Materials

Antibodies were obtained from the following sources: CK19 (TROMA-III) from the Developmental Studies Hybridoma Bank, University of Iowa; β-actin (A5316) and anti-GLDC (HPA002318) from Sigma-Aldrich; Glut1 (ab652) from Abcam; PCNA (13110), Cleaved caspase 3 (9579), DNMT1 (5032), DNMT3A (2160), histone H3 (4499), histone 3 trimethyl-lysine 4 (9727), histone 3 trimethyl-lysine 27 (9733) and histone 3 trimethyl-lysine 36 (4909) from Cell Signaling Technology; 5-methylcytosine 33D3 (MABE146) and 5-hydroxymethylcytosine HMC-MA01 (MABE317) from Millipore. Laminin (23017-95), 2NBDG (N13195), DCFDA (C6827), CellROX Green (C10444), CyQuant NF (C35006), bovine pituitary extract (13038-14), HBSS, RPMI, DMEM, DMEM:F12, MEM penicillin-streptomycin, pyruvate solution, fetal bovine serum (FBS) Alexa 488 and 568-conjugated secondary antibodies from Life Technologies; nicotinamide (N3376), trypsin inhibitor (T6522), dexamethasone (D4902), S-adenosylmethionine (A2408), 3,3,5-tri-iodo-L-thyronine (91990), oligomycin (75351), antimycin A (A8674), 2-deoxyglucose (D6134), dichloroacetate (347795), collagenase (C7657), glucose (G7528), aminooxyacetate (C13408), N-acetylcysteine (A9165), adenosine (A4036), guanosine (G6264), thymidine (T1895), uridine (U3003), cytidine (C4654), cycloleucine (A48105), cholera toxin (C8052), L-serine (S4500), betaine (61962), dimethylglycine (D1156), tamoxifen (T5148) and methylene blue (M4159) from Sigma; FCCP (0453), decitabine (2624), RG108 (3295), EGCG (4524), Compound C (3093), Torin 1 (4247) and galloflavin (4795) from Tocris; mouse EGF (354001), NuSerum IV (355104), ITS+ Premix (354352) and matrigel (354234) from Corning; SGI1027 (S7276) from Selleckchem; caspase-Glo 3/7 kit (G811A) and Celltiter-Glo kit (G755B) from Promega; ^{13}C-U-Glucose (CLM-1396-1) and ^{15}N-Glutamine (NLM-1016-1) from Cambridge Isotope Laboratories Inc; dispase (165-859) from Roche; lactate assay kit (K607-100) from Biovision Inc; Vectashield with DAPI (H1500) from Vector Laboratories; Bridge-IT SAM

assay kit (1-1-1003B) from Medionics; meDIP kit (55009) from Active Motif; 3DZA (9000785) from Cayman Chemicals; Adeno-FlpO (1760) from Vector Biolabs; Adeno-Cre-eGFP from the Viral Vector Core Facility, University of Iowa.

Genetically engineered mouse models

Mice were housed in pathogen-free animal facilities at Massachusetts General Hospital (MGH). All experiments were conducted under protocol 2005N000148, approved by the Subcommittee on Research Animal Care at MGH. The following mouse strains were used: LSL $KRAS^{G12D/+}$ [1], FSF $KRAS^{G12D/+}$ (Jackson Laboratory, strain #023590), $LKB1^{L/L}$ [2], Sox9-Cre^{ER} [3]. Mice were maintained on a mixed genetic background and each genotype was generated from intercrosses from the same colony. The Sox9-CreER transgene deletes floxed sequences in pancreatic ductal cells following treatment with tamoxifen. To activate Cre^{ER}, 8 week-old mice were injected intraperitoneally with 100 mg/kg tamoxifen dissolved in corn oil every other day for 6 days. Mice were euthanized when criteria for disease burden were reached (including abdominal distension that impeded movement, loss of >15% of body weight, labored breathing, and/or abnormal posture). Both male and female animals were used for these experiments.

Cell Culture

Primary pancreatic ductal epithelial cells were isolated from two LSL-$KRAS^{G12D/+}$, two LSL-$KRAS^{G12D/+}$;$LKB1^{L/L}$ or three FRT-$KRAS^{G12D/+}$;$LKB1^{L/L}$ mice as previously described[4] with modifications. In brief, mice were euthanized and the pancreata were rapidly collected, followed by microscopy-assisted removal of the bile duct. Tissues were washed once in PBS, suspended in 3-5 ml of 2 mg/ml collagenase in DMEM:F12 (filter sterilized) and incubated at 37°C for 15 min with rigorous agitation. 7-10 ml of PBS was added to each tube, the homogenate was left to settle for 5 min at room temperature and

the supernatant containing mainly acinar cells was discarded. The remaining tissue was transferred in 6 cm plates, mechanically dissociated with blades/scissors, transferred to a new tube, suspended in 2 ml freshly prepared dispase solution (4 mg/ml in PBS, filter sterilized) and incubated at 37°C for 8-10 min with agitation. Dispase was inactivated by addition of 10 ml G solution (sterile HBSS, 0.9 µg/L Glucose, 1X Pen/Strep). To capture the largely intact ductal structures and clear dissociated acinar cells, homogenate was filtered through a 100 µm strainer that retained only the ducts. After washing with G solution, ducts were recovered by inverting the strainer and washing it with 50 ml G solution followed by gently pelleting by centrifugation at 1000 rpm for 1 min. Supernatant was aspirated and ducts were washed twice more with 50 ml G solution each time. After the last wash, pellet was suspended in 2 ml trypsin, incubated for 5 min at room temperature then trypsin was inactivated by addition of 10 ml DMEM+10% FBS+1X Pen/Strep. Cells were collected by centrifugation, washed twice in ductal media (DMEM:F12, 5 mg/ml Glucose, 1.22 mg/ml nicotinamide, 5 nM 3,3,5-tri-iodo-L-thyronine, 1 µM Dexamethasone, 100 ng/ml cholera toxin, 5 ml/L ITS+, 1X Pen/Strep, 0.1 mg/ml trypsin inhibitor, 20 ng/ml mouse EGF, 5% NuSerum IV and 25 µg/ml bovine pituitary extract) and plated. To activate KRAS and/or delete LKB1 in the LSL-$KRAS^{G12D/+}$ and LSL-$KRAS^{G12D/+}$;$LKB1^{L/L}$ cells, cultures were infected with Ad-CreGFP (1-5x10^6 pfu/ml) leading to K and KL cells (Extended Data Figure 1A). Alternatively, in order to generate all four genotypes (WT, K, L, KL), FRT-$KRAS^{G12D/+}$;$LKB1^{L/L}$ primary ductal cells were infected with Adeno-Cre-eGFP and/or Adeno-FlpO to delete LKB1 or activate $KRAS^{G12D}$ respectively, while uninfected cells were used as WT (Extended Data Figure 1A). All pancreatic ductal epithelial cells were routinely maintained in ductal media on laminin-coated plates. KPC and KIC cells murine pancreatic cancer cells were derived from the Pdx1-Cre;$KRAS^{G12D/+}$;$p53^{Lox/+}$;$p16^{+/-}$ and Pdx1-Cre;$KRAS^{G12D/+}$;$CDKN2A^{Lox/+}$ GEMM, respectively[5]. Human cancer cell lines were obtained from the American Type Culture

Collection (PANC1, YAPC, 8988T), the Korean Cell Line Bank (SNU324), and Dr. Paul Chiao from MD Anderson Cancer Center (COLO357), and cultured in the following media: PANC1, YAPC, 8988T in DMEM supplemented with 10% FBS; COLO357, SNU324 in RPMI with 10% FBS. Status of LKB1 gene was validated by genomic sequencing and western blot analysis. Negative mycoplasma contamination status of all cancer cell lines and primary cells used in the study was established using LookOut Mycoplasma PCR Kit (Sigma, MP0035). STR profiling of all human cell lines was done at the Center for Molecular Therapeutics at Massachusetts General Hospital.

Cell proliferation, IC50 determination, and caspase 3/7 activity assays

For growth assays, cells were plated at a density of 1000 cells per well in black 96-well plates, using 3-4 replicates per time point and/or condition, and allowed to attach overnight. Cell growth was assessed by DNA content measurement using the Cyquant NF kit according to the manufacturer's instructions. Day 0 was considered the day after the initial seeding. For the inhibitor studies, the concentration used in each case was as follows: 5 mM 2-deoxyglucose, 5 mM dichloroacetate, 20 μM galloflavin, 250 μM aminooxyacetate, 1 mM N-acetyl-cysteine, 10 μM 3-deazaadenosine, 2 mM cycloleucine, 0.1-10 μM decitabine, 100 μM RG108, 25 μM SGI1027, 10 μM EGCG, 5 μM Compound C, 25 nM Torin. Inhibitor or vehicle in fresh media was administered at day 0 and replenished every 3 days except in the case of decitabine, which was replenished daily due to stability issues. For testing serine dependence, ductal cells were cultured in MEM-based ductal media, with or without 0.4 mM L-serine supplementation. For glucose restriction studies, ductal cells were cultured in modified ductal media based on DMEM without glucose, glutamine or pyruvate. For assessing the ability of metabolites to rescue shPSAT1-induced growth inhibition, duct-media was supplemented with 100 μM S-adenosyl-methionine, 1 mM betaine, 1 mM

dimethylglycine, or 1 mM nucleoside mixture (1 mM each of adenosine, guanosine, thymidine, cytidine and uridine). Soft agar assays were performed as previously described[6]. For IC50 determination, cells were treated with 0.0015-30 μM decitabine or 0.076-500 nM Torin for 4 days. Apoptosis was measured using the Caspase-Glo 3/7 Assay kit according to the manufacturer's instructions.

