

## **Supporting Information for**

## Histone methyltransferase SETDB1 safeguards mouse fetal hematopoiesis by suppressing activation of cryptic enhancers

Maryam Kazerani, Filippo Cernilogar, Alessandra Pasquarella, Maria Hinterberger, Alexander Nuber, Ludger Klein, Gunnar Schotta

Gunnar Schotta

Email: [gunnar.schotta@bmc.med.lmu.de](mailto:gunnar.schotta@bmc.med.lmu.de)

### **This PDF file includes:**

Supporting text  
Figures S1 to S8  
Tables S1 to S11

### **Other supporting materials for this manuscript include the following:**

none

## Supporting Information Text

### Extended Methods

#### ULI-NChIP-sequencing

5000 LSK cells were sorted from E13.5 *Setdb1<sup>vaV</sup>* and control fetal livers into low-binding tubes and centrifuged. The cell pellet was resuspended in 20  $\mu$ L of EZ nuclei isolation lysis buffer (Sigma) containing 0.1% Triton, 0.1% deoxycholate, 1x cOmplete EDTA-free Protease Inhibitor Cocktail (Roche Diagnostics), 1 mM PMSF, flash frozen and kept at -80 °C. Chromatin fragmentation and immunoprecipitation were performed following the ultra-low-input micrococcal nuclease-based native ChIP (ULI-NChIP) protocol with minor modifications (1). Briefly, after thawing cells in nuclei isolation lysis buffer, 10% of the volume of 1% Triton/1% deoxycholate solution was added. Chromatin was fragmented using MNase (Biolabs) enzyme at 1.5 U/ $\mu$ L in MNase digestion buffer (1X MNase Reaction Buffer, 100 mM DTT, 50% PEG 6000, and ultrapure H<sub>2</sub>O) for 7.5 minutes at 21°C. Reaction was stopped by adding 10% of the reaction volume of 100  $\mu$ M EDTA and 1% Triton/1% deoxycholate solution. To 120  $\mu$ L fragmented chromatin, 380  $\mu$ L of complete immunoprecipitation buffer (20 mM Tris-HCl pH 8.0, 2 mM EDTA, 150 mM NaCl, 0.1% Triton X-100, 1x cOmplete EDTA-free Protease Inhibitor Cocktail, 1 mM PMSF) was added. Chromatin was rotated for 1 hour at 4°C and 13 rpm. For input, 100  $\mu$ L of sample was taken, 10% volume of 10% SDS (10  $\mu$ L) was added and mixed with 90  $\mu$ L elution buffer (Qiagen). Chromatin was pre-cleared with 1:1 protein A:protein G Dynabeads (Thermo Fischer Scientific) and incubated for 3 hours on a rotator at 4°C and 13 rpm. In parallel, per IP tube, 0.25  $\mu$ g of H3K9me3 antibody (Active motif) was incubated with 5  $\mu$ L of pre-washed 1:1 protein A:protein G Dynabeads (Thermo Fischer Scientific) in 100  $\mu$ L complete immunoprecipitation buffer for 3 hours on a rotator at 4°C and 13 rpm. The antibody-coated beads were washed 1X with 200  $\mu$ L complete immunoprecipitation buffer

and the pre-cleared chromatin was then added to the antibody-beads complex. The immunoprecipitation was carried out overnight (12 hours) at 4°C whilst rocking at 13rpm. Chromatin-bound beads were first washed 3X, each for 10 min at 4°C and 20 rpm with 500 µL low salt wash buffer (20 mM Tris-HCl (pH 8.0), 2 mM EDTA, 150 mM NaCl, 1% Triton X-100, 0.1% SDS) and then 3X with high salt wash buffer (20 mM Tris-HCl pH 8.0, 2 mM EDTA, 500 mM NaCl, 1% Triton X-100, 0.1% SDS). Per sample, 2 IP tubes were pooled and were eluted in 30 µL freshly prepared ChIP elution buffer (100 mM NaHCO<sub>3</sub>, 1% SDS) for 1.5 hours at 65°C in a thermo-shaker. To maximize the elution, additional 70 µL freshly prepared ChIP elution buffer was added to the beads. DNA isolation was carried out by Agencourt AMPure XP beads (Beckman Coulter) from input and ChIP samples. Samples were quantified in a Qubit 3.0 Fluorometer with Qubit dsDNA HS Assay kit (Thermo Fischer Scientific). Fragmentation of MNase-treated chromatin was assessed on input sample by the Agilent High Sensitivity DNA Kit (Agilent Technologies). Input and ChIP samples were subjected to library preparation with MicroPlex Library Preparation Kit v2 (Diagenode). The quantity of the libraries was assessed in a Qubit 3.0 Fluorometer with Qubit dsDNA HS Assay kit (Thermo Fischer Scientific). Libraries were further qualified by the Agilent High Sensitivity DNA Kit (Agilent Technologies). Libraries were sequenced using Illumina's HiSeq 1500 sequencer for 50 bp single-end (SE) reads at the Laboratory for Functional Genome Analysis (LAFUGA) within the Gene Center (LMU Munich).

