

## STAR Methods

### KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
anti-p53	DAKO	DO-7
anti-Smad4	Santa Cruz Biotech	sc-7966
anti-Actin	Cell Signaling	4970
anti-BRCA2	Merck	OP95
anti-ARID1a	Novusbio	NBPI-88932
anti-mouse IgG-HRP	Merck	401253
anit-rabbit IgG-HRP	Cell Signaling	7074P2
Bacterial and virus strains		
Stbl3	Zymo Research	T3002
Chemicals, peptides, and recombinant proteins		
Drug Compounds	Listed also in Table S6	
TrypLE Express	Thermo Fisher Scientific	12605010
HEPES	Thermo Fisher Scientific	15630080
Penicillin-Streptomycin	Thermo Fisher Scientific	15140122
GlutaMAX Supplement	Thermo Fisher Scientific	35050038
Matrigel, growth factor reduced	Corning	356231
BME, Path Clear	Cultrex	3533-005-02
B-27 Supplement	Thermo Fisher Scientific	17504044
[Leu15]-Gastrin I human	Tocris	3006
Recombinant Mouse EGF	Peptotech	AF10015
Fibroblast growth Factor 10	Peptotech	10026
Afamin-Wnt-3A serum-free conditioned medium	Cell line gift from H. Clevers	N/A
R-spondin-1 conditioned medium	Cell line gift from H. Clevers	N/A
Noggin conditioned medium	Cell line gift from H. Clevers	N/A
A83-01	Tocris	2939
Y-27632	AbMole	M1817
Prostaglandin E2	Tocris	2296
Nicotinamide	Sigma	N0636
Fetal bovine serum	Sigma	F7524-500ML
Cell Recovery Solution	Corning	354253
Collagenase Type II	Thermo Fisher Scientific	17101015
Puromycin	InvivoGen	ant-pr-1
Blasticidin	InvivoGen	ant-bl-5b
Advanced DMEM/F12	Thermo Fisher Scientific	12634028
DMEM, high Glucose	Thermo Fisher Scientific	31966047
RPMI 1640	Thermo Fisher Scientific	61870010
PBS	Thermo Fisher Scientific	10010015
Polyethylenimine Max	Chemie Brunschweig AG	24765-2
Polybrene	Sigma	TR-1003-G
Thrombin	Baxter	Tisseel
Human Plasma	UZH Transfusion Center	N/A
Hematoxylin	Sigma	MHS32-1L

Eosin Y	Sigma	E4009-5G
Protease Inhibitor cOmplete	Roche	DRUM4-000-050
Phosphatase Inhibitor PhosSTOP	Roche	4906837001
NuPage Sample Reducing Agent 10x	Thermo Fisher Scientific	NP0004
NuPage LDS Sample Buffer 4x	Thermo Fisher Scientific	NP0007
NuPage 3-8% Tris-Acetate Gradient Gels	Thermo Fisher Scientific	EA0375BOX
Amersham Protean NC Nitrocellulose Membrane	GE Healthcare	10738328103
BSA Fraction V	Roche	10600015
Western Bright Quantum	Advansta	K-12042-D10
DMSO	Sigma	D8418
BsmBI	NEB	R0580S
Fast SYBR Green PCR Master Mix	Thermo Fisher Scientific	4385612
GoScript Reverse Transcription System	Promega	A5000
Promega Bright-Glo Reagent	Promega	E2610
Cell Titer Glo 3D	Promega	G9618
Critical commercial assays		
RNeasy Kit	QIAGEN	51106
Dneasy Blood and Tissue Kit	QIAGEN	69506
Pierce BCA Protein Assay	Thermo Fisher Scientific	23227
Deposited data		
DNA and RNA sequencing and SNP Array data	This study	SRA, GEO
Original Western blot images	This study	<a href="https://doi.org/10.6084/m9.figshare.18407564.v1">https://doi.org/10.6084/m9.figshare.18407564.v1</a>
Experimental models: Cell lines		
Human: pancreas organoids and cell lines: see Table S1	This study	
Mouse: pancreas organoids: see Table S1	This study	
Experimental models: Organisms/strains		
Mouse: NMRI nu/nu mice	Charles River	N/A
Mouse: NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ	Jackson Laboratory	N/A
Oligonucleotides		
sgRNA_ARID1a_1	CACCgTCCTGCAGCTCCTTTCCCAG	aaacCTGGGAAAGGAGCTGCAGGAc
sgRNA_ARID1a_2	CACCgGGCCGAGCGCGGGGAAATGA	aaacTCATTTCCCCGCGCTCGGCCc
sgRNA_ARID1a_3	CACCgAAAGCGAGGGCCCCGCCGTG	aaacCACGGCGGGGCCCTCGCTTTc
sgRNA_BRCA2_1	CACCgGGGTTTCTCTTATCAACACG	aaacCGTGTTGATAAGAGAAACCCc
sgRNA_BRCA2_2	CACCgCAAAGTTAAGGGAGTGTTAG	aaacCTAACACTCCCTTAACCTTTGc
sgRNA_BRCA2_3	CACCgACGTCTAGACAAAATGTATC	aaacGATACATTTGTCTAGACGTc