Metabolic measurements

For ATP measurements, cells were plated at a density of 10,000 cells per well in white 96-well plates at 3-4 replicates per condition, and allowed to attach overnight. Media were changed next day and ATP was measured 24 hrs later using the CellTiter Glo kit according the manufacturer's instructions. Luminescence was normalized to number of cells as measured by DNA content using CyQuant NF. Lactate was measured using the Lactate Colorimetric/Fluorimetric Assay Kit according to the manufacturer's instructions. Fluorescence was normalized to number of cells as measured by DNA content using CyQuant NF. For glucose uptake, 400,000 cells were treated with 100 μM 2-(*N*-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)Amino)-2-Deoxyglucose (2NBDG) for 30 min. Cells were then trypsinized and single-cell suspensions were analyzed by flow cytometry. Due to differences in endogenous fluorescence between genotypes under the conditions of the experiment, 2NBDG mediated fluorescence was normalized to that of unlabeled cells. S-adenosyl-methionine levels were measured using the Bridge-IT SAM Fluorescence kit according to the manufacturer's instructions. For reactive oxygen species analysis, cells were plated at a density of 10,000 cells per well in black 96-well plates at 3-4 replicates per condition, and allowed to attach overnight. Media were changed next day and ROS levels were measured 24 hrs later using DCFDA or CellROX staining according the manufacturer's instructions. Oxygen consumption rates were measured in an XF24 Analyzer (Seahorse). In brief, cells were plated in 96-well Seahorse plates at a density of

40,000 cells per well in duct media and were allowed to attach overnight. Media was replenished one hour prior to assay time. The sequential ports of the Seahorse cartridge were loaded with the following: port A, oligomycin, port B, 2-2-[4-(trfluoromethoxy) phenyl]hydrazinylidene]-propanedinitrile (FCCP), port C, antimycin A, each diluted in media. The final concentration of the inhibitors was 4 μM. Oxygen consumption rates were monitored in real time after injection using the XFe Analyzer (Seahorse). For normalization, equal numbers of cells were plated in black 96-well plates and cell numbers were assessed by CyQuant NF.

Quantitative RT-PCR

Total cellular RNA was extracted using RNeasy Mini Kit (Qiagen). Genomic DNA decontamination and reverse transcription were performed in two steps from 1 μg of total RNA using the QuantiTect Reverse Transcription Kit (Qiagen, #205310) according to the manufacturer's instructions. To test the effectiveness of the gDNA decontamination step, no-reverse-transcriptase control samples were included. Quantitative RT-PCR was performed with FastStart Universal SYBR Green (Roche) in a Lightcycler 480 (Roche). PCR reactions were performed in triplicate and the relative amount of cDNA was calculated by the comparative CT method using the 18S ribosomal RNA sequences as a control. Primer sequences:

MMU-PSAT1-F	TTAGCACCATGGAAGCCACC
MMU-PSAT1-R	TGCCGAGTCCTCTGTAGTCT
MMU-DNMT1-F	GTCGGACAGTGACACCCTTT
MMU-DNMT1-R	TTCGTGAAGTGAGCCGTGAT
MMU-DNMT3A-F	GTCATGGGAGGTTCCCTGTG

MMU-DNMT3A-R	ATTAGCACCAGCTTGGGACC
MMU-PSPH-F	AACTGGTTCTCCCGTCATCG
MMU-PSPH-R	CTCTTAAAAGCGCCGAACCG
MMU-PGK1_F	TACCTTGCCTGTTGACTT
MMU-PGK1_R	TGTCTCCACCACCTATGA
MMU-HK2_F	CCAGCTGTTTGACCACATT
MMU-HK2_R	TCATTCACCACAGCCACA
MMU-PDK1-F	ATCCGTACAGCTGGTGCAAA
MMU-PDK1-R	ACCCCGAAGCTCTCCTTGTA
MMU-LDHA-F	TGCACTAGCGGTCTCAAAAGA
MMU-LDHA-R	TCCATGACGTCAACAAGGGC
MMU-GLDC-F	GTGCAAGAGGGTATGTGGCT
MMU-GLDC-R	GACATGGTAGGGGCGTGAAA
MMU-SHMT1-F	GGAACAGACGTTTACGGCCA
MMU-SHMT1-R	GTCTGCCATTGCACTGGTTC
MMU-SHMT2-F	ACCCCGGTACTACACCGATA
MMU-SHMT2-R	AGACCAGCTGACCACATCTC
HSA-PSAT1-F	CAGTTCAGTGCTGTCCCCTT
HSA-PSAT1-R	CCAAGCTCCTGTCACCACAT
MMU-LINE1-1-F	GTTCCGGGACTCCGACAAAA
MMU-LINE1-1-R	AAAAGGGTGCTGCCTCAGAA
MMU-LINE1-2-F	TCTGGGGTGAGCTAGAACCT
MMU-LINE1-2-R	AGAAGCTCTGTGGCTCTTGC

18S-F	GTAACCCGTTGAACCCCATT
18S-R	CCATCCAATCGGTAGTAGCG

SDS-PAGE analysis

Cells were lysed in ice-cold lysis buffer (150 mM NaCl, 20 mM Tris (pH 7.5), 1 mM EDTA, 1 mM EGTA, 1% Triton X-100, 1% sodium deoxycholate, one tablet of EDTA-free protease inhibitors [Roche] per 10 ml). Samples were clarified by centrifugation and protein content measured using BCA protein assay kit (Thermo Scientific). 10 µg protein was resolved on 8-15% SDS-PAGE gels and transferred onto PVDF membranes (GE Healthcare Life Sciences, Pittsburgh, PA). Membranes were blocked in Tris-buffered saline (TBS) containing 5% non-fat dry milk and 0.1% Tween 20 (TBS-T), prior to incubation with primary antibody overnight at 4°C. The membranes were then washed with TBS-T followed by exposure to the appropriate horseradish peroxidase-conjugated secondary antibody for 45 min and visualized on Kodak X-ray film using the enhanced chemiluminescence (ECL) detection system (Thermo Scientific).

Methylated DNA immunoprecipitation (meDIP-PCR)

5-methylcytosine-enriched DNA was purified using the MeDIP assay kit (Active Motif) according to the manufacturer's instructions. The recovered methylated DNA was quantified by real-time PCR using input DNA for normalization. The primers used for the PCR step are as follows:

MMU-LINE1-1-F	GTTCCGGGACTCCGACAAAA
MMU-LINE1-1-R	AAAAGGGTGCTGCCTCAGAA
MMU-LINE1-2-F	TCTGGGGTGAGCTAGAACCT
MMU-LINE1-2-R	AGAAGCTCTGTGGCTCTTGC

18S-F	GTAACCCGTTGAACCCCATT
18S-R	CCATCCAATCGGTAGTAGCG

Xenograft studies

For subcutaneous xenografts, 5 x 10^5 cells were suspended in a 1:1 mixture of media:matrigel, and injected subcutaneously into the lower flank of NOD.CB17-Prkdcscid/J mice (6-10 weeks of age) (purchased from Jackson Laboratories, strain #001303). Tumor size was assessed at indicated time points by caliper measurements of length and width and the volume was calculated according to the formula (length × width^2/2). For the decitabine treatment studies, tumours were allowed to grow to ~125 mm^3, then mice were randomized into two groups and each group treated intraperitoneally with either decitabine (1 mg/kg in PBS) or vehicle (PBS) three times per week until mice in the vehicle-treated group had to be sacrificed. No mice were excluded from the analysis. For the shDNMT studies, tumors were allowed to grow to ~50 mm^3, then mice were randomized into two groups and doxycycline (200 mg/L) added to the water of one of the groups. Water was changed every 3 days. For volume-measurement-experiments were designed to detect a 50% change in tumor size with 80% power and a type I error of 5% using the T-test. All experiments were conducted under protocol 2005N000148 approved by the Subcommittee on Research Animal Care at Massachusetts General Hospital and no tumours exceeded the size allowed by it. Mice were housed in pathogen-free animal facilities. Both male and female animals were used for these experiments.

Statistics

In all cases, results are expressed as mean ± standard deviation, unless otherwise specified. Significance was analyzed using 2-tailed Student's *t* test, except in the case of Extended Data Figure 8l and m in which the χ^2 test was used. Equal variance was assumed and the assumption was not contradicted by the data. A p value of less than 0.05 was considered statistically significant. No samples or animals were excluded from analysis and sample size estimates were only used in xenograft experiments (see section Xenograft studies). Histology evaluation was done on a blind fashion. Tumour size measurements were not blinded.

Dot blot analysis

Genomic DNA was isolated with the Blood and Tissue DNA isolation kit (Qiagen) and sheared by passing 20 times through a 28G1/2 U-100 Insulin Syringe (Becton Dickinson). Two-fold serial dilutions of the prepared DNA were prepared in TE and they denatured in 0.4 M NaOH/10 mM EDTA at 95 °C for 10 min, followed by neutralization with an equal volume of cold 2M ammonium acetate (pH 7.0). Denatured DNA samples were spotted on a nitrocellulose membrane using an assembled Bio-Dot apparatus (Bio-Rad) or a PR648 Slot blot manifold (GE Healthcare Life Sciences) according to the manufacturers' instructions. The membrane was washed with 2 × SSC buffer and DNA was ultraviolet-crosslinked for 10 min. Then the membrane was blocked with 5% non-fat milk for 1 h and incubated with anti-5mC antibody overnight. Detection was carried out with HRP-conjugated secondary antibodies and enhanced chemiluminescence reagents (Thermo Scientific). The membrane was subsequently stained with methylene blue to confirm corresponding amounts of DNA for each sample. Densitometry was performed using ImageJ (NIH).

Expression and hairpin constructs

Full length wild type or kinase dead (K78I)[7] LKB1/STK11 protein was expressed from a pMSCV vector (blastocidin resistance). Human PSAT1 that is not targeted by hairpins against mouse PSAT1 was obtained from Harvard PlasmidID Database (HsCD00414859). shRNAs were obtained from The Molecular Profiling Laboratory (MPL) at Massachusetts General Hospital Cancer Center in partnership with the RNAi Consortium and have the following IDs: mouse PSAT1 TRCN0000346654 (CCATCAGTCCTTGACTACAAA), TRCN0000346659 (ACACTCGGTATTGTTGGAGAT), human PSAT1 TRCN0000035265 (CCAGACAACTATAAGGTGATT), TRCN0000035266 (GCACTCAGTGTTGTTAGAGAT), mouse AMKPa1 TRCN0000220674 (CGTAGTATTGATGATGAGATT), mouse AMPKa2 TRCN0000220717 (CGCCAGTCTTATCACTGCTTT), mouse DNMT1 TRCN0000039024 (GCTGACACTAAGCTGTTTGTA), TRCN0000039027 (CCCGAAGATCAACTCACCAAA) and mouse DNMT3A TRCN0000231273 (CTGCTACATGTGCGGGCATAA) and TRCN0000231275 (ACCACCAGGTCAAACTCTATA). A hairpin against GFP was used as control. Tet-inducible vectors expressing the DNMT1 and DNMT3A hairpins were obtained by annealing oligos corresponding to the constitutive hairpins and cloning them in the Age I/EcoRI site of the pLKO.1 tet-on vector as previously described[8].

