amigo/term/GO:0018205	9.76E-13	3.72E-10	HDAC6;SAE1;TRIM28;USPL1;MCRS1;TADA3;STAG2;MORF4L1;MSL3;PRDM5;TAF1L;ATF2;FAM76B;CTBP1;FAM76A;MTF2;SIRT2;SNW1;KDM1A;SETD1B;USP22;JADE2;SIRT5;SIN3A;ZNF451;BLOC1S1;ELP4;TAF5L;KANSL1;SENP1;MECP2;PIAS4;PHF1;GNL3L;ING3;KANSL2;MSL2;KANSL3;YEATS2;KDM3A;KIAA1586;RAD21;RANBP2;ARID4A;RNF2;RNF4;PRDM16;BLM;NSD1;SUMO2;SNCA;SOX4;SUPT6H;MAP3K7;TPR;WRN;SAP130;SETD6;EPC1;AAAS;L3MBTL2;CBX2;CAMK1;EED;RPS6KA4;PIAS2;MTA1;H2AFY;SETD1A;MED24;SETDB1;NUP153
Biological_Process	GO:0008380	RNA splicing	http://amigo.geneontology.org/amigo/term/GO:0008380	4.92E-12	1.25E-09	ISY1-RAB43;PDCD7;RBM7;BCAS2;PPIH;KHDRBS1;SRSF10;PAPOLA;WBP4;U2AF1L4;SNW1;KDM1A;SF3B3;TFIP11;FUS;KIAA1429;PRPF31;PABPC1;AKAP8L;GPKOW;ZNF638;HTATSF1;DCPS;HNRNPA1;HNRNPA2B1;NOVA1;CRNKL1;CDC40;CWC15;CDK12;PLRG1;PNN;PRMT7;RBM28;PSPC1;ZCCHC8;RBM22;CCAR1;PTBP1;METTL14;SUGP1;SCAF1;SRSF6;TRA2B;RBM15;SNRPB;SNRPC;SNRPE;SRPK2;SUPT6H;SNRNP25;TSEN2;PABPN1;SF3A2;RBM10;WDR83;DHX16;PPP1R9B;KHSRP;SRSF9;YTHDC1;ZRANB2;WTAP;TGS1;AQR;DHX38;DDX46;CDC5L;RBM8A;THOC1
Biological_Process	GO:0016570	histone modification	http://amigo.geneontology.org/amigo/term/GO:0016570	1.61E-10	3.07E-08	HDAC6;MCRS1;ZNHIT1;TADA3;MORF4L1;MSL3;PRDM5;LEO1;TAF1L;ATF2;CTBP1;MTF2;SIRT2;SNW1;KDM1A;SETD1B;SIN3B;USP22;JADE2;ZMYND8;SIN3A;ZNF451;ELP4;AKAP8L;TAF5L;KANSL1;MECP2;TRIM37;PHF21A;WAC;PHF1;PRMT7;ING3;KANSL2;MSL2;COPRS;OTUB1;PRKAA2;KANSL3;YEATS2;KDM3A;ATXN7L3;MTA3;ARID4A;RBBP4;RNF2;PRDM16;NSD1;SNCA;SUPT6H;MAP3K7;SAP130;SETD6;EPC1;KDM5C;BAP1;GSG2;ARID5B;BRMS1L;CAMK1;EED;RPS6KA4;BAZ1B;MTA1;PAXBP1;H2AFY;PPM1F;SETD1A;MED24;SETDB1;USP3
Biological_Process	GO:0006281	DNA repair	http://amigo.geneontology.org/amigo/term/GO:0006281	2.93E-09	4.47E-07	CHAF1A;ISY1-RAB43;TRIM28;MCRS1;SLC30A9;MORF4L1;PNKP;UBE2F;ESCO2;APLF;PRIMPOL;FANCA;FANCD2;FANCE;FANCB;FANCF;FANCG;KDM1A;PDS5A;SPIDR;TFIP11;MCM9;XRCC6;RCHY1;C9orf142;BABAM1;GTF2H1;HUS1;LIG1;MSH2;COPS7A;PIAS4;PMS1;POLA1;RNF111;FANCL;FIGN;RFWD3;RIF1;FANCI;OTUB1;WRNIP1;TAOK1;BARD1;RAD21;RBBP8;UPF1;RFC1;BLM;COPS7B;NUCKS1;INTS3;SUMO2;UBC;UBE2D3;UNG;WRN;C7orf49;NABP2;FTO;KLHL15;MND1;ATRIP;ASCC2;RAD54L;SMARCA5;BAZ1B;MTA1;ZNF830;ISG15;KIAA0430;AQR;CDC5L;USP3;REC8
Biological_Process	GO:1902275	regulation of chromatin organization	http://amigo.geneontology.org/amigo/term/GO:1902275	9.08E-06	0.0010753	TRIM28;ZNHIT1;TADA3;TLK2;SPTY2D1;CTBP1;MTF2;SNW1;KDM1A;SIN3A;ZNF451;AKAP8L;HMGA1;MECP2;PHF1;OTUB1;KDM3A;NSD1;SNCA;SUPT6H;TPR;CAMK1;EED;RPS6KA4;PAXBP1;H2AFY;SETD1A;SETDB1
Biological_Process	GO:1903311	regulation of mRNA metabolic process	http://amigo.geneontology.org/amigo/term/GO:1903311	9.88E-06	0.0010753	RBM7;KHDRBS1;AHCYL1;SRSF10;PAPOLA;LEO1;SNW1;PABPC1;HNRNPA2B1;ZC3HAV1;PTBP1;BARD1;UPF1;SRSF6;TRA2B;SRPK2;SUPT6H;SLTM;PABPN1;RBM10;KHSRP;SRSF9;YTHDC1;WTAP;RBM8A
