

Title

Genome-wide CRISPR Screen to Identify Genes that Suppress Transformation in the Presence of Endogenous *Kras*^{G12D}

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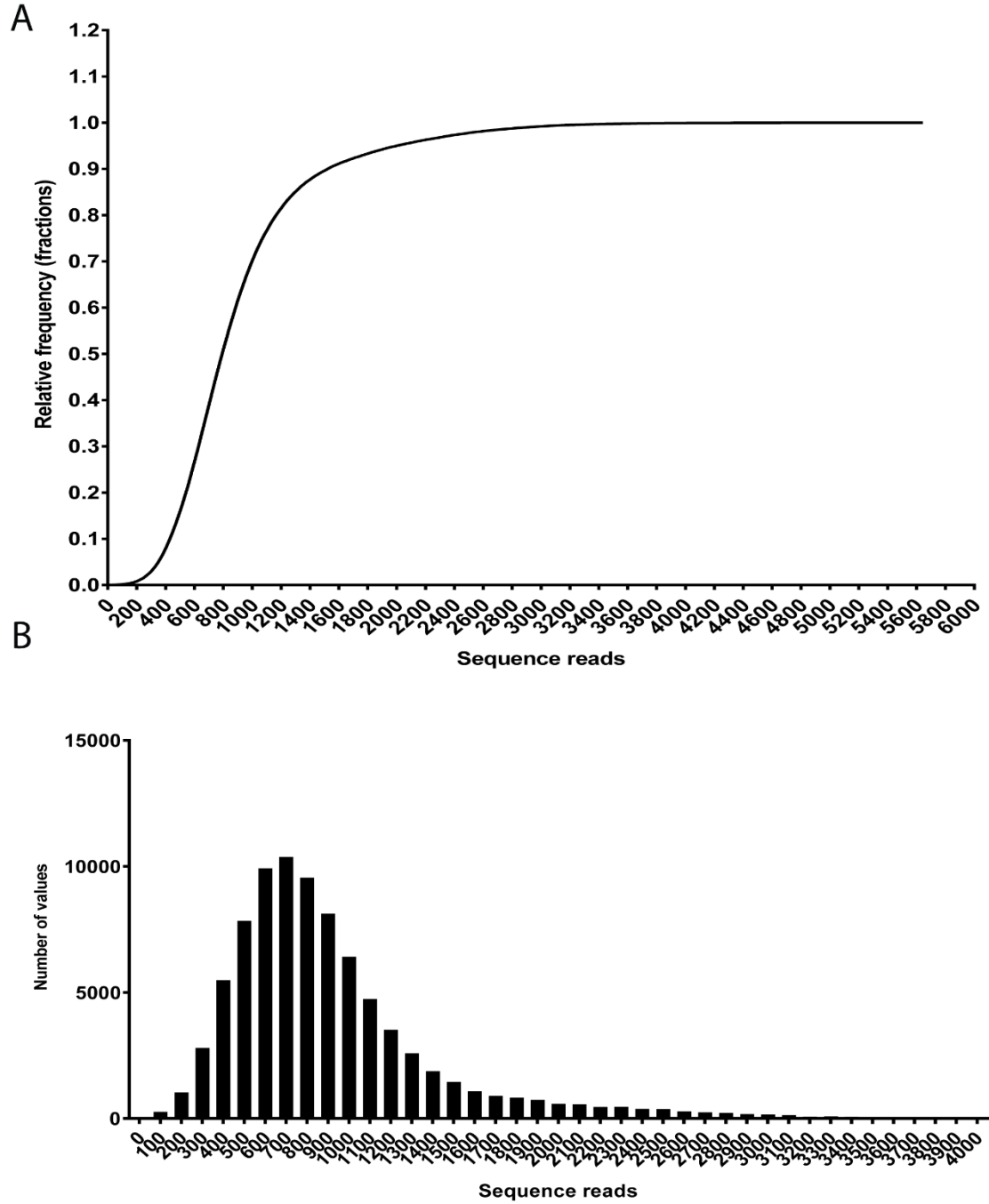
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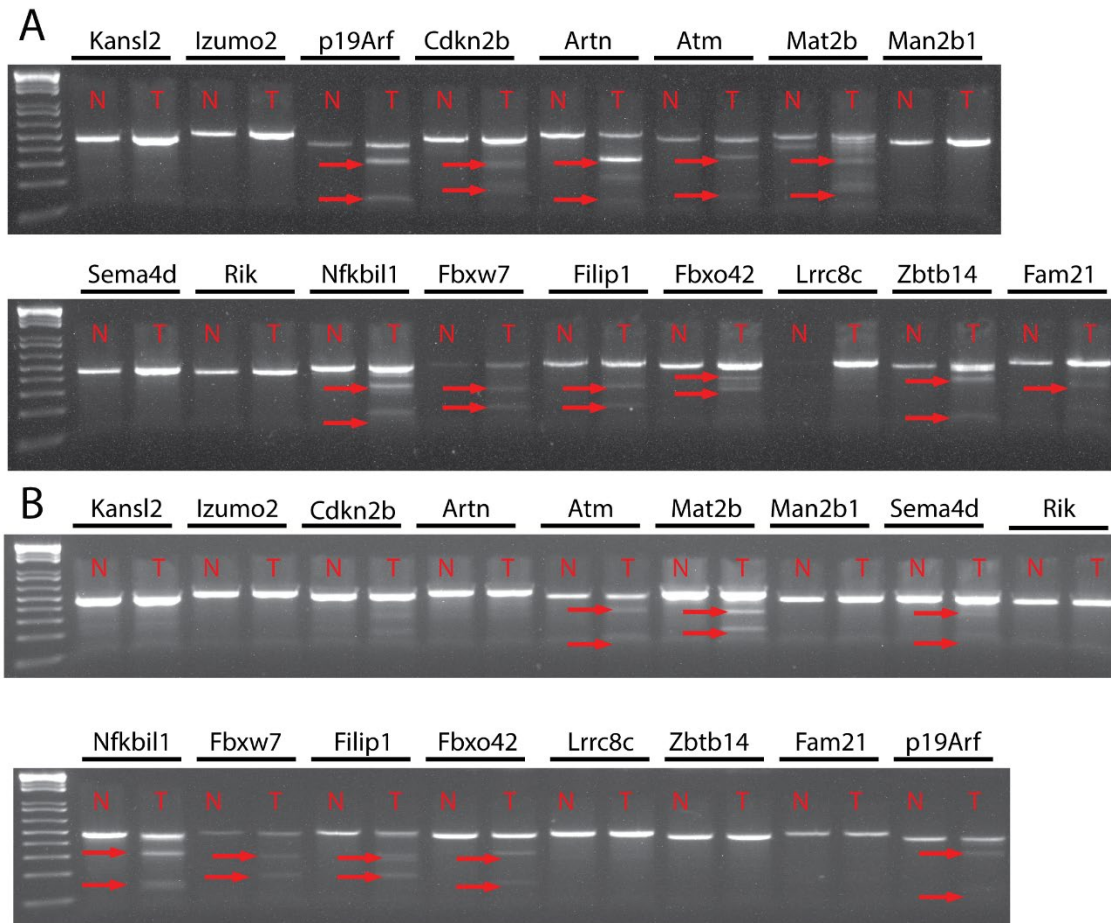
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Supplementary Information