Immunofluorescence and Immunohistochemistry

Cells were plated on poly-D-lysine/laminin coated 8-well culture slides (354688, BD Biosciences) at 40,000 cells/well. 12-16 hours later, the slides were rinsed with PBS once and fixed for 15 min with 4% paraformaldehyde at RT or for 5 min with -20 °C methanol. The slides were rinsed twice with PBS and cells were permeabilized with 0.05% Triton X-100 for 2 min or with 4N HCl for 5mC staining. HCl treated cells were

neutralized with 100 mM Tris-HCl pH 8.5 for 10 min in RT. After washing twice with PBS, the slides were incubated with primary antibody in 5% normal goat serum for 1hr at room temperature, rinsed four times with PBS, and incubated with secondary antibody produced in goat (diluted 1:400 in 5% normal goat serum) for 45 min at room temperature in the dark. Slides were mounted on glass slides using Vectashield (See Materials section) and imaged on Nikon ECLIPSE Ni microscope. Tissue samples were fixed overnight in 4% buffered formaldehyde, and then embedded in paraffin and sectioned (5 μm thickness) by the DF/HCC Research Pathology Core. Haematoxylin and eosin staining was performed using standard methods and stained slides were photographed with an Olympus DP72 microscope. For fluorescent immunohistochemistry, unstained slides were baked at 55 °C, deparaffinized in xylene (two treatments, 6 min each), rehydrated sequentially in ethanol (5 min in 100%, 3 min in 95%, 3 min in 75%, and 3 min 40%), and washed for 5 min in 0.3% Triton X-100/PBS (PBST) and 3 min in water. Endogenous peroxidase activity was blocked by incubating deparaffinized tissue sections with 3% Hydrogen Peroxide (20 min; Fisher Scientific), rinsed twice with water (3 min) and antigen retrieval was performed by boiling in 10 mM sodium citrate buffer (20 min, 95°C, pH 6). Sections were blocked 1 hour in TBS-0.05 % Tween 20-10% Normal Goat Serum (5425, Cell Signaling), and incubated overnight at 4°C with primary antibody. Primary antibodies were diluted in blocking solution as follows: PCNA (1:10,000), Cleaved Caspase 3 (1:150), CK19 (1:50). Specimens were then washed three times for 3 min each in PBST and incubated with fluorescent secondary antibodies produced in goat (diluted 1:400 in 5% normal goat serum) for 45 min at room temperature in the dark. Slides were mounted on glass slides using Vectashield (Vector Laboratories) and imaged on a Nikon ECLIPSE Ni microscope. For PCNA staining, fluorescent signal was amplified using the Tyramide Signal Amplification kit (Perkin Elmer) according to the manufacturer's instructions. Images were processed

using ImageJ software. For quantification of proliferation in tumor slides only the epithelial compartment was considered (CK19 positive). 4-6 fields containing 700-1500 cells per field from 4 different tumors in each case were analyzed. For quantitation of cleaved caspase 3 staining, 3-5 fields containing 500-1500 cells per field from 4 different tumours were analyzed. Apoptotic levels were calculated as the ratio of cleaved caspase 3 intensity to DAPI. For 5mC immunofluorescence staining deparafinized TMA slides were permeabilized with 4 N HCl for 1hr at 37°C followed by neutralization with 100mM Tris-HCl pH 8.5 for 10min at RT. Washes, primary and secondary antibody were applied as described above). Slides were mounted using Vectashield without DAPI. For 5mC immunofluorescence 77-889 cells per condition were analyzed. Image analysis was performed using ImageJ (NIH).

Gene Expression Profiling

RNA-sequencing was performed using total RNA isolated in duplicates from 2 independent cell lines from K or KL genotypes or from the two independent KL lines transduced with full length LKB1 cDNA (rescue). RNAseq library-preparation and sequencing were performed by the Tufts University Genomics Core Facility. Data was processed using a standard RNA-seq pipeline that used Tophat2[9] to align the reads to mm9, and the Cufflinks suite[10] to calculate differential expression. Gene Set Enrichment Analysis (GSEA) (http://www.broadinstitute.org/gsea/index.jsp) of the expression data was used to assess enrichment of the KEGG as well as the SGOC geneset[11-13]. In all cases, pairwise GSEA was performed by creating ranked lists of genes using the log2 ratio of K to KL or KL to rescue and p-values were obtained by permuting the gene set (1000 permutations). Raw sequencing files can be found under the Superseries record GSE86145 (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE86145).

^{13}C-Glucose and ^{15}N-Glutamine tracing

Cells were plated in 10 cm plates at a density of 10^6 cells/plate and allowed to attach overnight. Next day, they were washed with PBS to remove traces of unlabeled metabolites, then overlayed with ductal media based on DMEM without glucose, pyruvate or glutamine, supplemented with 25 mM regular of ^{13}C-glucose, 2 mM regular or ^{15}N-glutamine and 2 mM pyruvate. At the indicated time points, cells were washed three times with ice cold 0.9% NaCl, then collected by scraping in 50% methanol. After 30 sec vortexing, samples were pelleted and the clarified supernatant was transferred to a new tube. Protein was removed by chloroform extraction. The purified aqueous phase was dried under vacuum. Dessicated metabolites were derivatized as previously described[14]. In brief, samples were dissolved in 30 µl of 2% methoxyamine hydrochloride in pyridine (MOX, Pierce) and incubated at 37°C for 1.5 hrs. Further derivatization was achieved by addition of 45 µl of *N*-Methyl-*N*-*tert*-butyldimethylsilyltrifluoroacetamide (MTBSTFA + 1% TBDMSCl, 375934 Sigma) followed by vigorous mixing and incubation at 55°C for 1 hr. Samples were then pulse spun to remove insoluble material. Clarified solutions were transferred to inserts set in brown glass vials and capped prior to being loaded onto the column. Analysis was performed on an Agilent 6890 GC instrument. Samples were loaded onto a 30 m DB-35MS capillary column using helium as the carrier gas that was interfaced to an Agilent 5975B MS. Electron impact (EI) ionization was set at 70 eV. Each sample was injected at 270°C at a flow rate of 1 ml/min. To mobilize metabolites, the GC oven temperature was held at 100°C for 3 min and increased to 300°C at 3.5°C/min for a total run time of approximately 1 hr. For intracellular metabolites, 1 µl of each sample was injected in splitless mode. All analyses were operated in full scan mode while recording a mass to charge ratio (Δm/z) spectra in the range of 100-650 m/z. Specific metabolite Δm/z analyzed are available upon request. Fractional enrichments of ^{13}C and ^{15}N labeled metabolites have been corrected for the

natural abundance of ^{13}C and ^{15}N using METRAN[15-18] and in house scripts written in Matlab. In-house scripts are available upon request. For LC-MS analysis, cells were plated at a density of 500K cells/plate and allowed to attach overnight. Next morning, they were washed with PBS to remove traces of unlabeled metabolites, then overlayed with ductal media based on DMEM without glucose, pyruvate or glutamine, supplemented with 25 mM regular of ^{13}C-glucose, 2 mM regular or ^{15}N-glutamine and 2 mM pyruvate. At the indicated time points, cells were washed three times with ice cold 0.9% NaCl, then collected by scraping in methanol:acetonitrile:water (40:40:20) and cells were lysed by three freeze and thaw cycles (dry-ice bath and room temperature). After 30sec vortexing, samples were pelleted and the clarified supernatant was transferred to a new tube. Fifty microliters of the cleared extract were transferred to inserts set in brown glass vials and capped prior to being loaded onto the column. Samples were loaded by autosampler (FAMOS+) on a capillary (75 µm) 12cm ProntoSil C18 (3 µm, 200 Å, Bischoff) column that was interfaced with a Thermo Exactive MS. Metabolites were eluted applying a gradient of 3%-100% MeOH with tributylamine for ion pairing over 40 min at a flow rate of 150 µl/min using an Agilent 1260 infinity pump. The nanospray ionization source (NSI) spray was set to 1.8 kV, spray current at 2.1 µA, capillary voltage at -52.5V, tube lens voltage at -150V, simmer voltage at -42 V and capillary temperature was set to 300^{o}C. The scanner acquired full MS sprectrum (80-1000 m/z range; ultra-high resolution, R=100000 at 1 Hz; maximum injection time 100 ms). Raw data were transformed using MSConvert[19] and analyzed by MAVEN[20].

Multiplexed mass spectrometry-based quantitative proteomics

Protein Digestion and TMT Labeling. Proteomes were subjected to multiplexed quantitative proteomics analysis using tandem-mass tag (TMT) reagents on an Orbitrap Fusion mass spectrometer (Thermo Scientific). Disulfide bonds were reduced with

ditheiothreitol (DTT) and free thiols alkylated with iodoacetamide (IAA) as described previously[21]. Reduced and alkylated proteins were then precipitated with tricholoracetic acid (TCA). Precipitated proteins were reconstituted in 300 µL of 1M urea in 50mM HEPES, pH 8.5 and digested first with endoproteinase Lys-C (Wako) for 17 hours at room temperature (RT) and then with sequencing-grade trypsin (Promega) for 6 hours at 37˚C. The digest was acidified with trifluoroacetic acid (TFA). Peptides were desalted over Sep-Pak C_{18} solid-phase extraction (SPE) cartridges (Waters). The concentration of the desalted peptide solutions was measured with a BCA assay (Thermo Scientific) and a maximum of 50 µg of peptides were aliquoted, then were dried under vacuum and stored at -80˚C until they were labeled with TMT reagents. Peptides were labeled with 10-plex tandem mass tag (TMT) reagents (Thermo Scientific). TMT reagents were suspended in dry acetonitrile (ACN) at a concentration of 20 µg/µL. Dried peptides (50 µg) were re-suspended in 30% ACN in 200mM HEPES, pH 8.5 and 7.5 µL of the appropriate TMT reagent was added to the sample, which was incubated at RT for one hour. The reaction was then quenched by adding 6 µl of 5% (w/v) hydroxylamine in 200 mM HEPES (pH 8.5) and incubation for 15 min at RT. The solutions were acidified by adding 50 µl of 1% TFA.