Biological_Process	GO:0000075	cell cycle checkpoint	http://amigo.geneontology.org/amigo/term/GO:0000075	1.78E-05	0.00169482	FEM1B;PLK2;ATF2;ARID3A;FANCG;BABAM1;APC;HRAS;HUS1;MSH2;CNOT4;WAC;GTSE1;RFWD3;FANCI;PRCC;TAOK1;PTPN11;RBBP8;BLM;INTS3;SOX4;TPR;TTK;UBC;NABP2;MAD1L1;GSG2;ATRIP;TNKS1BP1;ZNF830;MAPKAPK2;MAD2L1BP;CDC5L;THOC1
Biological_Process	GO:0098732	macromolecule deacylation	http://amigo.geneontology.org/amigo/term/GO:0098732	3.07E-05	0.00259629	HDAC6;ZNHIT1;TADA3;MORF4L1;MSL3;PRDM5;CTBP1;SIRT2;KDM1A;SIN3B;SIRT5;SIN3A;AKAP8L;PHF21A;MTA3;ARID4A;RBBP4;BRMS1L;MTA1;PPT2
Biological_Process	GO:0043543	protein acylation	http://amigo.geneontology.org/amigo/term/GO:0043543	4.81E-05	0.00349969	MCRS1;TADA3;MORF4L1;MSL3;TAF1L;ATF2;CTBP1;ESCO2;USP22;JADE2;SIN3A;ZNF451;BLOC1S1;ELP4;TAF5L;KANSL1;ZDHHC1;MECP2;ZDHHC3;ING3;KANSL2;PPM1A;MSL2;KANSL3;YEATS2;SNCA;SOX4;MAP3K7;SAP130;EPC1;CAMK1;RPS6KA4;MED24
Biological_Process	GO:0040029	regulation of gene expression, epigenetic	http://amigo.geneontology.org/amigo/term/GO:0040029	5.05E-05	0.00349969	HDAC6;TRIM28;ADAR;MORF4L1;MSL3;WTIP;MTF2;SIRT2;ZCCHC11;SMCHD1;PUM2;SIRT5;SIN3A;HMGA1;HNRNPA2B1;MECP2;PHF1;DGCR8;PRMT7;NRDE2;SLC50A1;ARID4A;RBBP4;UPF1;SMARCD1;SUPT6H;EPC1;PABPC1L;SMARCA5;PRKRA;EED;BAZ1B;MTA1;H2AFY;SETDB1
Biological_Process	GO:0006260	DNA replication	http://amigo.geneontology.org/amigo/term/GO:0006260	0.0001584	0.0100583	CHAF1A;STAG2;PNKP;ESCO2;DUT;PRIMPOL;PDS5A;ZBTB38;MCM9;SIN3A;GLI2;HMGA1;HRAS;HUS1;JUN;LIG1;NF2;ORC1;GMNN;POLA1;WRNIP1;PTMS;BARD1;RBBP4;RBBP6;RBBP8;RBMS1;UPF1;RFC1;FAM111A;BLM;MAP2K4;NUCKS1;TTF1;WRN;SLBP;ATRIP;ZNF830;GINS1;THOC1
Biological_Process	GO:0032259	methylation	http://amigo.geneontology.org/amigo/term/GO:0032259	0.00053053	0.03109713	TRIM28;PEMT;PRDM5;METTL6;AHCY;LRTOMT;MTF2;SNW1;KDM1A;SETD1B;KIAA1429;GCSH;MAT2A;MECP2;METTL13;PHF1;PIK3CA;PRMT7;MPHOSPH8;GATAD2A;TRMT61B;COPRS;ATF7IP;KDM3A;CIAPIN1;GATAD2B;METTL14;ARID4A;PRDM16;NSD1;SNRPB;SUPT6H;SETD6;ASMTL;EED;METTL18;PAXBP1;H2AFY;WTAP;TGS1;SETD1A;SETDB1
Biological_Process	GO:0071166	ribonucleoprotein complex localization	http://amigo.geneontology.org/amigo/term/GO:0071166	0.00068321	0.03718622	SRSF10;UPF2;PRPF31;AKAP8L;HNRNPA2B1;CDC40;RANBP2;UPF1;SRSF6;SUPT6H;TPR;SLBP;AAAS;PABPN1;SRSF9;TGS1;DHX38;RBM8A;NUP153;THOC1
Biological_Process	GO:0031529	ruffle organization	http://amigo.geneontology.org/amigo/term/GO:0031529	0.00084068	0.04270654	KANK1;CYFIP1;SH3YL1;DBNL;HRAS;ARF6;LIMA1;RCC2;TPM1;PIP5K1A
Biological_Process	GO:0007034	vacuolar transport	http://amigo.geneontology.org/amigo/term/GO:0007034	0.00101942	0.04854984	SNF8;TRAK1;CHMP4A;RHOB;VPS36;VPS13D;SCYL2;VPS35;CHMP1B;KIF13A;RILP;BECN1;ATP6V0D1;HGS;TGFBRAP1;STX8;GOSR2;ZFYVE16
Cellular_Component	GO:0005681	spliceosomal complex	http://amigo.geneontology.org/amigo/term/GO:0005681	1.70E-09	2.51E-07	ISY1-RAB43;PDCD7;BCAS2;ADAR;PPIH;WBP4;U2AF1L4;SNW1;SF3B3;TFIP11;PRPF31;PABPC1;HTATSF1;HNRNPA1;HNRNPA2B1;WAC;CRNKL1;CDC