Supplementary Figure. S1: Deep sequencing of each sgRNA represented in the customized library.

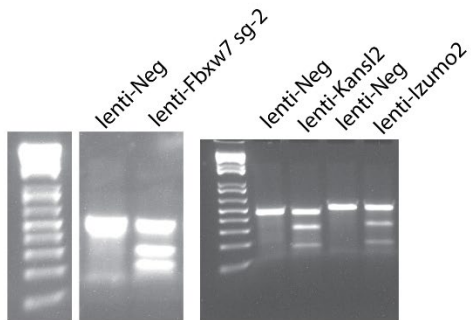


Supplementary Figure S2: (A) Surveyor assay on Tumor #1844. (B) Surveyor assay on Tumor #1846.

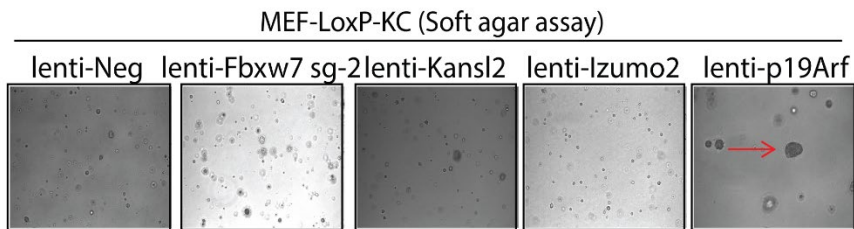


Supplementary Figure S3. (A) Surveyor assay on MEF-LoxP-KC infected with lentivirus that expresses a second sgRNA targeting *Fbxw7*, *Kansl2*, or *Izumo2*. The gel image of the marker and the gel image of the surveyor assay on lenti-Neg and lenti-*Fbxw7* sg-2 were cropped from the same gel which is shown in **Supplementary Figure S5**. (B) MEF-LoxP-KC infected with lentivirus that expresses a second sgRNA targeting *Fbxw7*, *Kansl2*, or *Izumo2* failed to form colonies in soft agar.