Basic pH Reversed-Phase Liquid Chromatography (bRPLC) Sample Fractionation. Sample fractionation was performed by basic pH reversed-phase liquid chromatography (bRPLC) with concatenated fraction combining[22,23]. Briefly, samples were re-suspended in 5% formic acid (FA)/5% ACN and separated over a 4.6 mm x 250 mm ZORBAX Extend C_{18} column (5 µm, 80 Å, Agilent Technologies) on an Agilent 1260 HPLC system outfitted with a fraction collector, degasser and variable wavelength detector. The separation was performed applying a gradient build from 22 to 35% ACN in 10 mM ammonium bicarbonate in 60 min at a flow-rate of 0.5 mL/minute. A total of 96 fractions were collected, which were combined in a total of 12 fractions. The combined fractions

were dried under vacuum, re-constituted with 8 µl of 5% FA/5% ACN, 3 µl of which were analyzed by LC-MS2/MS3 for identification and quantification.

Liquid Chromatography Mass Spectrometry. All LC-MS2/MS3 experiments were analyzed by microcapillary liquid chromatography tandem mass spectrometry on an Orbitrap Fusion mass spectrometer and using a recently introduced multistage (MS3) method to provide highly accurate quantification[21,24]. The mass spectrometer was equipped with an EASY-nLC 1000 integrated autosampler and HPLC pump system. Peptides were separated over a 100 µm inner diameter microcapillary column in-house packed with first 0.5 cm of Magic C4 resin (5 µm, 100Å, Michrom Bioresources), then with 0.5 cm of Maccel C_{18} resin (3 µm, 200 Å, Nest Group) and 29 cm of GP-C18 resin (1.8 µm, 120 Å, Sepax Technologies). Peptides were eluted applying a gradient of 8-27% ACN in 0.125% formic acid over 165 min at a flow rate of 300 nl/min. To identify and quantify the TMT-labeled peptides we applied a synchronous precursor selection MS3 method[21,24,25] in a data dependent mode. The scan sequence was started with the acquisition of a full MS or MS1 one spectrum acquired in the Orbitrap (m/z range, 500-1200; resolution, 60,000; AGC target, $5x10^5$; maximum injection time, 100 ms), and the ten most intense peptide ions from detected in the full MS spectrum were then subjected to MS2 and MS3 analysis, while the acquisition time was optimized in an automated fashion (Top Speed, 5 sec). MS2 scans were done in the linear ion trap using the following settings: quadrupole isolation at an isolation width of 0.5Th; fragmentation method, CID; AGC target, $1x10^4$; maximum injection time, 35 ms; normalized collision energy, 30%). Using synchronous precursor selection the 10 most abundant fragment ions were selected for the MS3 experiment following each MS2 scan. The fragment ions were further fragmented using the HCD fragmentation (normalized collision energy, 50%) and the MS3 spectrum was acquired in the Orbitrap (resolution, 60,000; AGC target, $5x10^4$; maximum injection time, 250ms).

Data analysis was performed on an in-house generated SEQUEST-based[26] software platform. RAW files were converted into the mzXML format using a modified version of ReAdW.exe. MS2 spectra were searched against a protein sequence database containing all protein sequences in the human UniProt database (downloaded 02/04/2014) as well as that of known contaminants such as porcine trypsin. This target component of the database was followed by a decoy component containing the same protein sequences but in flipped (or reversed) order [27]. MS2 spectra were matched against peptide sequences with both termini consistent with trypsin specificity and allowing two missed trypsin cleavages. The precursor ion m/z tolerance was set to 50 ppm, TMT tags on the N-terminus and on lysine residues (229.162932Da) as well as carbamidomethylation (57.021464Da) on cysteine residues were set as static modification, and oxidation (15.994915Da) of methionines as variable modification. Using the target-decoy database search strategy[27] a spectra assignment false discovery rate of less than 1% was achieved through using linear discriminant analysis with a single discriminant score calculated from the following SEQUEST search score and peptide sequence properties: mass deviation, XCorr, dCn, number of missed trypsin cleavages, and peptide length[28]. The probability of a peptide assignment to be correct was calculated using a posterior error histogram and the probabilities for all peptides assigned to a protein were combined to filter the data set for a protein FDR of less than 1%. Peptides with sequences that were contained in more than one protein sequence from the UniProt database were assigned to the protein with most matching peptides[28].

TMT reporter ion intensities were extracted as that of the most intense ion within a 0.03Th window around the predicted reporter ion intensities in the collected MS3 spectra. Only MS3 with an average signal-to-noise value of larger than 28 per reporter ion as well as with an isolation specificity[21] of larger than 0.75 were considered for quantification. Reporter ions from all peptides assigned to a protein were summed to

define the protein intensity. A two-step normalization of the protein TMT-intensities was performed by first normalizing the protein intensities over all acquired TMT channels for each protein based to the median average protein intensity calculated for all proteins. To correct for slight mixing errors of the peptide mixture from each sample a median of the normalized intensities was calculated from all protein intensities in each TMT channel and the protein intensities were normalized to the median value of these median intensities.

Whole Genome Bisulfite Sequencing (WBGS), processing and analysis

WBGS libraries were constructed as follows: 200 ng of genomic DNA was fragmented using a Covaris S2 for 6 min according to the following program: duty cycle 5%; intensity 5; cycle per burst 200. The sheared DNA was purified using the DNA Clean & Concentrator kit from Zymo Research and bisulfite conversion of purified DNA was then conducted using the EZ DNA Methylation-Gold kit (Zymo Research) per the manufacturer's instructions, eluting to 15 µl low TE buffer. To minimize degradation during storage, the converted DNA was immediately processed to generate the WGBS libraries using the Accel-NGS Methyl-Seq DNA library kit (Swift Biosciences) following the standard protocol. The libraries were sequenced for 100-bp paired-end reads on an Illumina HiSeq 2500 sequencer, as previously described[29]. WBGS raw sequencing reads were aligned to mm9 build of the mouse genome using BSMAP[30]. DNA methylation calling for individual CpG sites was performed using mcall from the MOABS package[31]. Calculation of the average methylation of individual features and identification of differentially methylated features was done as previously described[32]**.** Briefly, average methylation for a feature was calculated as the coverage-weighted average across replicates of methylation at each CpG within the feature. Differentially methylated tiles were identified using a coverage-weighted two-sample t-test with CpG

methylation levels within the tile as samples. Only CpGs with 5x coverage and features with at least 2CpGs satisfying this coverage threshold were used in the analysis. Feature definitions were downloaded from ENSEMBL for promoters, exons and introns and from UCSC for isnlands, shores, LINEs, SINEs, LTRs, satellites and microsatellites. Intersection between bed files was calculated using intersectBed from the Bedtools package[33]. Hierarchical clustering was done using the hclust function in R, with Euclidean distance as the distance metric. For all analyses, methylation at sex chromosomes was discarded. Bisulfite conversion rates and sequencing statistics can be found in Supplementary Data Table 3. Raw sequencing files can be found under the Superseries record GSE86145 (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE86145).

Generation of the list of SAM-dependent enzymes

The list of transferases (Class 2 enzymes) was downloaded from ExplorEnz (http://www.enzyme-database.org). This list was hand-curated for mammalian genes and the 183 genes collected are considered the complete class of SAM-utilizing enzymes.

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Supplementary Data Table 1: Metabolic signatures (KEGG) regulated by LKB1

Metabolic signatures (KEGG) enriched in KL vs K cells (RNA sequencing dataset)				
NAME	SIZE	ES	NES	p-val
KEGG_PROPANOATE_METABOLISM	31	-0.7186803	-1.7829708	0
KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	40	-0.679458	-1.7433939	0
KEGG_FATTY_ACID_METABOLISM	32	-0.6944716	-1.7170434	0
KEGG_HISTIDINE_METABOLISM	28	-0.6563128	-1.6154146	0.00524476
KEGG_STARCH_AND_SUCROSE_METABOLISM	28	-0.646282	-1.5846947	0.00525394
KEGG_GALACTOSE_METABOLISM	24	-0.6524891	-1.5631144	0.01587302
KEGG_STEROID_BIOSYNTHESIS	13	-0.7565442	-1.538193	0.01612903
KEGG_PRIMARY_BILE_ACID_BIOSYNTHESIS	15	-0.7265122	-1.5319933	0.03057554
KEGG_PORPHYRIN_AND_CHLOROPHYLL_METABOLISM	24	-0.6602504	-1.5217115	0.02094241
KEGG_PANTOTHENATE_AND_COA_BIOSYNTHESIS	15	-0.7188001	-1.5192944	0.02199662
KEGG_GLUTATHIONE_METABOLISM	48	-0.557875	-1.4967372	0.01768489
KEGG_NICOTINATE_AND_NICOTINAMIDE_METABOLISM	23	-0.6509498	-1.4900998	0.02298851
KEGG_GLYCINE_SERINE_AND_THREONINE_METABOLISM	30	-0.5975758	-1.4724112	0.03552398
KEGG_RIBOFLAVIN_METABOLISM	15	-0.6961117	-1.4565915	0.05714286
KEGG_BIOSYNTHESIS_OF_UNSATURATED_FATTY_ACIDS	19	-0.6523123	-1.4482579	0.04794521
KEGG_TERPENOID_BACKBONE_BIOSYNTHESIS	15	-0.6775882	-1.4469787	0.05776173
KEGG_PYRUVATE_METABOLISM	36	-0.5589771	-1.425023	0.04262295
KEGG_RETINOL_METABOLISM	27	-0.5892349	-1.4095078	0.0681431
KEGG_GLYCOLYSIS_GLUCONEOGENESIS	54	-0.507406	-1.3964497	0.03980099
KEGG_SELENOAMINO_ACID_METABOLISM	25	-0.5887506	-1.3894342	0.08783784
KEGG_TRYPTOPHAN_METABOLISM	39	-0.5403609	-1.37325	0.06589786
KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM	33	-0.5374658	-1.3576956	0.07363014
KEGG_BETA_ALANINE_METABOLISM	22	-0.583635	-1.3423203	0.09717315
KEGG_PURINE_METABOLISM	152	-0.4281466	-1.3391873	0.02008608
KEGG_LYSINE_DEGRADATION	43	-0.5028372	-1.3254603	0.07154742
KEGG_FOLATE_BIOSYNTHESIS	10	-0.6930894	-1.3254137	0.12037037
KEGG_ONE_CARBON_POOL_BY_FOLATE	17	-0.588681	-1.2873431	0.14962122
KEGG_GLYCEROLIPID_METABOLISM	47	-0.4739668	-1.2788787	0.12086093