Supplementary Table 4 - Overrepresentation analysis results for GO terms among the 1,390 significant growth interactions using the Webgestalt program.

						40;CWC15;PLRG1;PNN;NRDE2;RBM28;PRCC;ZCCHC8;RBM22;SUGP1;UPF1;SNRPB;SNRPC;SNRPE;SNRNP25;SF3A2;WDR83;DHX16;AQR;DHX38;CDC5L;RBM8A
Cellular_Component	GO:0016604	nuclear body	http://amigo.geneontology.org/amigo/term/GO:0016604	6.93E-08	5.13E-06	USPL1;PPIH;SRSF10;WBP4;ATXN2L;FAM76B;DGKQ;U2AF1L4;SETD1B;TFIP11;RCHY1;PNISR;KIAA1429;ZNF451;PRPF31;AKAP8L;ZNF638;GLI2;HNRNPA2B1;ZFHX3;WAC;CRNKL1;PIAS4;CDK12;PLRG1;PNN;GATAD2A;RFWD3;PSPC1;MAPK7;CCNL1;GATAD2B;RNF2;RNF4;BLM;SRSF6;NOC3L;RFWD2;RBM15;SUMO2;SNRPC;ZMYM2;FTO;RNF34;PABPN1;SF3A2;PIP5K1A;PIAS2;ZNF830;YTHDC1;WTAP;TGS1;SETD1A;BCLAF1;DDX46;CDC5L;RBM8A;THOC1
Cellular_Component	GO:0034708	methyltransferase complex	http://amigo.geneontology.org/amigo/term/GO:0034708	2.65E-06	0.00013053	MCRS1;C17orf49;MTF2;SETD1B;MGA;KIAA1429;PRPF31;KANSL1;TRIM37;PHF1;TRMT61B;CHD8;METTL14;RBBP4;RNF2;SNRPB;SNRPE;TAF4;EED;H2AFY;WTAP;SETD1A
Cellular_Component	GO:0044454	nuclear chromosome part	http://amigo.geneontology.org/amigo/term/GO:0044454	1.77E-05	0.00065629	CHAF1A;TRIM28;BCAS2;CITED2;MCRS1;ZNHIT1;CENPC;P3H4;MORF4L1;KLHDC3;ESCO2;DVL3;SIRT2;KDM1A;SIN3B;SMCHD1;TFIP11;XRCC6;SIN3A;NSMF;HUS1;JUN;TRNP1;MSH2;ORC1;PLRG1;PMS1;POLA1;ING3;MPHOSPH8;PPP1R10;MIS18BP1;WRNIP1;GATAD2B;PHF12;RAD21;RBBP4;RELA;UPF1;RNF2;BLM;NUCKS1;SMARCE1;SP1;TAF4;TCF4;WRN;NABP2;SAP130;DSN1;ZMIZ2;BRMS1L;SMARCA5;TNKS1BP1;EED;TRIM24;BAZ1B;H2AFY;SETD1A;GINS1;CDC5L;USP3;THOC1;REC8
Cellular_Component	GO:1902493	acetyltransferase complex	http://amigo.geneontology.org/amigo/term/GO:1902493	7.40E-05	0.00219181	MCRS1;TADA3;MORF4L1;MSL3;USP22;JADE2;ELP4;TAF5L;KANSL1;ING3;KANSL2;MSL2;KANSL3;YEATS2;ATXN7L3;TAF4;MAP3K7;SAP130;EPC1;UBAP2L
Cellular_Component	GO:0031519	PcG protein complex	http://amigo.geneontology.org/amigo/term/GO:0031519	0.00011714	0.00288941	CSNK2B;MTF2;CBX6;TRIM37;PHF1;RBBP4;RNF2;BAP1;CBX2;EED;H2AFY;UBAP2L
Cellular_Component	GO:0000785	chromatin	http://amigo.geneontology.org/amigo/term/GO:0000785	0.00021838	0.00461717	CHAF1A;TRIM28;CITED2;MCRS1;ZNHIT1;CENPC;STAG2;PLK2;MORF4L1;KLHDC3;ESCO2;DVL3;SIRT2;SNW1;KDM1A;PDS5A;SIN3B;CBX6;SIN3A;NSMF;AKAP8L;HMGA1;JUN;TRNP1;MECP2;POLA1;ING3;MPHOSPH8;PPP1R10;KDM3A;GATAD2B;PHF12;RAD21;RBBP4;RELA;UPF1;RNF2;FAM111A;NUCKS1;SMARCE1;SP1;SUPT6H;TAF4;TCF4;TMPO;SAP130;BRMS1L;CBX2;TNKS1BP1;EED;TRIM24;BAZ1B;H2AFY;SETD1A;USP3
Cellular_Component	GO:0098687	chromosomal region	http://amigo.geneontology.org/amigo/term/GO:0098687	0.00085672	0.01584928	CENPC;PTGES3;STAG2;MBD6;ESCO2;SIRT2;KDM1A;PDS5A;SMCHD1;TFIP11;XRCC6;SIN3A;KANSL1;HNRNPA2B1;APC;MSH2;PPP1R12A;ORC1;ERCC6L;PPP1R10;CENPQ;RIF1;MIS18BP1;RCC2;WRNIP1;RAD21;UPF1;BLM;TPR;TTK;WRN;NABP2;CENPO;DSN1;MAD1L1;TNKS1BP1;DYNLL1;BAZ1B;KNSTRN;H2AFY;THOC1;REC8
Cellular_Component	GO:0017053	transcriptional repressor complex	http://amigo.geneontology.org/amigo/term/GO:0017053	0.00110477	0.0181673	CTBP1;SIRT2;SIN3A;HDGF;JUN;GATAD2A;GATAD2B;PHF12;ARID4A;RBBP4;RBBP8;PRDM16;SKIL;SMARCE1;YWHAB;SMARCA5
Cellular_Component	GO:0048475	coated membrane	http://amigo.geneontology.org/amigo/term/GO:0048475	0.00181892	0.02692001	AP3S2;SEC24B;SEC23A;AP2M1;AP2S1;AP3S1;CLTC;COPA;COPB1;C3orf58;GGA2;AP4E1;CHMP4A;IGF2R;CHMP1B;EPS15L1