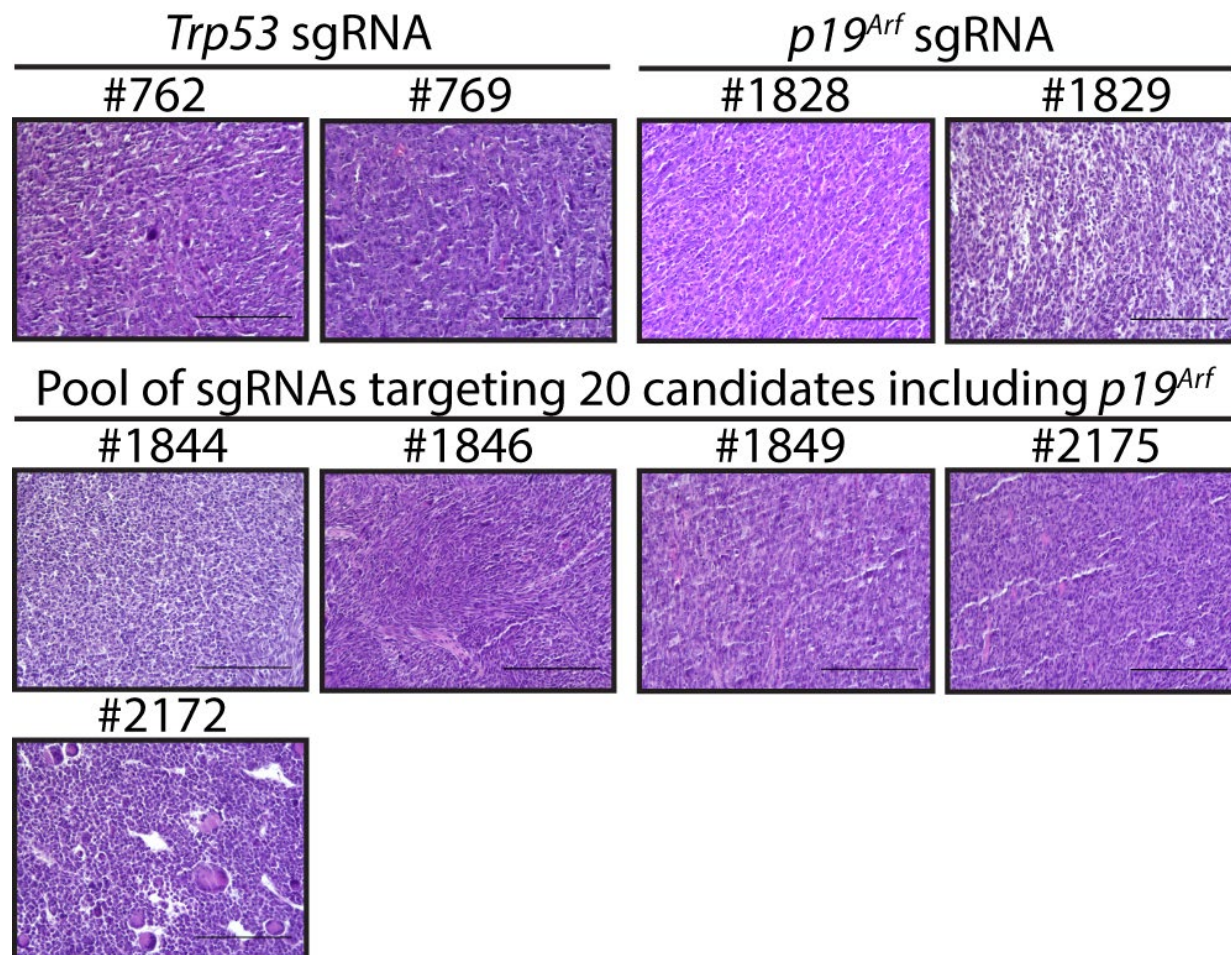
A



B



Supplementary Figure S4. Eight of the primary tumors generated in K-LoxP-C mice via IVE that delivered Cre recombinase and *Trp53* sgRNA, or *p19^{Arf}* sgRNA or mixed pool of sgRNAs targeting 20 candidates including *p19^{Arf}* were subject to histopathological analysis with haematoxylin and eosin staining. Scale bars, 200 μ m.



Supplementary Figure S5. All the uncropped images.

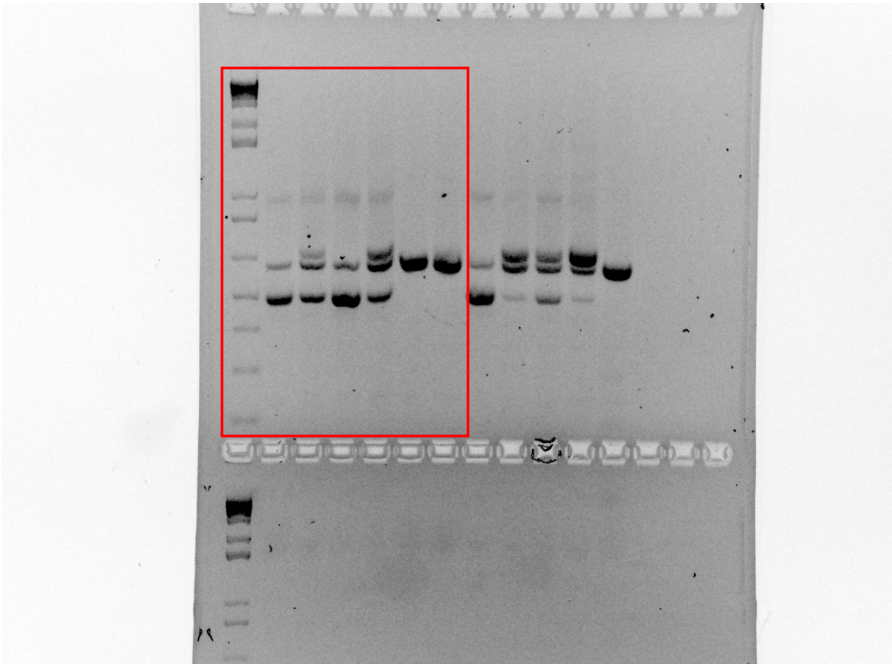


Figure 1A: Kras genotyping PCR.

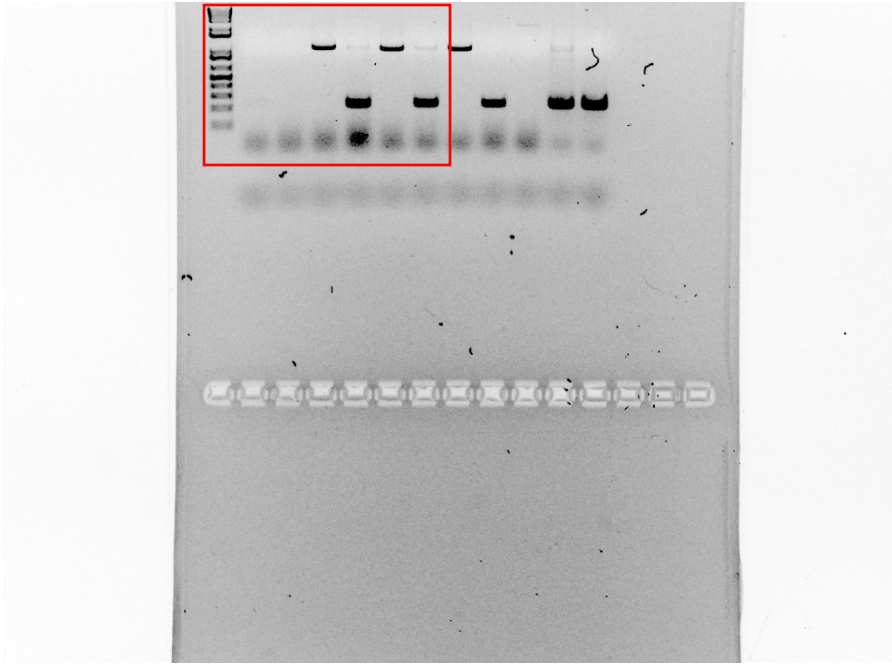


Figure 1A: Cas9 genotyping PCR.