Metabolic signatures (KEGG) enriched in KL vs rescue cells (RNA sequencing dataset)				
NAME	SIZE	ES	NES	p-val
KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	40	0.66869193	1.8479664	0
KEGG_PROPANOATE_METABOLISM	31	0.6962086	1.8133167	0
KEGG_STARCH_AND_SUCROSE_METABOLISM	28	0.696654	1.7876532	0.00217865
KEGG_GLYCINE_SERINE_AND_THREONINE_METABOLISM	30	0.67652786	1.748912	0.00220751
KEGG_FATTY_ACID_METABOLISM	32	0.6303722	1.6344188	0.00198413
KEGG_PANTOTHENATE_AND_COA_BIOSYNTHESIS	15	0.7128456	1.6132475	0.02340426
KEGG_PRIMARY_BILE_ACID_BIOSYNTHESIS	15	0.74161416	1.6063976	0.01008065
KEGG_PORPHYRIN_AND_CHLOROPHYLL_METABOLISM	24	0.6552958	1.5944029	0.01687764
KEGG_GLUTATHIONE_METABOLISM	48	0.55864984	1.5824784	0.00429185
KEGG_NICOTINATE_AND_NICOTINAMIDE_METABOLISM	23	0.63635606	1.5636767	0.01851852
KEGG_ARGININE_AND_PROLINE_METABOLISM	50	0.5277646	1.5208818	0.01515152
KEGG_GLYCOLYSIS_GLUCONEOGENESIS	54	0.52471715	1.5127068	0.00898876
KEGG_TERPENOID_BACKBONE_BIOSYNTHESIS	15	0.687989	1.4992368	0.03004292
KEGG_PYRUVATE_METABOLISM	36	0.564419	1.4891049	0.0209205
KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM	33	0.55810696	1.4866409	0.01458333
KEGG_STEROID_BIOSYNTHESIS	13	0.6918134	1.4702975	0.05263158
KEGG_HISTIDINE_METABOLISM	28	0.5746119	1.4504648	0.02453988
KEGG_SELENOAMINO_ACID_METABOLISM	25	0.5881608	1.4353648	0.05591398
KEGG_ONE_CARBON_POOL_BY_FOLATE	17	0.62294006	1.4341161	0.07188161
KEGG_GLYCEROLIPID_METABOLISM	47	0.5074729	1.4182684	0.04393305
KEGG_GALACTOSE_METABOLISM	24	0.5696987	1.3872246	0.07641921
KEGG_FOLATE_BIOSYNTHESIS	10	0.7132086	1.3835475	0.09765625
KEGG_BETA_ALANINE_METABOLISM	22	0.553447	1.3523191	0.08928572
KEGG_BIOSYNTHESIS_OF_UNSATURATED_FATTY_ACIDS	19	0.5832406	1.3460569	0.11201629
KEGG_PURINE_METABOLISM	152	0.39029574	1.3025622	0.02612827

Metabolic signatures (KEGG) enriched in KL vs K cells (Proteomics dataset)				
NAME	SIZE	ES	NES	p-val
KEGG_PURINE_METABOLISM	100	-0.4125574	-1.6301998	0.00172117
KEGG_GLYCINE_SERINE_AND_THREONINE_METABOLISM	16	-0.5559085	-1.488742	0.05454546
KEGG_PYRIMIDINE_METABOLISM	78	-0.36517	-1.3819337	0.03322259
KEGG_GLYCOLYSIS_GLUCONEOGENESIS	35	-0.4160941	-1.3632835	0.08156028

Supplementary Table 2. Curated list of S-adenosyl-methionine utilizing enzymes (RNAseq)

	K_FPKM			KL_FPKM				rescue_FPKM		
gene	K-2-1	K-1-2	K-2-2	KL-1-1	KL-2-1	KL-1-2	KL-L-2	rescue-1	rescue-1	q val (K vs KL)
6430573F11I	0.0499595	0.0358787	0.0615988	0.185944	0.0493373	0.187742	0.0649221	0.0646899	0	1
ALKBH8	6.02262	7.07688	7.8227	7.36679	7.8644	8.41918	8.94612	6.78247	6.32825	0.432551
AS3MT	5.80021	1.7827	3.20182	4.76161	4.16813	3.93943	6.04377	2.95299	4.53429	0.278058
ASH1L	7.95223	7.45242	8.23551	8.22104	8.52584	8.80987	8.08976	8.48311	8.41324	0.709296
ASH2L	39.7535	39.8612	47.7321	36.6427	36.3149	42.5642	41.7083	35.7729	37.8811	0.760743
ASMT	0	0	0	0	0	0	0	0	0.0569616	1
B630005N14	18.0488	15.2231	17.0044	16.9307	17.15	14.2784	14.5945	14.7285	16.5819	0.78032
BCDIN3D	5.29539	5.82815	5.43734	4.69844	5.76148	5.66287	7.97382	6.09074	5.56155	0.879689
BHMT	0	0	0	0	0	0	0	0	0	1
BHMT2	0	0	0	0	0	0	0	0	0	1
CAMKMT	1.46392	0.796361	0.774104	1.82252	2.13638	1.38566	1.25487	1.56035	1.72981	0.220986
CARM1	31.225	37.0963	33.5811	24.4907	22.0934	27.509	28.3831	30.7524	31.2672	0.202146
COMT	48.676	49.5746	49.2919	51.9787	47.1639	41.0381	38.3494	58.1419	50.3948	0.669337
COMTD1	6.56878	6.08153	7.11202	5.80925	5.79973	5.4446	4.64888	7.6248	7.08445	0.881544
COQ3	10.3862	9.81913	10.0682	11.3725	10.1833	12.9472	14.5505	10.632	11.6907	0.237787
COQ5	14.6302	13.9694	15.0903	15.9715	14.9505	15.0091	15.0978	14.2854	16.0783	0.835809
CXXC1	20.0041	15.7396	15.7594	21.4044	21.81	18.3914	17.8525	15.6082	16.7736	0.444395
DIMT1	4.26095	5.98205	4.7349	3.66751	4.00814	4.29743	4.82566	4.09071	4.49581	0.536316
DNMT3B	0.894253	0.613967	0.389261	0.650853	0.577863	0.707098	0.597913	0.688951	0.56012	0.992377
DNMT3L	0	0	0	0	0	0.0221452	0	0	0	1
DOT1L	10.3004	10.1132	8.31863	11.2398	11.1052	11.8523	13.0658	8.65611	9.34968	0.176978
DPH5	11.0409	12.2648	14.0387	11.991	11.0908	12.2951	14.0152	10.3317	13.9554	0.995984
ECE2	16.951	19.29	14.1867	13.5457	15.1498	12.6371	14.9581	15.8717	17.9828	0.534979
EHMT1	15.8335	16.5758	16.0039	14.9111	14.1132	15.0346	15.0632	14.1494	13.7078	0.696288
EHMT2	45.9126	47.1617	46.0484	47.6262	44.3401	47.1596	47.5047	46.8096	44.2448	0.997215
EMG1	59.1113	59.4921	68.0353	61.3942	59.0104	68.0575	81.0298	56.0878	71.9858	0.832992
EZH1	11.9273	10.5498	10.8606	12.6709	12.7078	11.6661	12.1495	12.0208	10.1924	0.56458
EZH2	29.3527	32.0834	35.6023	33.1317	28.9507	38.9901	39.3323	29.1342	40.1915	0.60116
FBL	4.32816	9.59078	8.6406	4.38846	5.18556	7.99761	9.06127	6.3262	10.182	0.785438
FBLL1	0	0	0	0	0.0503626	0	0	0	0	1
FDXACB1	4.11258	4.95528	4.88641	3.86908	3.61847	4.5879	5.14867	4.58361	4.67175	0.842309
FTSJ1	6.73112	7.21696	7.30663	7.4079	7.64127	7.86104	8.86397	6.88474	7.07356	0.590777
FTSJ2	4.60851	5.83221	6.27336	5.70705	6.61033	5.63859	7.07902	6.67166	5.40161	0.753792
FTSJ3	39.1203	44.2609	43.6933	36.5456	35.5456	44.4825	45.8651	43.2876	42.5018	0.905444
FTSJD1	9.47488	10.3342	10.7962	9.21122	10.5378	9.56468	10.8006	9.53937	8.24906	0.939501
FTSJD2	27.4656	28.4216	30.5178	30.511	29.6536	35.1598	27.6913	28.5095	30.2942	0.760934
GAMT	4.958	2.82938	3.59813	8.11316	5.96164	6.70019	6.66375	3.79454	2.86342	0.847298
GM17296	4.28367	2.93873	3.57805	4.05665	4.96808	3.52236	4.17232	2.88673	3.50289	0.613094
GNMT	1.17951	1.22854	1.43049	1.79386	2.63151	2.26009	2.37908	1.23992	1.55552	0.186882
HEMK1	3.26117	2.56248	2.97409	3.09384	5.88701	2.91322	4.8612	2.38203	4.87273	0.144108
HENMT1	0	0.165209	0.0209623	0.162364	0.130529	0.134564	0	0.0660279	0.0936177	1
ICMT	33.3428	35.1869	29.8025	28.3064	29.8728	31.3329	30.8414	36.1323	33.5983	0.607972
INMT	0	0	0	0	0	0	0	0	0	1
IRF4	0.00896499	0.00675387	0.0310312	0	0	0	0.00825208	0	0	1
LCMT1	21.4369	25.4335	25.5532	29.8526	29.6246	29.8021	29.925	26.0564	29.2566	0.196346
LCMT2	5.4327	6.69266	7.06394	5.48798	6.69382	6.75546	8.26037	7.59335	7.19359	0.864741
LOC1005046(	0.200681	0.193478	0	0.277451	0.186796	0.0651892	0.075431	0.298938	0	1
MEN1	20.5942	21.9127	20.8865	19.6747	19.3838	17.8321	17.8685	15.6481	17.8446	0.483953
MEPCE	19.3681	18.0825	16.3473	21.3565	21.7647	19.7355	19.1719	18.9057	17.1735	0.545882
METTL1	15.6196	15.6188	15.5382	15.1857	15.7675	13.4369	16.8554	16.8844	18.5137	0.963971
METTL10	14.7645	19.7195	15.6593	16.1394	17.9199	18.8507	18.6057	16.1321	22.2588	0.806036
METTL11B	0	0	0	0	0	0	0	0	0	1
METTL13	6.75054	7.0688	6.16272	7.81137	7.04956	6.41337	6.12869	6.02674	6.96469	0.939899
METTL14	9.8352	13.415	12.9633	10.6937	10.6558	14.1896	16.1725	12.2867	13.1887	0.748893
METTL15	5.3843	3.18035	3.43159	4.26861	4.70387	3.79393	4.81982	3.51403	4.75466	0.761538
METTL16	16.3208	18.0537	18.3183	14.1656	13.3474	15.406	15.0618	16.9602	17.5263	0.242956
METTL17	8.09335	8.76846	6.69453	8.37207	7.61389	6.73612	8.05917	8.12655	8.00546	0.951806
METTL18	3.73501	4.52036	4.7249	4.58619	4.01163	4.57365	4.18656	3.68679	4.32052	0.999196
METTL2	11.8577	13.927	13.3403	12.7408	12.9659	12.2459	13.2441	14.0987	12.4701	0.963878
METTL21A	5.56299	10.2774	6.84044	8.61716	8.06393	8.31193	7.55859	6.57373	7.34974	0.815706
METTL21C	0.0409801	0.0323952	0.0747846	0.0383936	0	0.137264	0.239068	0	0.0668495	1
METTL21D	12.5746	16.3382	13.7991	15.2966	14.5762	15.1101	17.2479	14.7152	16.0433	0.778973
METTL21E	0	0	0	0	0.0121362	0	0	0.0111804	0	1
METTL22	7.18179	6.14448	6.42318	7.64938	7.13903	6.39706	6.31023	7.08699	7.50552	0.906071
METTL23	12.1925	11.1016	12.449	13.7434	13.6659	10.0388	10.2329	9.54214	12.2967	0.998285