Cellular_Component	GO:0005813	centrosome	http://amigo.geneontology.org/amigo/term/GO:0005813	0.00237449	0.03142635	PROCR;PLK2;SDCCAG8;CCDC85B;TUBGCP5;LEO1;MPLKIP;PLEKHA7;TTBK2;DYNC1LI2;ATF5;DZIP1;SIRT2;TTLL5;CAMSAP2;UBR4;G6PD;AATF;B9D1;VPS4A;GNAI1;CEP57L1;TRIM59;APC;ID1;RILPL1;SMAD7;MAP3K11;PPP1R12A;PARD6A;IFT52;NIN;ERCC6L;CEP192;SPPL2B;MIB1;BBS4;RANBP1;KIF13A;RFWD2;STIL;WRN;AUNIP;TTC26;TSEN2;CEP44;AAAS;MAD1L1;GSG2;CEP89;DYNLL1;ATP6V0D1;MAPKAPK2;SNAP29;CEP104;CEP170
Cellular_Component	GO:0044440	endosomal part	http://amigo.geneontology.org/amigo/term/GO:0044440	0.00261688	0.03142635	SLC9A6;EHD1;AP4S1;SNF8;AP2M1;AP2S1;CLCN5;ZFYVE27;CLTC;ARL8A;ABCA2;GGA2;PLEKHM2;VPS8;AP4E1;VPS4A;LAMTOR2;CHMP4A;ANXA1;ARF6;RHOB;LRPAP1;SLC11A2;VPS36;PLD1;NDFIP2;SCYL2;VPS35;RCC2;SPPL2B;CHMP1B;RAB5A;KIF13A;MAP3K7;UBC;UBE2D3;LDLRAD4;FZD7;RILP;WDR83;SPPL2A;BECN1;CD164;MTMR4;ATP6V0D1;HGS;TGFBRAP1;STX8;GOSR2;ZFYVE16;SNX17
Cellular_Component	GO:0000118	histone deacetylase complex	http://amigo.geneontology.org/amigo/term/GO:0000118	0.00276042	0.03142635	HDAC6;MORF4L1;SIN3B;SIN3A;HINT1;PHF21A;GATAD2A;GATAD2B;PHF12;RBBP4;SAP130;BRMS1L
Molecular_Function	GO:0003682	chromatin binding	http://amigo.geneontology.org/amigo/term/GO:0003682	7.63E-08	2.05E-05	CHAF1A;TRIM28;CITED2;SLC30A9;ZNHIT1;MORF4L1;MBD6;KLHDC3;ATF2;CSNK2B;NKX2-5;ARID3A;PRIMPOL;ATF5;SIRT2;KDM1A;FOXC2;CAMTA2;SIN3B;CABIN1;ZMYND8;SIN3A;GLI2;GTF2H1;HMGA1;JUN;MECP2;TRIM37;ORC1;PHF21A;WAC;PHF1;POLA1;PRKAA2;KDM3A;GATAD2B;MTA3;PHF12;CHD8;RAD21;RBBP4;RELA;UPF1;RNF2;RNF4;NOC3L;NSD1;NUCKS1;SKIL;SMARCD1;SMARCE1;SOX15;SUPT6H;TPR;TTF1;WRN;TDRD3;BAP1;SMARCA5;CBX2;EED;TRIM24;BAZ1B;MTA1;H2AFY;SETDB1;USP3;REC8
Molecular_Function	GO:0019787	ubiquitin-like protein transferase activity	http://amigo.geneontology.org/amigo/term/GO:0019787	1.10E-06	0.00013443	FEM1B;TRIM28;MAEA;KLHL41;TRIM3;UBE2F;RNF217;FANCF;FBXO21;UBR4;UFL1;PPIL2;HECTD1;RCHY1;KBTBD2;ZNF451;FBXO22;UBE2S;RABGEF1;RNF149;TRIM59;TRIM37;CNOT4;RNF181;UFC1;PIAS4;MPHOSPH8;RNF111;KLHL28;UBE2R2;FANCL;RFWD3;MSL2;RNF130;PELI1;MIB1;KIAA1586;BARD1;RANBP2;RBBP6;RNF2;RNF4;RNF5;RFWD2;UNKL;RMND5B;TRAF2;TTC3;UBE2D3;UBE2E2;FBXL15;RNF34;KLHL15;CBL;TRIM24;UBE3B;KLHL13;PIAS2;MED17;MED24
Molecular_Function	GO:0016874	ligase activity	http://amigo.geneontology.org/amigo/term/GO:0016874	1.50E-06	0.00013443	SAE1;TRIM28;FARS2;UBE2F;ADSS;ACSL1;MYCBP2;TTLL5;UBR4;UFL1;FPGS;PPIL2;RCHY1;ZNF451;TTLL3;RNF149;GSS;SLC27A1;LIG1;ASNS;TRIM37;CNOT4;RNF181;PIAS4;RNF111;FANCL;RFWD3;MSL2;UBA6;RNF130;TRIM39;KCMF1;PELI1;MIB1;KIAA1586;RANBP2;RBBP6;RNF2;RNF4;RNF5;MCCC2;RFWD2;UNKL;TRAF2;TTC3;CAD;UBA5;RNF34;CBL;SUCLA2;TRIM24;PIAS2
Molecular_Function	GO:0042393	histone binding	http://amigo.geneontology.org/amigo/term/GO:0042393	3.98E-05	0.00267377	IPO7;MSL3;TAF1L;SPTY2D1;MTF2;ZMYND8;PHF21A;PHF1;PRMT7;ING3;MPHOSPH8;PHIP;COPRS;PTMA;PHF12;CHD8;RBBP4;BRD9;SNCA;SUPT6H;TDRD3;L3MBTL2;SMARCA5;CBX2;TRIM24;BAZ1B;USP3
Molecular_Function	GO:0001076	transcription factor activity, RNA polymerase II transcription factor binding	http://amigo.geneontology.org/amigo/term/GO:0001076	0.00011461	0.00616585	TRIM28;CITED2;TCERG1;TAF1L;ATF2;NKX2-5;CTBP1;MED19;SIN3B;ZMYND8;SIN3A;ZNF451;HDGF;JUN;PHF12;RBBP8;SOX4;SOX12;TCF4;TTF1;MINA;MED17;MED24;CDC5L