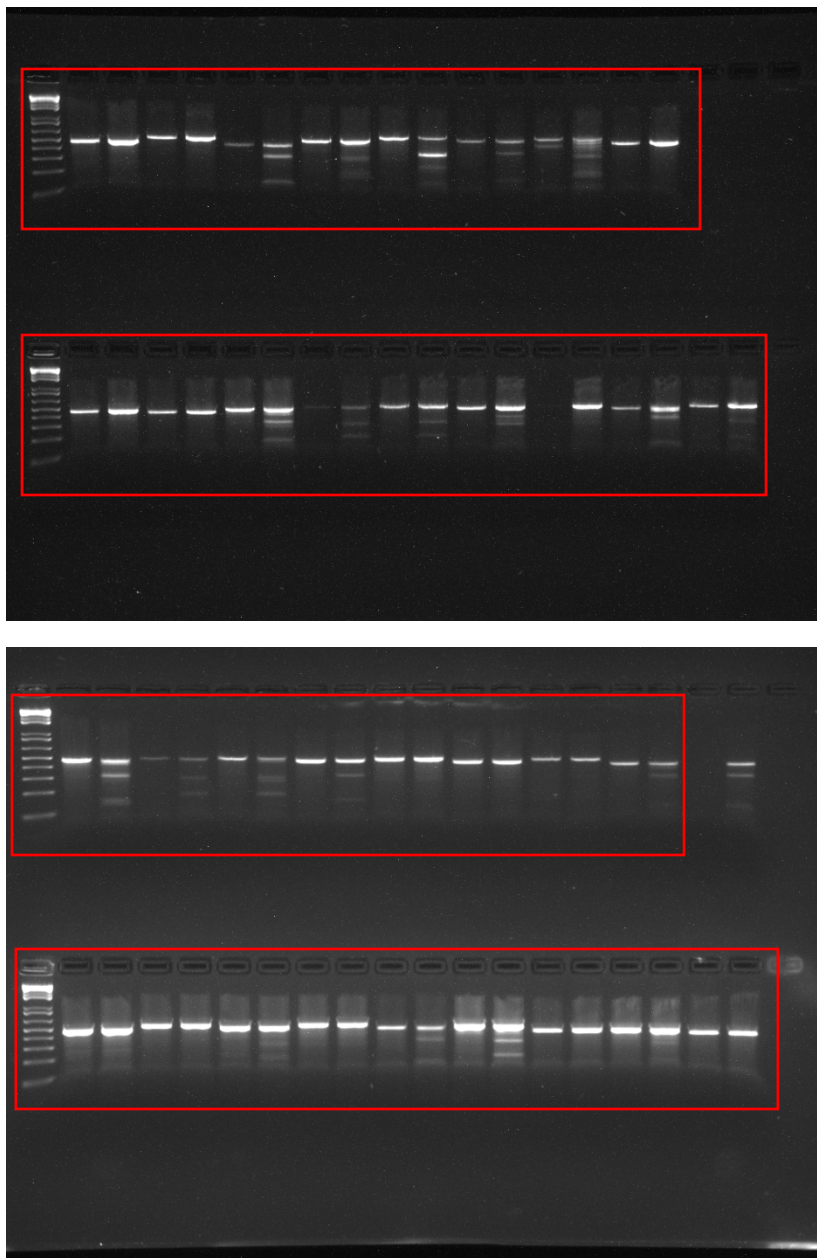


Figure S2: Surveyor assay gel images.

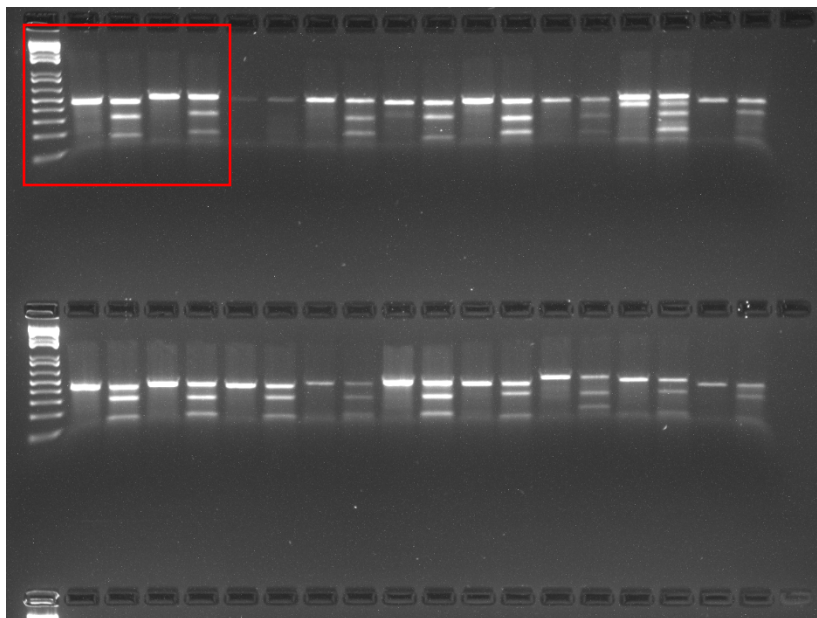
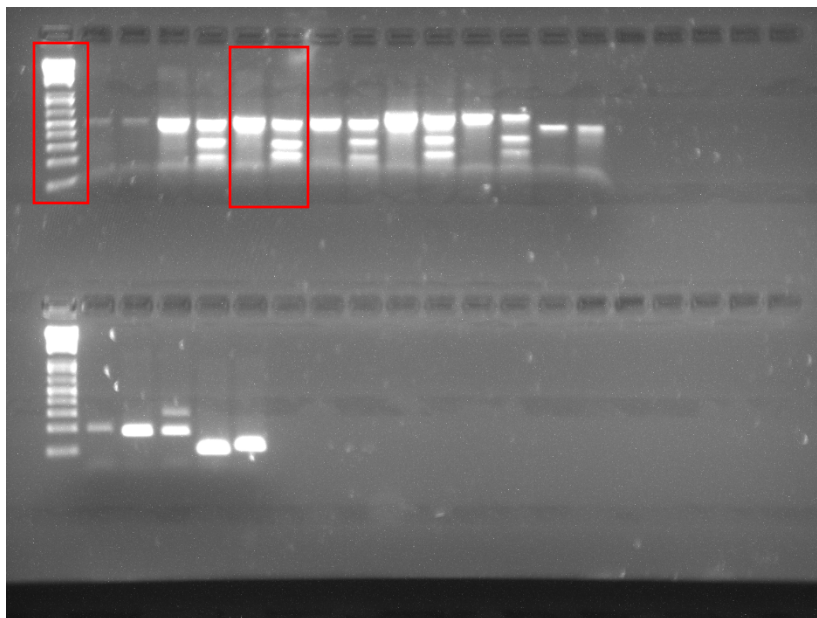