qPCR Primer: ACTB	TGCGTGACATTAAGGAGAAG	TGAAGGTAGTTT CGTGGATG
qPCR Primer: BRCA2	TGCCTGAAAACCAGATGACTAT C	AGGCCAGCAAAC TTCCGTTA
qPCR Primer: TBP	TGGACTGTTCTTCACTCTTGGC	TTCGGAGAGTTC TGGGATTGT
qPCR Primer: BNIP3	CTGGGTAGAACTGCACTTCAG	GGAGCTACTTCG TCCAGATTCAT
qPCR Primer: CAIX	GCAGGAGGATTCCCCCTTG	GGAGCCTCAACA GTAGGTAGAT
qPCR Primer: GLUT1	ATTGGCTCCGGTATCGTCAAC	GCTCAGATAGGA CATCCAGGGTA
qPCR Primer: HK2	GAGCCACCACTCACCTACT	CCAGGCATTTCG CAATGTG
qPCR Primer: PKM1	GCCTGCTGTGTCCGAGAAG	CAGATGCCTTGC GGATGAATG
qPCR Primer: VEGFA	CGCAGCTACTGCCATCCAAT	TCGGCTTGTCAC ATTTTTCTTGT
qPCR Primer: ATF4	AGCACTCAGACTACGTGCACCT CT	GAAGAGTCAATA CCGCCAGAATCC
qPCR Primer: CHOP	CAGAACCAGCAGAGGTCACA	AGCTGTGCCACT TTCCTTTC
qPCR Primer: GABARAPL1	TCGGAAAAAGGAAGGAGAAA	TGGCCAACAGTA AGGTCAGA
qPCR Primer: P62	CCCGTCTACAGGTGAACTCC	CTGGGAGAGGGA CTCAATCA
sgRNA_ARID1a_1	CACCgTCCTGCAGCTCCTTTCCC AG	aaacCTGGGAAAG GAGCTGCAGGAc
Recombinant DNA		
pLenti HRE-Luc pGK Hygro	Addgene	118706
lentiCRISPR v2-Blast	Addgene	83480
Software and algorithms		
BWA mem	arXiv:1303.3997	<a href="https://github.com/lh3/bwa">https://github.com/lh3/bwa</a>
Picard Tools (MarkDuplicates)	Broad Institute	<a href="http://broadinstitute.github.io/picard/">http://broadinstitute.github.io/picard/</a>
BamClipOverlap	N/A	<a href="https://github.com/mgag/ngs-bits/blob/master/doc/tools/BamClipOverlap.md">https://github.com/mgag/ngs-bits/blob/master/doc/tools/BamClipOverlap.md</a>
GATK IndelRealigner	Broad Institute	<a href="https://software.broadinstitute.org/gatk/">https://software.broadinstitute.org/gatk/</a>
GATK Unified Genotyper	Broad Institute	<a href="https://software.broadinstitute.org/gatk/">https://software.broadinstitute.org/gatk/</a>
Bcftools caller	doi:10.1093/bioinformatics/btx100	<a href="https://samtools.github.io/bcftools/bcftools.html">https://samtools.github.io/bcftools/bcftools.html</a>
Freebayes	arXiv:1207.3907	<a href="https://github.com/freebayes/freebayes">https://github.com/freebayes/freebayes</a>
MuTect	doi:10.1038/nbt.2514	<a href="https://github.com/broadinstitute/mutect">https://github.com/broadinstitute/mutect</a>

VarScan2	doi:10.1101/gr.129684.111	<a href="https://github.com/Jeltje/varsan2">https://github.com/Jeltje/varsan2</a>
Strelka	doi:10.1093/bioinformatics/bts271	<a href="https://github.com/target/strelka">https://github.com/target/strelka</a>
Snpeff, SnpSift	doi:10.4161/fly.19695	<a href="http://pcingola.github.io/SnpEff/">http://pcingola.github.io/SnpEff/</a>
dbNSFP	doi:10.1002/humu.22376	<a href="http://database.liulab.science/dbNSFP">http://database.liulab.science/dbNSFP</a>
SeqPurge	doi:10.1186/s12859-016-1069-7	<a href="https://github.com/mgag/ngs-bits/blob/master/doc/tools/SeqPurge.md">https://github.com/mgag/ngs-bits/blob/master/doc/tools/SeqPurge.md</a>
Biceseq2	doi:10.1093/nar/gkw491	<a href="https://github.com/ding-lab/BICSEQ2">https://github.com/ding-lab/BICSEQ2</a>
Picnic	doi:10.1093/biostatistics/kxp045	<a href="https://www.sanger.ac.uk/tool/picnic/">https://www.sanger.ac.uk/tool/picnic/</a>
Cellario 3.2	HighRes Biosolutions Ltd.	<a href="http://hiresbio.s1084.sureserver.com/software/cellario-32.php">http://hiresbio.s1084.sureserver.com/software/cellario-32.php</a>
CLC Genomic Workbench 11	Qiagen Bioinformatics	<a href="https://www.qiagenbioinformatics.com/products/clc-genomics-workbench/">https://www.qiagenbioinformatics.com/products/clc-genomics-workbench/</a>
Prism 8	GraphPad	<a href="https://www.graphpad.com/scientific-software/prism/">https://www.graphpad.com/scientific-software/prism/</a>
MuSiCa	doi:10.1186/s12859-018-2234-y	<a href="http://bioinfo.ciberehd.org:3838/MuSiCa/">http://bioinfo.ciberehd.org:3838/MuSiCa/</a>