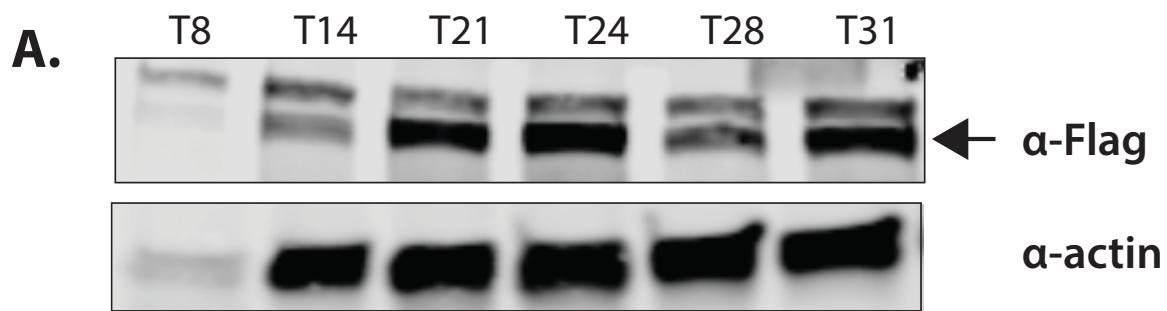


**Figure 3.1: Schematic design of PA-1 screen.**

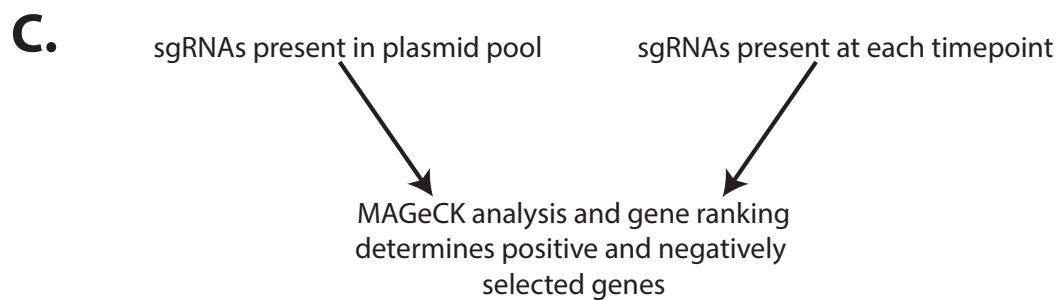
**Figure 3.2: Expression of Cas9 and essential gene dropout over time.**

A) *Representative western blot.* Whole cell lysates were collected from PA-1 cells that had been transduced with LCv2. Whole cell lysates were recovered from Day 8, 14, 21, 24, 28, and 31 PA-1 cells (indicated as T8, T14, T21, T24, T28, and T31, respectively). Anti-FLAG antibody was used to visualize Cas9, top image, bottom band, indicated with an arrow to the right of the blot. The lower image depicts the actin loading control obtained from the same whole cell lysates. The assay was repeated three times with similar results B) *Summary of sequencing information.* Headers indicate gDNAs collected from specific time points (T8, T21, T31) or plasmid DNA (Plasmid) used for sequencing. Note, only the LCv2 “A” plasmid pool was sequenced. Rows indicate the total number of mappable reads (Read count), the number of unique guide sequences from those reads (# Guides), the mean read count per sgRNA (Mean), and the median read count per sgRNA (Median). C) *Schematic of pathway analysis using the MAGeCK software.* Sequencing reads representing guide sequences from the plasmid pool are compared to sequencing reads representing guides from T8, T21, or T31. D) *Results from pathway analysis.* Header of the first column for each table indicates pathway analysis from a specific time point (e.g. Pathway (T8)). Listed below are the KEGG annotated pathways that were significantly depleted at that time point. The second column (# genes in pathway) for each table indicates the total number of KEGG annotated genes in that pathway. The final column (# genes depleted) indicates the number of genes depleted in that pathway as determined from MAGeCK analysis.



**B.**

	PA1 (T8)	PA1 (T21)	PA1 (T31)	Plasmid
<b>Read Count</b>	208499	310942	443982	55067662
<b># Guides</b>	45599	49017	51124	62764
<b>Mean</b>	2	3	4	877
<b>Median</b>	4.6	6.3	8.7	664



**Figure 3.2: Expression of Cas9 and essential gene dropout over time.**

D.