Figure S3: Surveyor assay gel images.

Supplementary Table S1

Correlation of *FBXW7* and *SLC9A3* with *KRAS* in all human cancer patients in the TCGA database.

Gene A	Gene B	Mutation Tendency: Co-occurrence/Mutual exclusivity (N/A: Not Applicable)	p-Value	Adjusted p-Value
<i>KRAS</i>	<i>FBXW7</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>SLC9A3</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>KANSL2</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>IZUMO2</i>	Co-occurrence	0.31	0.31
<i>KRAS</i>	<i>SLMAP</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>FILIP1</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>FBXO42</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>MAN2B1</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>CDKN2B</i>	Co-occurrence	0.08	0.08
<i>KRAS</i>	<i>MAT2B</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>FAM21</i>	N/A		
<i>KRAS</i>	<i>4930452B06RIK</i>	N/A		
<i>KRAS</i>	<i>OBSL1</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>SEMA4D</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>CCDC18</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>NFKBIL1</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>ZBTB14</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>MUP14</i>	N/A		
<i>KRAS</i>	<i>ARTN</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>LRRC8C</i>	Co-occurrence	< 0.001	< 0.001
<i>KRAS</i>	<i>ATM</i>	Co-occurrence	< 0.001	< 0.001

Supplementary Table S2

sgRNA sequences.

Target gene	gRNA ID	Target sequence (5' to 3')
<i>Trp53</i>	gTrp53	GTGTAATAGCTCCTGCATGG
<i>Negative</i>	gNegtive	GCGAGGTATTCGGCTCCGCG
<i>p19Arf</i>	gp19Arf	GGGCCGCCCACTCCAAGAGA
<i>Kansl2</i>	gKansl2	TTGATCACTGTCTATGCTAT
<i>Izumo2</i>	glzumo2	GTCTGCAGTCGTGGATCAAC
<i>SImap</i>	gSImap	ATACTCACTCTGAACGAAGT
<i>Fbxw7</i>	gFbxw7 sg-1	GTGTTGCTGAACATGGTACA
<i>Fbxw7</i>	gFbxw7 sg-2	GTATGTCACAGATTCTAACG
<i>Filip1</i>	gFilip1	GTGGAGAGGGAAATCAACCG
<i>Fbxo42</i>	gFbxo42	GTCCTTGTACACGACCAGAG
<i>Man2b1</i>	gMan2b1	AGCTCCCAGAGGTAACACGT
<i>Cdkn2b</i>	gCdkn2b	GTCGTGCACAGGTCTGGTAA
<i>Mat2b</i>	gMat2b	GCTGCTTCCCAGCTGAATGT
<i>Fam21</i>	gFam21	ATTATGCAGACGACAATGTG
<i>4930452B06Rik</i>	gRik	CTGGCAGACGGAATAACCTA
<i>Obsl1</i>	gObsl1	TGTATGTGAGACCCGAGATG
<i>Sema4d</i>	gSema4d	GGCTGGATTCAGGACATGAG
<i>Ccdc18</i>	gCcdc18	AAAGGAGCACAGTTTACAAG
<i>Nfkbil1</i>	gNfkbil1	AGTGGCAGGAGGTCATCGGG
<i>Zbtb14</i>	gZbtb14	TTGCCGTCCTCTTGACTION
<i>Mup14</i>	gMup14	CTTCTGCATGGACACACACT
<i>Artn</i>	gArtn	AGGGCTAGAACAGCTAGGGT
<i>Lrrc8c</i>	gLrrc8c	TGGTTGACAAATCTGCTGCG
<i>Atm</i>	gAtm	TAAGTCATATAGGAAGCCGA
<i>Slc9a3</i>	gSlc9a3 sg-1	CTTCATAGTGTAGCGCACAG
<i>Slc9a3</i>	gSlc9a3 sg-2	CATAGTGTAGCGCACAGTGG

Supplementary Table S3

Primer sequences.