Supplementary Table 4 - Overrepresentation analysis results for GO terms among the 1,390 significant growth interactions using the Webgestalt program.

Molecular_Function	GO:0070491	repressing transcription factor binding	http://amigo.geneontology.org/amigo/term/GO:0070491	0.00034506	0.01523331	TCERG1;PRDM5;CTBP1;ZMYND8;SIN3A;GMNN;BBS4;RBBP8;RELA;SKIL;DDRGK1;SP1;MTA1
Molecular_Function	GO:0036002	pre-mRNA binding	http://amigo.geneontology.org/amigo/term/GO:0036002	0.00039641	0.01523331	U2AF1L4;HNRNPA2B1;RBM22;PTBP1;SRSF6;TRA2B;SNRPC;SLBP
Molecular_Function	GO:0003713	transcription coactivator activity	http://amigo.geneontology.org/amigo/term/GO:0003713	0.00092718	0.03117649	TRIM28;CITED2;SLC30A9;TADA3;TCERG1;SUB1;NCOA7;ATF2;FGF2;SNW1;KDM1A;USP22;FUS;TAF5L;HMGA1;JUN;CCAR1;ATXN7L3;RNF4;PRDM16;SMARCD1;SMARCE1;SOX4;SOX12;TAF4;ZFX;SAP130;TDRD3;ZMIZ2;ARID5B;EDF1;TRIM24;PIAS2;MTA1;MED17;TBPL1;MED24
Molecular_Function	GO:0004674	protein serine/threonine kinase activity	http://amigo.geneontology.org/amigo/term/GO:0004674	0.00136732	0.04055157	STK25;CAMKK2;PLK2;TLK2;CIT;TAF1L;CSNK2B;TTBK2;NIM1K;AAK1;ICK;TNIK;DSTYK;RPS6KA6;GTF2H1;ARAF;LTBP1;MAP3K11;PAK1;CDK18;CAB39;CDK12;PIK3CA;ULK4;PRKAA2;PRKCE;MAPK7;MAP2K5;CAMK1D;ADCK1;TAOK1;BCR;MAP2K4;WNK1;BRAF;SRPK2;STK3;STK10;MAP3K7;TTK;GSG2;ULK1;CAMK1;RIOK3;CCND3;RPS6KA4;MAP3K6;ACVR2A;MAPKAPK2;CDC42BPB
Molecular_Function	GO:0008022	protein C-terminus binding	http://amigo.geneontology.org/amigo/term/GO:0008022	0.00165805	0.04055157	SAE1;TRIM3;PRDX3;YWHAQ;SNF8;CTBP1;XRCC6;PABPC1;VPS4A;DBNL;HRAS;ID1;BCAM;MSH2;VPS36;IFT52;PIAS4;PEX1;FIGN;SP1;TAF13;TCF4;YWHAB;SNX17
Molecular_Function	GO:0019213	deacetylase activity	http://amigo.geneontology.org/amigo/term/GO:0019213	0.00165824	0.04055157	HDAC6;SIRT2;KDM1A;SIN3B;SIN3A;PHF21A;MTA3;ARID4A;RBBP4;BRMS1L;MTA1

Supplementary Table 5 - Plasmids used in this study.