METTL24	0.0415403	0.0275155	0.0612987	0.0765396	0	0.0834978	0	0	0.0532221	1	
METTL25	2.39737	3.32597	3.08043	3.19505	3.93625	3.10593	3.99429	3.28242	4.50011	0.563791	
METTL3	12.0028	12.9546	11.5872	11.3423	10.898	10.0163	9.43897	13.5886	12.1805	0.763867	
METTL4	4.27909	3.77298	4.2411	5.28571	4.7556	4.88478	4.50762	3.47985	4.18331	0.525689	
METTL5	20.2198	18.4199	19.4808	17.0362	17.2759	20.1505	19.6536	17.4916	16.6394	0.99461	
METTL6	19.7363	17.2525	17.6192	19.5149	20.4373	21.8093	17.3588	17.5219	18.6702	0.66607	
METTL7A1	7.34745	6.45986	7.10881	10.2298	10.6836	7.71048	10.5445	9.05638	9.06917	0.0691547	
METTL7A3	0	0.0269398	0	0	0	0	0	0	0	1	
METTL7B	0.522331	0.0303506	0.0697036	0.0818787	0.587875	0.253675	0.147049	0.0364259	0.121111	1	
METTL8	4.67032	3.76136	4.10976	4.72083	4.19947	4.59889	4.71734	3.78026	4.53949	0.823409	
METTL9	45.9156	44.9255	45.4999	56.5468	59.886	51.4213	54.9516	41.0877	45.1262	0.153237	
MGMT	55.9383	48.5363	50.2758	54.9927	56.6051	45.0326	40.1303	52.3992	53.3647	0.847298	
MLL1	3.51784	3.38486	3.3928	2.64628	2.80356	2.80016	2.42717	3.93069	3.08348	0.0680466	
MLL2	1.88018	1.90596	1.61022	1.65311	1.73643	1.80451	1.40548	2.04674	1.69758	0.700966	
MLL3	1.42159	1.33616	1.30667	1.46039	1.74934	1.44336	1.29156	1.26299	1.16518	0.613279	
MLL5	10.7138	8.90417	10.1284	10.7243	11.9977	10.7759	12.3048	9.70562	9.26196	0.554818	
MRM1	6.11171	8.11919	7.76894	7.23132	6.67197	5.99758	6.88909	7.77083	6.61328	0.76315	
MTR	3.22584	4.94333	2.91632	3.21919	3.06318	3.73289	3.48878	2.56261	3.63384	0.798388	
MTRR	6.23416	6.61275	4.46584	7.42483	7.63737	6.1715	6.03487	6.147	6.11428	0.392437	
N6AMT1	11.4532	11.1516	13.0501	12.0531	12.9639	10.0183	11.2389	10.3144	11.8465	0.99461	
N6AMT2	24.5725	28.0766	27.0431	27.9446	26.3728	24.6557	26.9482	22.8231	29.1612	0.994149	
NDUFAF5	3.89318	3.28404	4.59418	3.35739	2.80407	3.76232	4.76681	3.02837	3.60115	0.87237	
NDUFAF7	9.43063	7.50058	9.92143	10.7363	9.78353	10.3414	11.319	8.59575	9.78638	0.403745	
NNMT	0	0.0374888	0	0.778077	0.977505	0.473299	0.592843	0.227655	0.0378442	0.28801	
NOP2	36.836	39.5947	44.2824	33.1138	32.866	36.8623	40.9471	38.7452	37.9215	0.526289	
NSD1	10.0921	14.4732	9.53292	11.1714	10.9934	11.3909	11.2575	9.88678	9.93282	0.96749	
NSUN2	55.1281	81.6171	57.8207	64.3274	68.174	66.3768	89.7614	58.9172	63.9059	0.519316	
NSUN3	3.89601	4.28715	4.31293	5.11915	5.37655	4.62557	4.33253	5.09318	5.0625	0.693795	
NSUN4	7.67734	6.75308	5.34688	7.57648	8.82234	5.7338	5.89288	5.86234	7.70531	0.824364	
NSUN5	6.98372	6.72174	6.39017	7.03041	4.94865	7.54784	7.40012	6.22304	6.93846	0.999196	
NSUN6	2.59403	2.41608	2.3213	2.82455	3.00494	2.6768	2.21173	2.37551	2.64669	0.823788	
NSUN7	0.0165888	0.0837546	0.0414476	0.0156947	0	0	0.0145907	0.0290085	0.0246809	1	
NTMT1	32.4014	38.499	41.188	28.5498	26.2958	32.3685	33.8762	32.8842	31.4952	0.230425	
OCLN	38.3946	51.6282	42.0906	33.4541	37.1448	34.9876	37.2189	40.5535	38.9758	0.15408	
PCMT1	53.3328	61.0315	60.0232	50.2368	48.1917	53.1181	55.7503	50.8233	52.76	0.523544	
PCMTD1	8.83384	7.53091	7.82722	8.03702	7.32474	6.97313	6.77249	8.47831	6.84064	0.654466	
PCMTD2	22.1663	16.2817	19.4683	21.5016	22.4165	16.8422	17.1585	18.4648	16.8238	0.954665	
PEMT	3.08276	2.07972	4.06632	3.96206	4.07287	3.64748	4.49341	2.35604	4.65637	0.553861	
PNMT	0	0	0	0	0	0	0	0	0	1	
PRDM1	0.117424	0.86606	0.15179	0.39386	0.29018	0.364397	0.10748	0.242791	0.257382	1	
PRDM10	2.37809	2.34528	2.37315	2.12231	2.30201	2.24076	2.08283	2.03168	2.1934	0.88348	
PRDM11	0.0799678	0.0723006	0.102169	0.173239	0.175722	0.296503	0.192636	0.404348	0.176039	1	
PRDM12	0	0	0	0.0234559	0	0	0.0398663	0	0.0163636	1	
PRDM13	0	0	0	0	0	0	0	0	0	1	
PRDM14	0	0	0	0	0.0189476	0.0144766	0.0335797	0	0.0139762	1	
PRDM15	2.58118	2.53758	1.78814	2.19449	2.11045	2.2718	1.74182	2.15117	1.96924	0.798388	
PRDM2	11.4049	10.1316	8.47125	9.52272	8.65231	8.2441	7.01049	7.72479	7.4398	0.244194	
PRDM4	16.7491	18.4436	17.2134	15.9719	16.8413	16.0974	15.1055	15.5784	15.5585	0.751995	
PRDM5	7.5622	6.98802	6.59049	7.52472	8.18111	8.04133	7.22515	8.05284	7.76095	0.667891	
PRDM6	0	0	0	0	0	0	0	0.0180316	0	1	
PRDM9	1.01923	0.789558	0.621377	1.00552	0.921209	1.28656	1.09528	0.862402	0.758308	0.390757	
PRMT1	105.705	149.138	133.512	84.2463	91.5802	106.311	118.394	120.579	120.877	0.0502682	
PRMT10	5.4373	5.83688	5.63624	5.85593	4.6767	5.29425	4.02002	5.22166	5.60455	0.674515	
PRMT2	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	0.710755	
PRMT3	23.1393	27.9448	28.9898	26.7911	28.4664	27.2832	30.6519	28.8247	29.1178	0.768779	
PRMT5	43.5165	43.4203	47.0423	42.0711	41.9911	43.5736	45.2323	37.0634	43.1398	0.910169	
PRMT6	11.1115	12.8823	13.0306	14.9727	16.8371	15.5495	14.3096	13.1656	12.9584	0.23935	
PRMT7	25.593	28.9606	33.9714	26.9096	25.5127	29.9437	33.1699	27.89	33.0323	0.981129	
PRMT8	0	0	0	0	0.0190041	0	0	0	0	1	
RBBP5	10.9776	12.0551	11.4705	11.654	11.03	12.2143	12.0036	10.5311	11.3442	0.948088	
RNMT	15.9042	15.9588	16.9895	14.5062	16.6209	15.1839	14.8023	16.2485	14.5968	0.812471	
RNMTL1	5.25003	5.11532	4.72669	7.27445	6.46951	6.24497	5.39715	4.8968	5.58694	0.383404	
RRNAD1	7.3253	6.56614	5.64503	6.12774	6.15181	5.41264	5.55645	6.26158	6.06069	0.812471	
RRP8	12.2907	13.0347	12.2394	10.663	10.2911	12.5769	12.5451	11.7541	12.271	0.881507	
SETD1A	12.569	15.1051	14.0807	11.0732	11.3527	13.6367	14.1929	13.2645	13.8962	0.588621	
SETD1B	3.35127	3.52708	3.38245	3.18514	3.89777	3.40198	3.77716	3.72063	3.2034	0.931733	
SETD2	10.3888	11.1185	10.4364	9.35066	9.53652	11.5479	10.4661	11.0786	10.3658	0.939822	
SETD3	31.5992	34.6059	34.8055	27.3595	27.4013	28.1125	34.7574	33.3345	34.9738	0.416462	