Primer ID	Sequence (5' to 3')	Use
gTrp53 5.1	CACCGTGAATAGCTCCTGCATGG	Cloning gTrp53
gTrp53 3.1	AAACCCATGCAGGAGCTATTACAC	
gNegative 5.1	CACCGGCGAGGTATTCGGCTCCGCG	Cloning gNegative
gNegative 3.1	AAACCGCGGAGCCGAATACCTCGCC	
gp19Arf 5.1	CACCGGGGCCGCCACTCCAAGAGA	Cloning gp19Arf
gp19Arf 3.1	AAACTCTCTGGAGTGGGCGGCCCC	
gKans12 5.1	CACCGTTGATCACTGTCTATGCTAT	Cloning gKans12
gKans12 3.1	AAACATAGCATAGACAGTGATCAAC	
glzumo2 5.1	CACCGgtctgcagTCGTGGATCAAC	Cloning glzumo2
glzumo2 3.1	AAACGTTGATCCACGActgcagacC	
gSImap 5.1	CACCGATACTCACTCTGAACGAAGT	Cloning gSImap
gSImap 3.1	AAACACTTCGTTCAGAGTGAGTATC	
gFbxw7 sg-1 5.1	CACCGGTGTTGCTGAACATGGTACA	Cloning gFbxw7 sg-1
gFbxw7 sg-1 3.1	AAACTGTACCATGTTTCAGCAACACC	
gFbxw7 sg-1 5.1	CACCGGTATGTCACAGATTCTAACG	Cloning gFbxw7 sg-2
gFbxw7 sg-2 3.1	AAACCGTTAGAATCTGTGACATACC	
gFilip1 5.1	CACCGGTGGAGAGGGAAATCAACCG	Cloning gFilip1
gFilip1 3.1	AAACCGGTTGATTTCCCTCTCCACC	
gFbxo42 5.1	CACCGGTCCTTGACACGACCAGAG	Cloning gFbxo42
gFbxo42 3.1	AAACCTCTGGTCGTGTACAAGGACC	
Man2b1 5.1	CACCGAGCTCCCAGAGGTAACACGT	Cloning gMan2b1
Man2b1 3.1	AAACACGTGTACCTCTGGGAGCTC	
gCdkn2b 5.1	CACCGGTCGTGCACAGGTCTGGTAA	Cloning gCdkn2b
gCdkn2b 3.1	AAACTTACCAGACCTGTGCACGACC	
gMat2b 5.1	CACCGGCTGCTTCCCAGCTGAATGT	Cloning gMat2b
gMat2b 3.1	AAACACATTGAGCTGGGAAGCAGCC	
gFam21 5.1	CACCGATTATGCAGACGACAATGTG	Cloning gFam21
gFam21 3.1	AAACCACATTGTCGTCTGCATAATC	
gRik 5.1	CACCGCTGGCAGACGGAATAACCTA	Cloning gRik
gRik 3.1	AAACTAGGTTATTCCGTCTGCCAGC	
gObsl1 5.1	CACCGTGTATGTGAGACCCGAGATG	Cloning gObsl1
gObsl1 3.1	AAACCATCTCGGTTCTCACATACAC	
gSema4d 5.1	CACCGGGCTGGATTGAGGACATGAG	Cloning gSema4d
gSema4d 3.1	AAACCTCATGTCTGAATCCAGCCC	
gCcdc18 5.1	CACCGAAAGGAGCACAGTTTACAAG	Cloning gCcdc18
gCcdc18 3.1	AAACCTTGAAACTGTGCTCCTTTC	
gNfkbil1 5.1	CACCGAGTGGCAGGAGGTCATCGGG	Cloning gNfkbil1

gNfkbil1 3.1	AAACCCCGATGACCTCCTGCCACTC	
gZbtb14 5.1	CACCGTTGCCGTCTCTTGACTCGG	Cloning gZbtb14
gZbtb14 3.1	AAACCCGAGTCAAGAGGACGGCAAC	
gMup14 5.1	CACCGCTTCTGCATGGACACACT	Cloning gMup14
gMup14 3.1	AAACAGTGTGTGCCATGCAGAAGC	
gArtn 5.1	CACCGAGGGCTAGAACAGCTAGGGT	Cloning gArtn
gArtn 3.1	AAACACCCTAGCTGTTCTAGCCCTC	
gLrrc8c 5.1	CACCGTGGTTGACAAATCTGCTGCG	Cloning gLrrc8c
gLrrc8c 3.1	AAACCGCAGCAGATTTGTCAACCAC	
gAtm 5.1	CACCGTAAGTCATATAGGAAGCCGA	Cloning gAtm
gAtm 3.1	AAACTCGGCTTCTATATGACTTAC	
gSlc9a3 sg-1 5.1	CACCGCTTCATAGTGTAGCGCACAG	Cloning gSlc9a3 sg-1
gSlc9a3 sg-1 3.1	AAACCTGTGCGCTACACTATGAAGC	
gSlc9a3 sg-2 5.1	CACCGCATAGTGTAGCGCACAGTGG	Cloning gSlc9a3 sg-2
gSlc9a3 sg-2 3.1	AAACCCACTGTGCGCTACACTATGC	
gTrp53 svg 5.1	TGCCGAACAGGTGGAATATC	Amplify Trp53 locus for Surveyor
gTrp53 svg 3.1	CATCCTGACTGTGTGAACTAGGCCCC	
gp19Arf svg 5.1	CACCGGGGCCGCCCACTCCAAGAGA	Amplify Cdkn2a locus for Surveyor
gp19Arf svg 3.1	AAACTCTCTTGAGTGGGCGGCCCC	
gKansl2 svg 5.1	CGGATACTGGGTAAGGATCC	Amplify Kansl2 locus for Surveyor
gKansl2 svg 3.1	TAAGGGCAAGACTCAGTTCC	
glzumo2 svg 5.1	GTGAGGTCACAAAGTCCCCA	Amplify Izumo2 locus for Surveyor
glzumo2 svg 3.1	TTCTCCCTCTCAACCCCTTC	
gSlmap svg 5.1	AGGCAGTAGACTAGGTGTGA	Amplify Slmap locus for Surveyor
gSlmap svg 3.1	CCTACATTAACACCACAGGC	
gFbxw7 svg 5.1	CCCTGAGAGTAGCAAGCGAA	Amplify Fbxw7 locus for Surveyor
gFbxw7 svg 3.1	TCTTCTGTACTCCCACCCTG	
gFilip1 svg 5.1	ACTGTGATGCTGGTGGACGA	Amplify Filip1 locus for Surveyor
gFilip1 svg 3.1	TTGCCTTATCCTGCTCGGTT	
gFbxo42 svg 5.1	GGCCATTGTGGCACTGTTGT	Amplify Fbxo42 locus for Surveyor
gFbxo42 svg 3.1	CCAGACACAGACTGGGTTCT	
Man2b1 svg 5.1	ACCTATTGGATTCTGTGGG	Amplify Man2b1 locus for Surveyor
Man2b1 svg 3.1	ACCAGTGCTTCCAGCTGGTT	
gCdkn2b svg 5.1	TAAGCCATTTCTCCGCCCTT	Amplify Cdkn2b locus for Surveyor
gCdkn2b svg 3.1	AACCCGCAGTCAATCTCCAG	
gMat2b svg 5.1	CCCAGTTCTTTAGACAGAGG	Amplify Mat2b locus for Surveyor
gMat2b svg 3.1	CTCCAAGGACCCACATGAAT	
gFam21 svg 5.1	CAGGGCTTTAAATCCCTGTA	Amplify Fam21 locus for Surveyor
gFam21 svg 3.1	CAAGAACCAATCTATCCACC	
gRik svg 5.1	GCTCCTCCCTGCTTCTAAA	