Pathway (T8)	# genes in pathway	# genes depleted
KEGG_PROTEASOME	44	18
KEGG_SPLICEOSOME	125	40

Pathway (T21)	# genes in pathway	# genes depleted
KEGG_SPLICEOSOME	125	60
KEGG_AMINOACYL_TRNA BIOSYNTHESIS	41	24
KEGG_RIBOSOME	86	39
KEGG_PROTEASOME	44	23
KEGG_RNA_PolyMERASE	29	16
KEGG_RNA_DEGRADATION	56	25

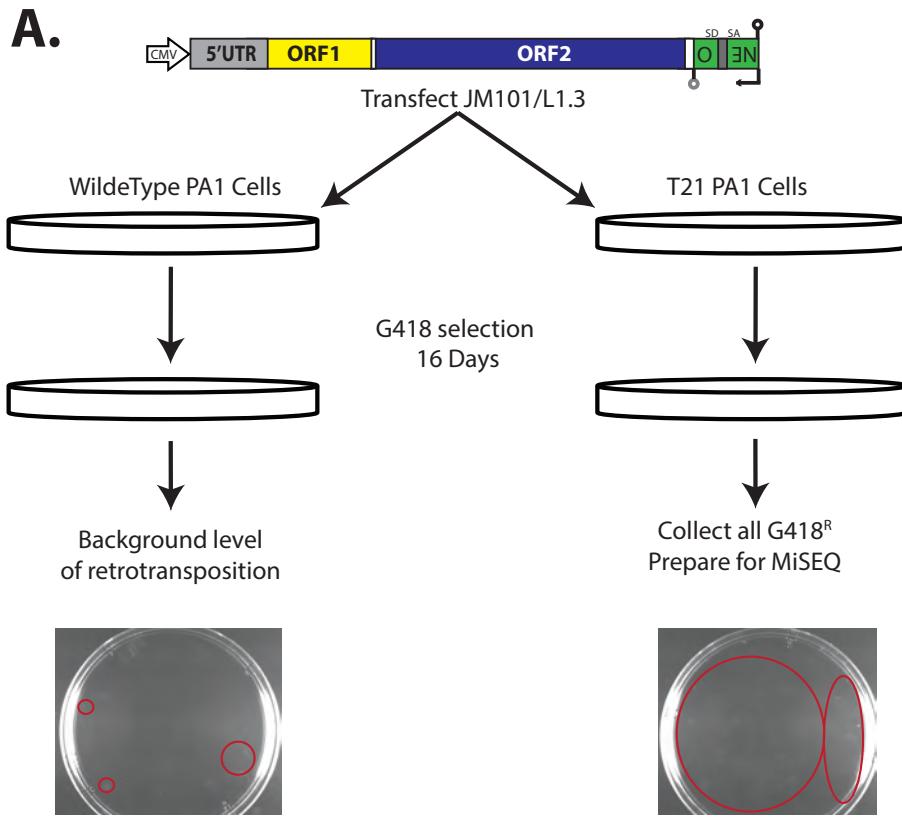
  

Pathway (T31)	# genes in pathway	# genes depleted
KEGG_SPLICEOSOME	125	56
KEGG_PYRIMIDINE_METABOLISM	96	46
KEGG_RNA_DEGRADATION	56	30
KEGG_VALINE LEUCINE AND ISOLEUCINE BIOSYNTHESIS	11	8
KEGG_AMINOACYL_TRNA BIOSYNTHESIS	41	35
KEGG_RIBOSOME	86	12
KEGG_VALINE LEUCINE AND ISOLEUCINE DEGRADATION	44	14
KEGG_RNA_PolyMERASE	29	16
KEGG_DNA_REPLICATION	35	19

Figure 3.2: Expression of Cas9 and essential gene dropout over time.