Not altered

SETD4	2.84898	2.99329	1.76323	2.0788	1.52669	1.19756	0.667002	2.00847	1.53061	0.0653856
SETD6	21.7058	24.5056	25.9376	16.4846	18.6153	19.7729	22.1381	21.3143	20.9355	0.179924
SETD8	110.15	114.45	104.198	88.8003	92.7398	81.4738	104.002	89.5518	100.35	0.225088
SETDB1	11.3657	11.5966	10.7985	11.4902	12.4822	13.3575	13.1869	11.3585	12.1092	0.823788
SETDB2	3.20008	3.56511	3.74514	4.44647	4.65429	4.20396	3.92703	3.42944	4.5673	0.361722
SETMAR	2.00888	1.78468	2.2434	1.8883	2.56429	2.29972	2.68704	2.38533	1.75748	0.667891
SMYD1	0.0252614	0.0284692	0.0108494	0.0470658	0.0251803	0.0198276	0	0.0228655	0.0191434	1
SMYD2	48.8248	52.5835	49.6562	45.5615	43.4334	43.679	47.5784	52.294	52.1613	0.580626
SMYD3	3.0473	2.69189	2.95383	3.07952	3.57349	2.99045	3.32077	2.60437	3.21693	0.748347
SMYD4	1.98703	1.7333	1.86602	2.24684	2.01037	2.14547	2.06716	1.51427	1.83343	0.710936
SMYD5	12.3271	13.5175	14.4247	12.6034	13.0419	12.6853	14.4807	13.635	16.3357	0.986059
SUV39H1	16.9396	18.0085	19.1684	14.3775	13.569	18.8393	20.7771	16.4017	21.0107	0.797632
SUV39H2	3.03624	2.56893	2.854	2.86624	2.63969	5.04864	4.63617	2.72963	3.7636	0.232282
SUV420H1	10.059	8.69793	9.7962	11.0573	11.5573	8.91064	9.98304	9.10293	8.55732	0.696964
SUV420H2	14.492	11.9458	10.0663	14.8636	12.2944	15.6642	13.8978	12.2206	12.7864	0.513735
TFB1M	3.88829	4.34729	5.09018	6.30016	6.01507	5.52062	5.32923	3.86731	5.62711	0.569074
TFB2M	3.64959	4.0878	3.91009	3.50825	3.80706	3.34244	3.23368	3.34936	3.36576	0.783161
TGS1	5.63973	5.35109	4.61018	5.43413	5.45779	5.89394	5.56188	5.59032	5.89842	0.710151
THUMPD2	1.98478	2.03208	2.91106	1.7906	1.8629	2.31153	1.79566	2.05932	2.69159	0.698894
THUMPD3	23.0158	23.3196	24.8967	22.0365	23.6528	24.1481	22.8393	27.6816	24.0228	0.980243
TOMT	0.809417	1.09796	0.947787	1.13095	0.9706	1.03953	1.79082	0.855639	0.999326	0.8763
TPMT	2.00216	3.73534	2.7549	2.3734	2.37646	2.46829	2.66134	1.85255	1.79961	0.719472
TRDMT1	1.93996	1.84426	2.05122	2.16298	1.92421	2.69469	3.2173	2.32648	2.54866	0.393998
TRMT1	31.2716	31.5435	32.1308	34.6614	38.4021	29.2803	34.4204	31.9359	35.6423	0.722206
TRMT10A	4.25335	5.05374	4.021	3.88799	3.56777	4.9319	5.02261	5.64296	5.89424	0.951247
TRMT10B	7.95717	6.85041	6.4949	6.92603	7.35147	6.45203	7.61444	6.81928	6.79426	0.993072
TRMT10C	20.7095	22.8587	23.2784	21.125	24.1935	24.4561	26.7661	24.0543	23.1127	0.672255
TRMT11	8.85693	7.80389	9.01131	10.2335	10.4113	9.16322	11.2792	8.74564	10.705	0.288404
TRMT112	19.7703	19.6373	20.6276	24.0887	28.2461	22.0163	28.4115	17.9576	21.8752	0.587811
TRMT12	1.77757	2.29075	2.04736	2.21264	2.41774	2.58346	2.32312	2.83962	2.23841	0.589913
TRMT13	2.22855	2.88012	2.13585	2.89847	2.24263	2.84007	2.31734	2.78978	2.2114	0.931733
TRMT1L	13.3176	11.4693	9.52417	12.402	13.1193	9.71121	9.18714	10.6974	10.5661	0.967105
TRMT2A	13.3284	14.4173	14.565	14.6356	12.5095	16.7774	16.519	15.9253	16.0155	0.765334
TRMT2B	13.3606	16.7085	15.4098	18.8957	15.5417	18.459	19.3475	16.8248	16.922	0.390892
TRMT44	2.75077	3.08392	2.38426	2.85372	3.2329	2.98673	2.6834	3.15105	2.53438	0.872037
TRMT5	14.657	14.3388	15.2679	15.2799	14.5427	15.0219	15.0212	15.8138	15.9246	0.948088
TRMT6	23.4516	25.8003	24.7108	20.1913	20.3924	22.6723	24.7633	22.1072	23.4763	0.559677
TRMT61A	8.41775	7.96898	8.20089	8.47931	8.47027	8.4851	8.53371	9.25589	9.62946	0.944468
TRMT61B	12.6108	15.9977	15.8251	12.4412	12.0685	12.9992	12.7567	18.5399	17.074	0.667444
TRMU	5.03164	5.04924	5.23824	5.67908	5.00818	5.32968	5.1436	5.86967	5.30146	0.940492
TYW3	0.583674	0.693735	0.638416	0.825401	0.776054	0.734505	0.653149	0.430021	0.660877	0.821456
WBP7	10.0876	10.0939	9.53541	8.86454	8.44965	9.62627	8.31503	10.088	8.55964	0.486998
WBSCR22	31.9264	32.3937	35.4031	32.7078	30.8665	35.235	39.5557	32.3592	31.154	0.921286
WBSCR27	7.01364	5.96102	4.97991	5.69112	6.04684	4.83113	4.10661	5.57905	6.09378	0.643248
WDR4	9.15756	10.7359	9.40643	9.17896	9.29545	8.92328	10.0065	8.59572	11.3281	0.881507
WDR5	35.6568	34.4646	37.5691	30.9836	32.1388	33.3064	36.352	31.6773	37.7096	0.726234
WDR82	24.6898	25.6915	25.9649	25.9911	27.7902	26.5122	28.1793	23.8283	25.0166	0.743452
WHSC1	19.7873	20.6953	22.5922	20.6437	20.1106	25.2013	28.2441	19.5204	25.6301	0.449895
WHSC1L1	12.5716	12.6514	13.257	11.3957	11.953	13.1631	13.2444	12.788	11.8762	0.929952
ZCCHC4	4.49342	5.39814	4.12001	3.71085	3.59143	4.42052	4.18071	4.62315	4.72993	0.634771
DNMT1	21.105	26.9581	24.8415	29.3271	26.1587	39.8165	32.7572	26.4514	31.2404	0.0181179
DNMT3A	2.8983	2.32813	2.21564	4.07874	4.48797	3.32995	3.62358	2.59661	2.86093	0.00137803
HNMT	0.213158	0	0.0221341	0.779368	0.916959	1.37678	1.33482	0.751757	0.344345	0.0115951
METTL20	10.9273	5.02089	9.1461	16.0794	20.9864	17.2483	24.3454	7.18788	8.88697	0.000509378
PRDM8	0.921814	1.44237	1.16091	0.470453	0.454765	0.244426	0.29933	1.32359	0.616615	0.00488246
SETD7	27.9871	33.4685	27.0955	22.0261	19.5296	16.4429	13.1429	31.3229	25.6157	0.000509378

Significant changes

Suplementary Table 2. Curated list of S-adenosyl-methionine utilizing enzymes (Proteomics)