gRik svg 3.1	TCAGGCACATAGTCAGCTTC	Amplify 4930452B06Rik locus for Surveyor
gObsl1 svg 5.1	TGTATTGGAGAGGCAGGGAG	Amplify Obsl1 locus for Surveyor
gObsl1 svg 3.1	CACCGGAAGCTCTGCACAAA	
gSema4d svg 5.1	CCTGAGTCCTCCTTACACTT	Amplify Sema4d locus for Surveyor
gSema4d svg 3.1	GCGTGACACTTGACTTCTGT	
gCcdc18 svg 5.1	GCTGTGAATATACCTGTGCC	Amplify Ccdc18 locus for Surveyor
gCcdc18 svg 3.1	TGAGCAATACAGTTCAGTGG	
gNfkbil1 svg 5.1	GAGCGTTCAAACTCCACAC	Amplify Nfkbil1 locus for Surveyor
gNfkbil1 svg 3.1	AGGTTGTCGGAGAGAGGCTA	
gZbtb14 svg 5.1	AGCTAGAAGTAGACAGCTCG	Amplify Zbtb14 locus for Surveyor
gZbtb14 svg 3.1	ACTCCACTTCCTGGCCGTAA	
gArtn svg 5.1	GTGAGTCGCTGGCTTTCCTT	Amplify Artn locus for Surveyor
gArtn svg 3.1	TCACITTCGGAGGTGTGGGT	
gLrrc8c svg 5.1	CCACTGGTATGCCAAGTACT	Amplify Lrrc8c locus for Surveyor
gLrrc8c svg 3.1	ACTTTGGAAACCAGGGCACT	
gAtm svg 5.1	TCCCATGTGGAAGAAGGGCA	Amplify Atm locus for Surveyor
gAtm svg 3.1	CAAGCATCCAGCAGAGAGAA	
gSlc9a3 svg 5.1	CTAGTCTTGGAGCATGGAAG	Amplify Slc9a3 locus for Surveyor
gSlc9a3 svg 3.1	GGGAGCCTAGCTACTACTAA	

Supplementary Table S4

Top 10 genes co-mutated with *Kras* each type of cancer.