**Figure 3.3: Scheme of retrotransposition assay in T21 PA-1 cells and list of top candidate genes.**

A) *Schematic of retrotransposition assay.* The L1 used in this study (pJM101/L1/3) is indicated. It consists of a full-length L1 driven by both a CMV promoter (white arrow) and the endogenous L1 5'UTR (grey rectangle). The 3' UTR contains the *mneol* retrotransposition indicator cassette (Green box with backwards “NEO”). The lollipops indicate engineered polyadenylation signals and the small backwards arrow indicates a promoter driving expression of the *mneol* cassette. pJM101/L1.3 retrotransposition delivers a *neomycin phosphotransferase* resistance gene conferring resistance to the drug G418 only if the integrated *mneol* reporter (*L1-retro-mneol*) is expressed. Wild-type PA-1 cells (left half of the schematic) or T21 PA-1 cells (right half of the schematic) were transfected with pJM101/L1.3 and selected for 16 days with the drug G418. G418 resistant colonies represent *L1-retro-mneol* events that escape silencing. Wild-type PA-1 cells contain far fewer (~35) G418 resistant colonies (circled in red, left half of schematic), than T21 PA-1 (~150-300) colonies (circled in red, right half of the schematic). B) *List of candidate genes identified from the screen.* The table indicates the gene name (Gene ID) and the number of unique guides targeting each gene (# guides). These candidate genes are represented by at least two guides in at least two replicates (see text for more details) C) *List of candidate genes using the HE-guide criteria.* The table indicates the gene ID. These candidate genes represent those targeted by one HE-guide at least one other single replicate guide (see text for more details).



**B.**

Gene ID	# guides	Gene ID	# guides	Gene ID	# guides	Gene ID	# guides	Gene ID	# guides
NF2	5	LALBA	2	ZBTB44	2	DISP2	2	PRODH	2
XPO7	4	LAMB3	2	ZNF177	2	DSG1	2	PRRT2	2
CABP1	3	LDLRAD4	2	ZNF320	2	ECE1	2	PTGDR	2
CEACAM7	3	LIPH	2	ZNF768	2	EPM2A	2	PTPN14	2
GPATCH8	3	LMO7	2	ZSCAN10	2	ERVMER34	2	RBM47	2
KRTAP5	3	LOC100129361	2	FAM153A	2	RRAGB	2	ESD	2
PMAIP1	3	LYNX1	2	FAM187B	2	RTP3	2	FAM115C	2
SOX5	3	LYRM2	2	FAM189B	2	RXFP4	2	RET	2
ADARB2	2	MAP7D1	2	FAM192A	2	S100A4	2	RPS6KA3	2
ADRB1	2	MAR	2	FAM196B	2	SCN3A	2	TLDC2	2
ANK2	2	MCIDAS	2	FAM21B	2	SLC44A4	2	TMEM63C	2
ANKRD66	2	MCL1	2	FBXL8	2	SLC6A13	2	TMEM81	2
AP1M1	2	MMP10	2	FBXO38	2	SLC6A16	2	TMPRSS6	2
APOBR	2	MMP23B	2	FCGR1A	2	SLC6A5	2	TRABD2A	2
AQP10	2	MN1	2	FGF13	2	SMURF1	2	TRIM15	2
ARIH2	2	MPV17L	2	FGF20	2	SP9	2	TRIM3	2
AS3MT	2	MRAS	2	GAGE12D	2	SPANXE	2	TRIM46	2
ASTL	2	MYRF	2	GAL3ST3	2	SSTR3	2	TRPV5	2
AXL	2	NDE1	2	GLIS1	2	SUCLG2	2	UGT1A10	2
B3GNT4	2	NELL1	2	GNG10	2	SYT11	2	UQCC	2
BABAM1	2	NFIA	2	GPR176	2	TADA2B	2	USP17L20	2
BLOC1S4	2	NLK	2	HBD	2	TAF5L	2	WDR83OS	2
C19ORF26	2	NOD1	2	HELT	2	TAS2R46	2	PMM1	2
C19ORF54	2	NR0B2	2	HHIP1	2	TBC1D2B	2	PRDM15	2
CALCB	2	OR51S1	2	HMG4	2	THPO	2	DCAF12L1	2
CCDC147	2	OR52B2	2	HNF1A	2	KCNJ3	2	DDI2	2
CCL22	2	OR5W2	2	IL1RAPL1	2	KCNMB3	2	DEF6	2
CDX4	2	PARG	2	IL21R	2	KIAA1456	2	DGKK	2
CFI	2	PCP2	2	IL3	2	KLHL21	2	DHRS1	2
CLDN18	2	PDAP1	2	ITPK1	2	KRTAP12	2		
CRIP1	2	PHGR1	2	KCND1	2	PIK3CD	2		
CSK	2	PHOX2A	2	KCNE3	2	PIKFYVE	2		
CTNND2	2	PIH1D2	2	KCNJ16	2	PLSCR4	2		