	K cells				K cells			
Name	K-1-1	K-2-1	K-1-2	K-2-2	KL-1-1	KL-2-1	KL-1-2	KL-2-2
AS3MT	263016.554	375524.261	257327.136	292989.071	291409.169	318404.437	253289.521	272850.151
ASH1L	272229.112	282100.649	240983.889	223796.889	302254.612	332189.331	322267.842	304036.204
ASH2L	238541.823	332388.084	235621.035	294893.272	305059.171	286718.112	296546.17	295272.611
CARM1	298020.697	291367.191	301665.491	282830.231	318474.69	297958.931	251003.454	238157.203
COMTD1	234867.041	327426.184	305559.572	426500.479	216398.734	196070.989	270681.404	235198.712
COQ3	364453.02	267959.746	323839.535	252603.667	335120.145	272936.358	225623.821	227260.118
COQ5	314429.216	227609.241	296117.559	279863.803	286092.618	315736.321	251305.115	254276.616
CXXC1	220759.651	285810.256	240321.647	328944.855	268395.561	305093.753	303541.505	307343.175
DIMT1	347007.454	224579.63	264253.761	208295.334	341243.809	289859.639	330034.19	321965.469
DOT1L	267109.856	300093.619	238557.968	249826.131	283257.63	301129.168	350947.651	330180.516
DPH5	283953.509	309243.131	267779.749	245535.979	322789.29	296865.457	303025.459	278112.88
EHMT1	250625.024	292407.031	222213.75	257106.613	288235.907	303714.004	328579.764	354287.824
EHMT2	281190.32	314162.972	251374.98	281116.048	303948.078	273310.578	309663.07	300728.792
EMG1	226266.098	268909.211	200582.655	273842.485	315205.028	357807.732	274735.262	349688.193
EZH1	220806.356	291089.238	233843.449	303084.562	273279.438	314527.902	304245.839	322260.99
EZH2	250026.905	285211.973	208612.687	252144.08	301173.305	304607.619	350613.957	367166.629
FBL	342194.042	292668.883	253987.087	276521.728	295656.284	258684.671	248203.151	281495.861
FTSJ1	300924.22	294284.69	276049.66	262925.485	363464.52	247443.419	322612.164	299447.799
FTSJ2	268687.109	257640.284	291486.067	382676.845	241152.664	257955.634	242552.929	274242.404
FTSJ3	255194.529	234595.733	208404.949	244185.866	281637.142	318364.993	351172.574	363840.671
ICMT	256954.181	216459.638	324269.524	249455.214	282900.053	258001.102	299416.871	348016.746
MEN1	245806.046	368905.043	209750.365	304319.843	248457.732	320556.593	293522.865	301572.969
MEPCE	209493.979	247258.172	205106.902	283712.497	324705.088	351864.577	286393.949	293591.608
METTL1	368541.408	258794.787	375977.881	230675.031	371118.715	276030.01	259529.597	212865.456
METTL10	391179.722	318159.775	351597.146	230646.361	273158.439	294696.42	245173.3	265107.346
METTL13	308951.361	262064.375	247642.866	216708.145	336223.014	312137.785	285996.005	298849.647
METTL14	301180.528	328610.028	249316.323	204464.293	349545.917	311752.932	272317.608	325369.707
METTL15	252650.103	309123.325	289486.361	337215.75	242819.991	244097.224	292148.216	271823.43
METTL16	222511.72	317046.262	268980.863	330655.686	282380.647	291610.954	297134.69	263744.126
METTL17	258182.608	235422.592	278011.249	300954.564	278873.225	259422.907	289862.356	304525.026
METTL18	260118.329	323546.18	248154.595	258895.821	340954.693	276339.991	363730.668	314830.532
METTL3	323203.772	228929.004	244107.498	202680.964	386535.639	354877.357	302034.434	279749.002
METTL7A1	161125.044	331080.314	236074.58	409205.989	245460.722	281214.908	272102.161	246000.988
METTL9	369786.632	153411.536	317276.837	248489.999	408730.845	381231.731	144653.535	146750.788
MGMT	358106.938	295374.348	191253.439	292759.01	463578.797	369518.595	176617.857	197014.931
MRM1	232244.071	288007.796	263434.951	324013.414	239088.066	316687.1	243799.577	261375.475
MTR	308149.324	234961.503	399856.963	206004.7	259641.925	300643.095	256945.603	275566.769
MTRR	354326.738	224952.212	381596.268	225334.795	283345.077	221719.158	330471.408	272648.169
N6AMT1	342066.073	272870.078	337823.037	265222.918	338809.158	248842.024	275027.465	242131.261
NDUFAF5	315362.524	277105.331	332021.019	320175.897	245955.357	242518.757	252547.067	244454.87
NDUFAF7	243472.238	292305.012	279791.922	347054.981	257083.325	282016.699	229202.972	238653.391
NOP2	232907.347	283639.969	215314.776	241550.192	292195.859	281315.078	331755.703	374817.3
NSD1	349964.63	284049.085	271299.134	244081.293	312758.574	284459.995	295400.751	286115.008
NSUN2	293215.984	248068.14	234822.122	233500.231	430104.706	305149.563	291690.639	288577.94
NSUN3	232904.009	267875.095	333136.434	260831.456	301570.142	268848.713	280011.939	260519.919
NSUN4	246722.406	288222.844	270957.788	295020.633	252759.477	316096.618	255586.129	293962.505
NSUN5	219421.068	299274.036	231170.406	273813.422	285625.716	270518.846	360473.724	330983.359
NTMT1	318319.155	296675.664	333835.279	261569.961	237682.193	249646.235	338635.087	348050.039
PCMT1	386981.396	261278.53	327424.738	271679.745	289166.417	255611.418	261874.301	258671.726
PCMTD2	327478.985	320587.683	261052.693	291176.248	404023.902	339878.956	193937.369	194382.03
PRDM10	241230.872	413497.427	247479.501	310449.642	220699.248	252681.105	297858.995	314280.334
PRDM15	238371.886	315040.057	221124.508	311608.569	248419.924	278607.836	322989.055	341332.739
PRDM2	312018.619	248602.988	259982.941	212748.858	326650.936	368198.121	299431.958	267280.218

Not altered

PRDM5	191462.01	312154.358	209900.216	286450.597	273553.562	334106.35	282611.122	324573.734	
PRMT1	333199.107	235865.078	291631.314	244318.134	367872.777	326025.367	238390.974	239856.526	
PRMT3	280367.52	280030.168	263710.308	238852.919	337939.314	278521.46	300908.661	306672.271	
PRMT5	260043.82	278796.235	244246.334	258861.453	334133.979	324693.334	282991.094	289819.308	
PRMT7	300851.962	302452.572	271263.753	235427.929	315501.823	284060.229	306135.962	293669.01	
RBBP5	220505.591	357242.003	257259.44	346846.148	242747.024	254008.603	290106.896	314735.795	
RNMT	260832.215	328839.402	284858.861	331698.393	277179.139	307221.9	223585.392	212424.155	
RNMTL1	262016.762	277789.088	262266.235	340564.772	268435.919	263736.832	258425.391	274542.369	
RRP8	198469.336	229544.666	207455.842	306206.632	246013.237	311361.719	310884.864	340781.886	
SETD1A	232934.367	249788.99	257480.227	288004.591	300387.529	341162.576	287844.26	277934.678	
SETD1B	222061.879	293028.167	262564.627	349048.344	249574.494	317682.819	247893.965	258128.033	
SETD2	244142.83	301706.347	238876.239	271277.28	275323.954	303538.985	325483.525	325262.813	
SETD3	339617.06	274780.606	314488.829	264630.421	251505.784	257797.563	283173.485	284749.91	
SETD6	335681.478	404564.785	332083.099	240943.487	311993.924	265961	305877.716	232646.743	
SETD8	269477.272	374403.601	329300.843	333763.336	208092.97	248006.229	275933.464	243696.79	
SETDB1	272463.743	312478.194	240399.574	248080.597	308391.57	318374.204	335996.349	297336.102	
SMYD2	264248.562	330901.771	278708.877	296371.478	234511.016	269506.504	279603.598	302642.318	
SMYD3	280421.422	343455.341	281525.976	385042.559	209465.955	225663.166	270218.619	289539.536	
SMYD5	269982.241	311702.582	288075.938	258919.567	289926.819	297630.112	284398.605	295891.978	
SUV39H1	209727.788	386868.341	158755.383	254382.637	215924.924	225792.617	413845.84	433806.993	
SUV39H2	200684.273	328098.261	193049.305	293772.187	257974.793	277848.856	332608.99	354179.083	
TFB1M	225483.314	240577.851	257459.633	353255.008	283336.053	280207.79	279985.268	277543.66	
TFB2M	232291.598	275312.19	287484.415	352074.555	225485.515	228156.484	289411.045	280772.463	
TGS1	237920.773	291055.628	380818.86	195742.068	248664.621	248098.333	319741.669	346906.87	
THUMPD3	279924.076	257843.993	239272.847	210120.948	393164.023	354432.909	294359.329	264196.437	
TPMT	384361.528	284035.457	446976.305	202625.385	216859.178	283507.624	250679.596	243584.609	
TRMT1	266589.374	301877.116	285473.987	271211.885	363679.433	323612.546	254240.949	231275.259	
TRMT10A	265900.751	271510.282	270018.68	272482.589	438351.103	315520.487	263133.95	240833.5	
TRMT10C	209729.143	238003.659	292638.225	342383.997	199496.087	276316.483	265428.221	300727.163	
TRMT11	198227.587	324568.269	228701.15	385797.37	235069.565	277680.687	230357.7	270231.224	
TRMT112	336110.922	250592.718	278812.742	275801.91	333094.222	271066.241	282939.976	272096.975	
TRMT1L	231541.085	252390.182	262612.128	275410.22	379695.215	345481.242	257097.952	230083.362	
TRMT2B	239455.727	312577.175	345945.239	331270.524	212739.413	227569.32	264320.653	284380.613	
TRMT5	247588.923	311866.257	263730.627	265771.114	380861.672	359880.547	264621.255	219847.653	
TRMT6	248390.067	258410.573	293644.701	261866.373	400951.134	315641.476	261482.011	237345.233	
TRMT61A	256053.551	199175.158	256502.39	285138.623	439827.452	342899.473	233679.434	241086.084	
TRMU	232118.366	249670.515	290290.603	314671.735	246857.961	317271.14	236895.99	272077.856	
WBSCR22	261592.307	266941.248	247975.407	280382.933	325300.423	282386.553	364884.481	311768.875	
WBSCR27	311602.086	318527.905	317798.251	293376.895	334793.96	307271.862	220771.185	217504.536	
WDR4	257562.742	357582.172	310402.003	262944.729	357930.943	316795.72	234621.387	229220.677	
WDR5	214203.786	301780.463	229413.289	299542.124	269224.961	296059.462	314559.987	321929.851	
WDR82	205411.434	313144.187	251307.704	337012.788	227374.982	268251.796	291314.147	321829.412	
WHSC1L1	212943.29	366181.062	270228.909	341087.754	246326.367	269265.983	277934.025	276798.375	
ZCCHC4	249753.798	303910.755	301558.208	277149.045	284869.617	286093.421	269078.547	289583.534	
DNMT1	197725.832	240930.743	160614.592	185084.683	355969.106	317622.407	446453.499	430659.147	Significant changes
DNMT3A	189858.827	306977.783	158339.612	259927.332	272720.685	376006.029	323817.783	439092.305	
METTL20	102663.273	281023.793	126545.126	271889.924	270150.796	499788.149	316175.993	364290.876	
TRMT2A	267183.42	249402.062	212541.005	180536.729	444629.885	297370.835	387480.486	302504.095	
WHSC1	229196.512	280026.47	185209.5	228423.312	305683.5	295789.758	415621.12	384048.086	
SETDB2	230231.458	234233.358	230133.152	216864.875	290748.632	321188.122	356630.52	373027.882	
ALKBH8	274343.97	267142.454	214756.683	198324.592	422960.069	381248.486	268083.263	277208.146	
SETD7	374766.585	418773.403	371751.411	294233.998	261921.88	220555.902	208468.845	190327.211	
COMT	314197.76	305330.046	371488.356	352978.649	236113.488	254348.824	197167.065	188746.281	
METTL5	311930.837	395036.531	396823.336	308077.173	151035.644	189240.972	360276.804	251047.162	
OCLN	275437.8	373971.776	294286.316	365866.633	184607.808	239172.69	220922	252005.169	

Supplementary Data Table 3. Bisulfite conversion rates and sequencing statistics for WGBS

Sample	Genotype	Used reads	Number of CpGs	Mean depth	Bisulfite conversion
K1	KRASG12D/+	608,145,650	21,225,289	11.70	0.9964
K2	KRASG12D/+	584,203,381	21,199,148	10.53	0.9965
KL1	KRASG12D/+;LKB1-/-	583,916,832	21,192,517	11.03	0.9964
KL2	KRASG12D/+;LKB1-/-	688,180,303	21,234,711	12.49	0.9963