	Plasmid ID	plasmid name	Purpose	Source	Insert	Promoter	Marker(s)
*	DA007	pDA007	ORFeus expression, WT	Burns Lab	ORFeus-Hs, ORF2-3xFlag	Tet, 2nd	puromycin
*	DA019	pDA019	control expression vector	Burns Lab	Multiple Cloning Site	Tet, 2nd	puromycin
*	DA025	pDA025	ORFeus expression, mutant	Burns Lab	ORFeus H230A En, ORF2-3xFlag	Tet, 2nd	puromycin
*	DA027	pDA027	ORFeus expression, mutant	Burns Lab	ORFeus H230A/D702Y, ORF2-3xFlag	Tet, 2nd	puromycin
*	DA034	pDA034	ORFeus expression, mutant	Burns Lab	ORFeus D702Y RT, ORF2-3xFlag	Tet, 2nd	puromycin
	DA055	pDA055	ORFeus expression, WT	Burns Lab	ORFeus-Hs, ORF2-3xFlag	Tet, 3rd	hygromycin
*	DA056	pDA056	ORFeus expression, WT	Burns Lab	ORFeus-Hs	Tet, 3rd	blasticidin
	DA064	psPAX2	lentivirus packaging	AJ Holland			
	DA065	pMD.G	lentivirus packaging	AJ Holland			
*	DA077	pDA077	L1RP expression	Burns Lab	L1RP	CMV	neomycin
	DA079	pOT_p53shRNA_Lentivirus_TagRFP_T	TP53 shRNA lentivirus	AJ Holland	p53 shRNA	H1	TagRFP
	DA081	pSicoR_mCh_empty	control for TP53 shRNA lenti	Addgene	empty	H1	mCherry
*	DA083	pDA083	eGFP expression	Burns Lab	eGFP	CMV	neomycin
	DA090	pCMV(CAT)T7-SB100	generation of Tet-On RPE	Addgene	sleeping beauty	CMV	
	DA091	pSBtet-RN	generation of Tet-On RPE	Addgene	Luciferase	Tet, 2nd	G418, RFP
*	DA093	pDA093	generation of Tet-On RPE	Burns Lab	ORFeus	Tet, 2nd	G418, RFP
	DA094	pSBtet-GN	generation of Tet-On RPE	Burns Lab	Luciferase	Tet, 2nd	G418, eGFP
*	DA095	pDA095	generation of Tet-On RPE	Burns Lab	ORFeus	Tet, 2nd	G418, eGFP
	DA097	pLentiGuide-Puro	generation of CRISPR KO cells	Addgene		U6	puromycin
	JM111	pJM111	L1RP retrotransposition reporter, negative control	Kazazian Lab	L1RP (inactive) GFP-AI	CMV	puromycin
*	MT525	pMT525	L1RP retrotransposition reporter	Boeke Lab	L1RP GFP-AI	CMV	puromycin

* Plasmid available at https://www.addgene.org/Kathleen_Burns/
Please contact the indicated source lab for all other plasmids

Supplementary Table 6 - Oligonucleotides used in this study.

Method	Category	Primer Name	Sequence (5' - 3')
PCR	Screen Library Preparation	GECKO_PCR2_F01	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNAAGTAGAGtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F02	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNACACGATCtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F03	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNNCGCGCGGTtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F04	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNNNCATGATCGtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F05	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNCGTTACCAtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F06	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNTCCTTGGTtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F07	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNNAACGCATTtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F08	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNNNACAGGTATtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F09	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNAGGTAAGGtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F10	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNAACAATGGtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F11	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNNACTGTATCtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_F12	AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGATCTNNNNNNNAGGTCGCAtcttgtggaaaggacgaaacaccg
PCR	Screen Library Preparation	GECKO_PCR2_R02	CAAGCAGAAGACGGCATACGAGATACACGATCGTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNTCTACTATTCTTTCCCCTGCACTGT
PCR	Cloning	SB-ORFeus-5	GTACCACTTCCTACCCTCGAAAGGCCTCTGATGGGCAAGAAGCAGAACCG
PCR	Cloning	SB-ORFeus-3	TCATGTCTATCGATGGAAGCTTGGCCTGACATCAGTTGCCGCCGATCAGGC
PCR	qRT-PCR	DA.q13.CDKN1A.left	TGTCTTGTACCCTTGTGCCT
PCR	qRT-PCR	DA.q14.CDKN1A.right	AAGATGTAGAGCGGGCCTTT
PCR	qRT-PCR	DA.q45.GAPDH.forward	GGATTTGGTCGTATTGGG
PCR	qRT-PCR	DA.q46.GAPDH.reverse	GGAAGATGGTGATGGGATT
PCR	qRT-PCR	DA.q.IFNB1.forward	AGCTGCTTAATCTCCTCAGGG
PCR	qRT-PCR	DA.q.IFNB1.reverse	TCTCCTGTTGTGCTTCTCCA
PCR	qRT-PCR	DA.q.TLR3.forward	TGTCTCATAATGGCTTGTCATCT
PCR	qRT-PCR	DA.q.TLR3.reverse	GGCCAAATAATCTTCCAATTGCG
PCR	qRT-PCR	DA.q.IFIT2.forward	AAACAACTGCTCCATCTGCG
PCR	qRT-PCR	DA.q.IFIT2.reverse	TGCAAAGCCTCAGAATCTGC
PCR	qRT-PCR	DA.q.IFIT1.forward	GCTTTCAAATCCCTTCCGCT
PCR	qRT-PCR	DA.q.IFIT1.reverse	TAGGCAGAGATCGCATACCC
PCR	qRT-PCR	DA.q15.ORFeus.left	AAGATCATCCGCGCCATCTA
PCR	qRT-PCR	DA.q16.ORFeus.right	TCAGCTTCACCTCCTCCTTG