**Figure 3.3: Scheme of retrotransposition assay in T21 PA-1 cells and list of top candidate genes.**

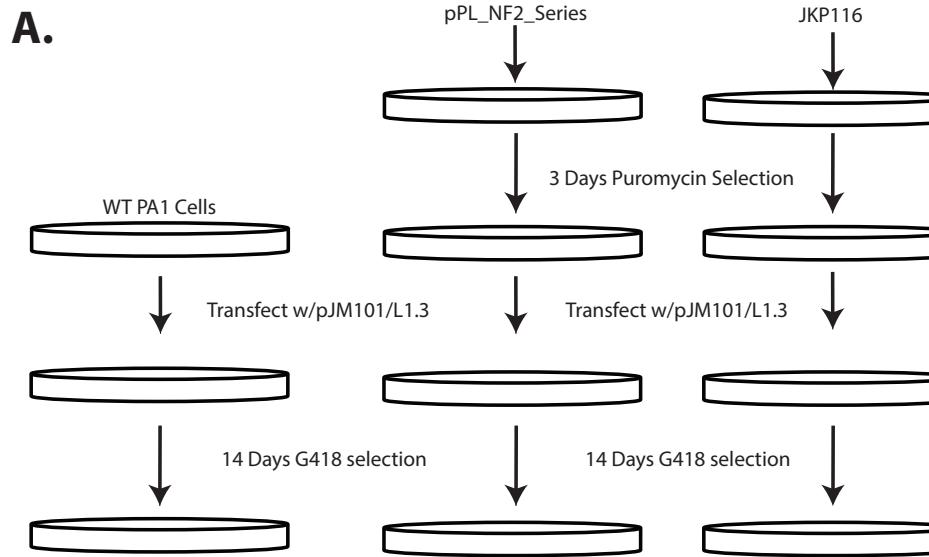
C.

Gene ID
CCNA1
ULBP3
TFF3
FAM213A
TMEM135
MAP1B
C5orf49
NOTCH1
DAXX
MSMB
PEX3
TIMP2
ZC3H12B
SMG1
RIBC1
HSFX2
MKX
SLC18A2
SNX8
TTC23
DMRTC2
PREX1
TP53
FOXJ1
BAX
HOXD1
ACAP1

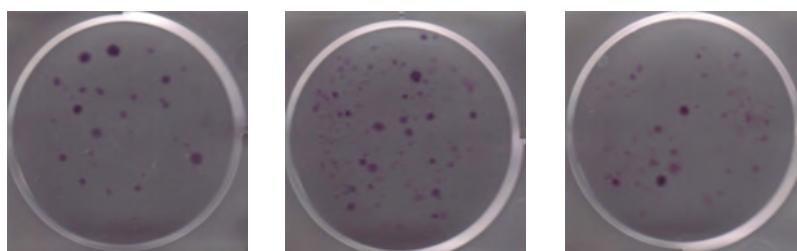
**Figure 3.3: Scheme of retrotransposition assay in T21 PA-1 cells and list of top candidate genes.**

**Figure 3.4: Validation of *NF2* as a potential candidate gene.**

A) *Schematic of validation experiment.* Wild-type PA-1 cells (WT, left), PA-1 cells transfected with plasmids expressing Cas9 and guides targeting the *NF2* gene (central, pPL\_NF2\_Series), or PA-1 cells transfected with a non-targeting control (JKP116) are indicated. pPL\_NF2\_Series and JKP116 transfecteed cells were selected with puromycin three days yielding only cells that contained the transfected plasmid. Wild-type PA-1 cells, pPL\_NF2\_Series and JKP116 cells were subsequently transfected with pJM101/L1.3 and selected with the drug G418 for 14 days. B) *Results of retrotransposition assay.* pPL\_NF2\_31718, pPL\_NF2\_31760, or pPL\_NF2\_31761 cells transfected with pJM101/L1.3 are resistant to the drug G418, suggesting that in some cells, *L1-retro-mneol* events are not silenced. JKP116 cells, and wild-type PA-1 cells transfected with pJM101/L1.3 are not resistant to the drug G418. C) *Control for retrotransposition assay.* pPL\_NF2\_31718, pPL\_NF2\_31760, or pPL\_NF2\_31761 untransfected cells are susceptible to treatment with G418. These images are representative of two independent experiments.

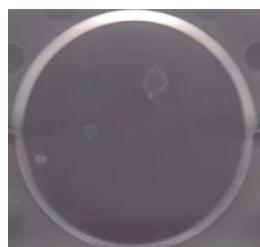


**B.** pPL\_NF2\_31718 pPL\_NF2\_31760 pPL\_NF2\_31761



JKP116

WT PA1



**Figure 3.4: Validation of *NF2* as a potential candidate gene.**

**C.**

UTF

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**Figure 3.4: Validation of *NF2* as a potential candidate gene.**

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