	Gene	Cytoband	Altered group	Unaltered group	Log Ratio	p-Value	q-Value	Tendency
Colon Cancer	<i>PIK3CA</i>	3q26.32	752 (24.55%)	531 (13.60%)	0.85	1.45E-31	4.87E-29	Co-occurrence
	<i>APC</i>	5q22.2	2119 (69.18%)	2230 (57.14%)	0.28	2.79E-25	7.02E-23	Co-occurrence
	<i>SMAD4</i>	18q21.2	508 (16.59%)	448 (11.48%)	0.53	5.63E-10	9.43E-08	Co-occurrence
	<i>SMAD2</i>	18q21.1	110 (3.59%)	59 (1.51%)	1.25	1.80E-08	2.58E-06	Co-occurrence
	<i>FBXW7</i>	4q31.3	394 (12.86%)	342 (8.76%)	0.55	2.31E-08	2.90E-06	Co-occurrence
	<i>AMER1</i>	Xq11.2	127 (4.15%)	77 (1.97%)	1.07	7.58E-08	8.46E-06	Co-occurrence
	<i>CTNNB1</i>	3p22.1	171 (5.58%)	166 (4.25%)	0.39	6.16E-03	0.238	Co-occurrence
	<i>TGFBR1</i>	9q22.33	29 (0.95%)	17 (0.44%)	1.12	6.98E-03	0.246	Co-occurrence
	<i>SOX9</i>	17q24.3	243 (7.93%)	253 (6.48%)	0.29	0.0111	0.3	Co-occurrence
	<i>TCF7L2</i>	10q25.2-q	198 (6.46%)	201 (5.15%)	0.33	0.0111	0.3	Co-occurrence
Non Small Cell Lung Cancer	Gene	Cytoband	Altered group	Unaltered group	Log Ratio	p-Value	q-Value	Tendency
	<i>STK11</i>	19p13.3	605 (19.25%)	595 (7.59%)	1.34	2.68E-64	1.78E-61	Co-occurrence
	<i>ATM</i>	11q22.3	359 (11.42%)	394 (5.03%)	1.18	1.42E-30	4.71E-28	Co-occurrence
	<i>RBM10</i>	Xp11.3	236 (7.51%)	290 (3.70%)	1.02	3.52E-16	9.35E-14	Co-occurrence
	<i>MAX</i>	14q23.3	49 (1.56%)	24 (0.31%)	2.35	9.04E-12	1.33E-09	Co-occurrence
	<i>KEAP1</i>	19p13.2	371 (11.80%)	603 (7.70%)	0.62	1.53E-11	2.04E-09	Co-occurrence
	<i>NKX2-1</i>	14q13.3	81 (2.58%)	73 (0.93%)	1.47	2.75E-10	3.32E-08	Co-occurrence
	<i>U2AF1</i>	21q22.3	72 (2.29%)	70 (0.89%)	1.36	2.05E-08	1.91E-06	Co-occurrence
	<i>IDH1</i>	2q34	63 (2.00%)	63 (0.80%)	1.32	2.97E-07	2.32E-05	Co-occurrence
	<i>AMER1</i>	Xq11.2	76 (2.42%)	87 (1.11%)	1.12	7.02E-07	4.66E-05	Co-occurrence
<i>NTRK3</i>	15q25.3	167 (5.31%)	268 (3.42%)	0.64	4.77E-06	3.02E-04	Co-occurrence	
Pancreatic Cancer	Gene	Cytoband	Altered group	Unaltered group	Log Ratio	p-Value	q-Value	Tendency
	<i>TP53</i>	17p13.1	1398 (73.93%)	127 (18.76%)	1.98	4.17E-142	3.77E-139	Co-occurrence
	<i>CDKN2A</i>	9p21.3	415 (21.95%)	25 (3.69%)	2.57	6.81E-34	2.05E-31	Co-occurrence
	<i>SMAD4</i>	18q21.2	415 (21.95%)	56 (8.27%)	1.41	3.58E-17	5.40E-15	Co-occurrence
	<i>KDM6A</i>	Xp11.3	80 (4.23%)	9 (1.33%)	1.67	1.04E-04	7.24E-03	Co-occurrence
	<i>RNF43</i>	17q22	99 (5.24%)	14 (2.07%)	1.34	1.83E-04	0.0118	Co-occurrence
	<i>RBM10</i>	Xp11.3	35 (1.85%)	2 (0.30%)	2.65	1.13E-03	0.0513	Co-occurrence
	<i>TGFBR2</i>	3p24.1	48 (2.54%)	5 (0.74%)	1.78	1.91E-03	0.0695	Co-occurrence
	<i>U2AF1</i>	21q22.3	24 (1.27%)	1 (0.15%)	3.1	4.59E-03	0.143	Co-occurrence
	<i>AKT3</i>	1q43-q44	16 (0.85%)	0 (0.00%)	>10	7.35E-03	0.195	Co-occurrence
<i>SMAD3</i>	15q22.33	32 (1.69%)	3 (0.44%)	1.93	8.37E-03	0.21	Co-occurrence	
Soft Tissue Sarcoma	Gene	Cytoband	Altered group	Unaltered group	Log Ratio	p-Value	q-Value	Tendency
	<i>PIK3CA</i>	3q26.32	7 (21.21%)	69 (3.29%)	2.69	1.12E-04	0.111	Co-occurrence
	<i>KDM5A</i>	12p13.33	4 (12.12%)	19 (0.91%)	3.74	3.43E-04	0.17	Co-occurrence
	<i>SMO</i>	7q32.1	3 (9.09%)	13 (0.62%)	3.88	1.65E-03	0.391	Co-occurrence
	<i>POLE</i>	12q24.33	4 (12.12%)	32 (1.52%)	2.99	1.98E-03	0.391	Co-occurrence
	<i>PARP1</i>	1q42.12	2 (6.06%)	3 (0.14%)	5.41	2.26E-03	0.391	Co-occurrence
	<i>CSF1R</i>	5q32	3 (9.09%)	16 (0.76%)	3.58	2.77E-03	0.391	Co-occurrence
	<i>NTRK2</i>	9q21.33	3 (9.09%)	16 (0.76%)	3.58	2.77E-03	0.391	Co-occurrence
	<i>CHEK1</i>	11q24.2	2 (6.06%)	4 (0.19%)	4.99	3.35E-03	0.415	Co-occurrence
	<i>NOTCH2</i>	1p12	4 (12.12%)	42 (2.00%)	2.6	4.91E-03	0.54	Co-occurrence
<i>PIK3CD</i>	1p36.22	2 (6.06%)	6 (0.29%)	4.41	6.14E-03	0.608	Co-occurrence	
All four cancer types combined	Gene	Cytoband	Altered group	Unaltered group	Log Ratio	p-Value	q-Value	Tendency
	<i>SMAD4</i>	18q21.2	1018 (12.52%)	771 (5.31%)	1.24	2.42E-79	1.52E-76	Co-occurrence
	<i>APC</i>	5q22.2	2313 (28.45%)	2687 (18.51%)	0.62	1.01E-65	4.76E-63	Co-occurrence
	<i>STK11</i>	19p13.3	679 (8.35%)	662 (4.56%)	0.87	4.27E-30	1.34E-27	Co-occurrence
	<i>CDKN2A</i>	9p21.3	655 (8.06%)	638 (4.40%)	0.87	4.17E-29	1.12E-26	Co-occurrence
	<i>PIK3CA</i>	3q26.32	992 (12.20%)	1152 (7.94%)	0.62	2.35E-25	5.53E-23	Co-occurrence
	<i>ATM</i>	11q22.3	671 (8.25%)	758 (5.22%)	0.66	5.36E-19	1.01E-16	Co-occurrence
	<i>AMER1</i>	Xq11.2	216 (2.66%)	179 (1.23%)	1.11	1.32E-14	2.07E-12	Co-occurrence
	<i>FBXW7</i>	4q31.3	467 (5.74%)	527 (3.63%)	0.66	1.52E-13	2.04E-11	Co-occurrence
	<i>SMAD3</i>	15q22.33	103 (1.27%)	76 (0.52%)	1.27	2.72E-09	2.70E-07	Co-occurrence
<i>TGFBR1</i>	9q22.33	83 (1.02%)	57 (0.39%)	1.38	1.41E-08	1.26E-06	Co-occurrence	