Supplementary Table 6 - Oligonucleotides used in this study.

CRISPR oligo	Non-target-control	GPP_76767	CCATTCACAATCCCACTACA
CRISPR oligo	Non-target-control	GPP_77342	TGAGCATTCGTAGCCCAGCA
CRISPR oligo	TP53 Knockout	GPP_19455	GATCCACTCACAGTTTCCAT
CRISPR oligo	TP53 Knockout	GPP_19456	GGTGCCCTATGAGCCGCCTG
CRISPR oligo	CDKN1A Knockout	GPP_02927	GTCACCGAGACACCACTGGA
CRISPR oligo	CDKN1A Knockout	GPP_02925	AGTCGAAGTTCCATCGCTCA
CRISPR oligo	FANCM Knockout	GPP_46254	TGACGGTGGTTACAACACGC
CRISPR oligo	FANCA Knockout	GPP_06027	GACACACAGAACCTTCCGAG
CRISPR oligo	FANCL Knockout	GPP_41632	CGAGATGAATCCCTCATACA
CRISPR oligo	FANCI Knockout	GPP_41960	TATGACTGTATTCTTATACC
CRISPR oligo	FANCD2 Knockout	GPP_06034	AGTTGACTGACAATGAGTCG
CRISPR oligo	ATRIP Knockout	GPP_52946	TCCTAGGAAAAACCCTTCTG
CRISPR oligo	PPHLN1 Knockout	GPP_38975	AGGTGTTAGACAAACCCAGT
CRISPR oligo	TASOR Knockout	GPP_32305	GGAAAACGAAATAACTCAAG
CRISPR oligo	MPP8 Knockout	GPP_40459	ATACATCGGATGATGATACC
CRISPR oligo	MORC2 Knockout	GPP_31095	ACATTAGAAGTACGCCTAGG
CRISPR oligo	SETDB1 Knockout	GPP_26249	AAGGAAAGAGTCTACTGTCG

Supplementary Methods – Key Reagents In This Study

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Anti-Mouse Alexa Fluor 568	ThermoFisher	Cat# A-11004
Anti-Rabbit Alexa Fluor 488	ThermoFisher	Cat# A-11034
IRDye® 680RD Goat anti-Mouse IgG	LI-COR	Cat# 925-68070
IRDye® 680RD Goat anti-Rabbit IgG	LI-COR	Cat# 925-68071
IRDye® 800CW Goat anti-Mouse IgG	LI-COR	Cat# 925-32210
IRDye® 800CW Goat anti-Rabbit IgG	LI-COR	Cat# 925-32211
Mouse Anti-Flag	Sigma	F1804
Mouse Anti-Human FANCD2 Clone FI17	Santa Cruz	Cat# sc-20022
Mouse Anti-Human ORF1p Clone 4H1	Millipore Sigma	MABC1152
Mouse Anti-Human p53 Clone D0-1	CalBiochem	Cat# OP43
Mouse Anti-human γH2A.X, Clone JBW301	EMD Millipore	Cat# 05-636
Mouse Anti-RPA2, Clone 9H8	Abcam	Cat# ab2175
Rabbit Anti 53BP1	Novus Bio	Cat# NB100-904
Rabbit Anti p-RPA S4/S8	Bethyl	Cat# A300-245A
Rabbit Anti-H3	Abcam	Cat #1791
Rabbit Anti-Human Beta-Tubulin Clone 9F3	Cell Signaling Technology	Cat# 2128
Rabbit Anti-Human FANCD2	Novus Bio	Cat# NB100-182
Rabbit Anti-Human FANCI Clone 589	Agata Smogorzewska	Clone 589
Rabbit Anti-Human ORF2p Clone MT49	In-house production	MT49
Chemicals, Peptides, and Recombinant Proteins		
3-8% Tris-Acetate Gel	ThermoFisher	Cat# EA0375BOX

Supplementary Methods – Key Reagents In This Study

4-12% BisTris Gel	ThermoFisher	Cat# NP0322BOX
4-20% Mini TGX Gel	Biorad	Cat# 4561094
50% Gluteraldehyde		
7.5% Mini TGX Gel	Biorad	Cat# 4561023
CellTiter-Glo 2.0	Promega	Cat# G9241
Crystal Violet	Sigma	Cat# C6158-50G
DMEM/F12	ThermoFisher	Cat# 11320033
Doxorubicin	Cell signaling Technology	Cat# 5927S
Doxycycline	Takara	Cat# 631311
Fugene HD	Promega	Cat# E2311
G418	Corning Cellgro	Cat# 61-234-RF
HCS CellMask deep red cytoplasmic stain	ThermoFisher	Cat# H32721
HiFi 2X Assembly Master Mix	New England Biolabs	Cat# E2621S
Hoechst 33342	Sigma	
Immobilon PVDF Membrane	LI-COR	
Laemmli Sample Buffer	Biorad	Cat# 1610747
ONE-Glo	Promega	Cat# E6110
Opti-MEM I Reduced Serum Media	Gibco	Cat# 31985062
Poly-D-Lysine	Sigma	Cat# P6407-5MG
Polybrene	Millipore Sigma	Cat# TR-1003-G
Protease/Phosphatase Inhibitor	Cell Signaling Technology	Cat# 5872
Proteinase K	New England Biolabs	Cat# P8107S
Puromycin	Millipore Sigma	Cat# P8833-25MG
Q5 Hot-start polymerase master mix	New England Biolabs	Cat# M0494
RNase A	ThermoFisher	Cat# EN0531
Sodium Bicarbonate 7.5% solution	ThermoFisher	Cat# 25080094

Tet System Approved FBS	Takara	Cat# 631367
Tris-Acetate SDS Running Buffer	ThermoFisher	Cat# LA0041
Viafect	Promega	Cat# E4981
Critical Commercial Assays		
Click-IT EdU Alexa Fluor 647 Imaging Kit	ThermoFisher	Cat# C10340
DAKO EnVision+ System-HRP kit	Agilent	Cat# K4006
iScript cDNA Synthesis Kit	Biorad	Cat# 1708891
NEBNext Library Quant Kit	New England Biolabs	Cat# E7630S
PureLink HiPure Plasmid Filter Maxiprep Kit	ThermoFisher	Cat# K210016
PureLink HiPure Plasmid Filter Midiprep Kit	ThermoFisher	Cat# K210014
Quick-RNA Microprep kit	Zymo	Cat# R1051
SsoAdvanced™ Universal SYBR® Green Supermix	Biorad	Cat# 1725270
TruSeq Stranded mRNA Library Prep	Illumina	Cat# 20020594
ZymoPURE Plasmid Miniprep Kit	Zymo	Cat# D4212
Deposited Data		
All raw sequencing files and processed screen and RNAseq data have been uploaded to the GEO database under accession GSE119999.		
Experimental Models: Cell Lines		
HEK293FT	AJ Holland	
hTERT-RPE-Cas9-p53_shRNA, Clone 2	This study	
hTERT-RPE-Cas9-p53_shRNA, Tet-On codon-optimized L1	This study	
hTERT-RPE-Cas9-p53_shRNA, Tet-On Luciferase	This study	
hTERT-RPE-Cas9$^{\text{puroS}}$	Lambrus et al., 2016	
hTERT-RPE, Tet-On codon-optimized L1	This study	
hTERT-RPE, Tet-On Luciferase	This study	
hTERT-RPE1$^{\text{puroS}}$	Lambrus et al., 2016	
Tet-On 3G HEK293	Takara	Cat# 631182

Tet-On 3G HeLa	Takara	Cat# 631183
Tet-On HEK293T$_{LD}$	Taylor et al., 2013	
Recombinant DNA		
see Supplemental Table 5 for plasmids used in this study		
Oligonucleotides		
see Supplemental Table 6 for oligos used in this study		
Software and Algorithms		
BD C6 Software	BD	
Bowtie	Langmead et al., 2009	http://bowtie-bio.sourceforge.net/manual.shtml
DESeq2	Love et al., 2014	https://bioconductor.org/packages/release/bioc/html/DESeq2.html
GSEA v2.0	Subramanian et al., 2005	http://software.broadinstitute.org/gsea/index.jsp
HTSeq	Anders et al., 2015	https://htseq.readthedocs.io/en/release_0.10.0/
Image Studio Software v4.0	LI-COR	https://www.licor.com/bio/products/software/image_studio_lite/
ImageJ	NIH	https://imagej.nih.gov/ij/

MAGeCK v0.5.6, v0.5.7	Liu et al., 2014	https://sourceforge.net/p/mageck/wiki/Home/
MATLAB		https://www.mathworks.com/
R v3.4, v3.5		https://www.r-project.org/
STAR v2.4.5	Dobin et al., 2013	https://github.com/alexdobin/STAR
StringDB	Szklarczyk et al., 2017	https://string-db.org/
WebGestalt 2017	Wang et al., 2017	http://www.webgestalt.org/option.php
Other		
BD Accuri C6 Flow Cytometer	BD	
Glomax Multi+ Detection System	Promega	
HiSeq 2500	Illumina	
Licor Odyssey Scanner	LI-COR	
MyIQ Thermocycler	Biorad	
NextSeq 500	Illumina	
Nikon TE300 epifluorescent microscope	Nikon	
Trans-Blot-Turbo	Biorad	
Xcell II Blot Module	ThermoFisher	