### **Omni-ATAC-sequencing**

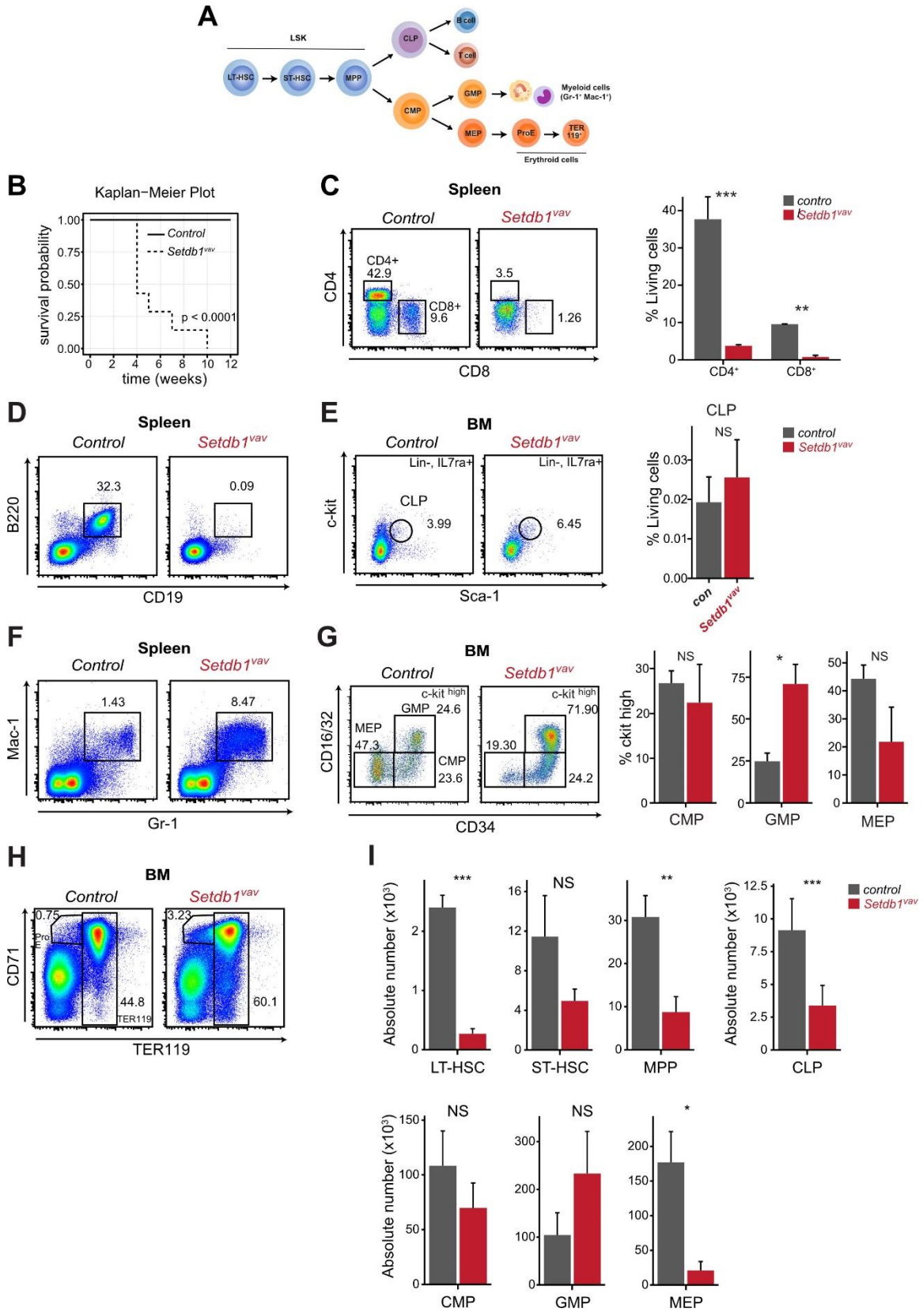
ATAC-seq was performed as previously described (2). Briefly, 10,000 LSK cells were sorted from E13.5 Setdb1<sup>val</sup> and control fetal livers into low-binding tubes. Cells were spun at 500 g for 5 min at 4°C. Cell pellets were resuspended and lysed in cold ATAC Resuspension Buffer (10mM Tris-HCl pH 7.4, 10 mM NaCl, 3 mM MgCl<sub>2</sub>) containing 0.1% NP40, 0.1% Tween-20, and 0.01% digitonin. Cell lysis reaction was incubated on ice for

3 min and then 1 ml of ATAC Resuspension Buffer containing only 0.1% Tween-20 was added and centrifuged at 500 g for 5 min at 4°C. Nuclei were then resuspended in 10 µL of Transposition Mix containing 25 µL 2x Tagmentation Buffer (20 mM Tris-HCl pH 7.6, 10 mM MgCl<sub>2</sub>, 20% dimethyl Formamide, H<sub>2</sub>O), 2.5 µL Tn5 Transposase (Illumina), 5.25 µL H<sub>2</sub>O, 16.5 µL PBS, 0.25 µL of 2% digitonin (Promega) and 0.5 µL of 10% Tween-20. Reactions were proceeded by incubation for 30 min at 37°C in a thermo-shaker at 900 rpm. DNA was subsequently purified using PCR clean-up MinElute kit (Qiagen). Libraries were amplified in 50 µL reactions with custom primers. Amplified libraries were purified with the PCR clean-up MinElute kit (Qiagen) and size selected for fragments less than 600 bp using the Agencourt AMPure XP beads (Beckman Coulter). Libraries were quantified in a Qubit 3.0 Fluorometer with Qubit dsDNA HS Assay kit (Thermo Fischer Scientific). Further quantification of the libraries was performed by the Agilent High Sensitivity DNA Kit (Agilent Technologies). Libraries were sequenced using Illumina's HiSeq 1500 sequencer for 50 bp single-end (SE) reads at the Laboratory for Functional Genome Analysis (LAFUGA) within the Gene Center (LMU Munich).

### **RNA-sequencing**

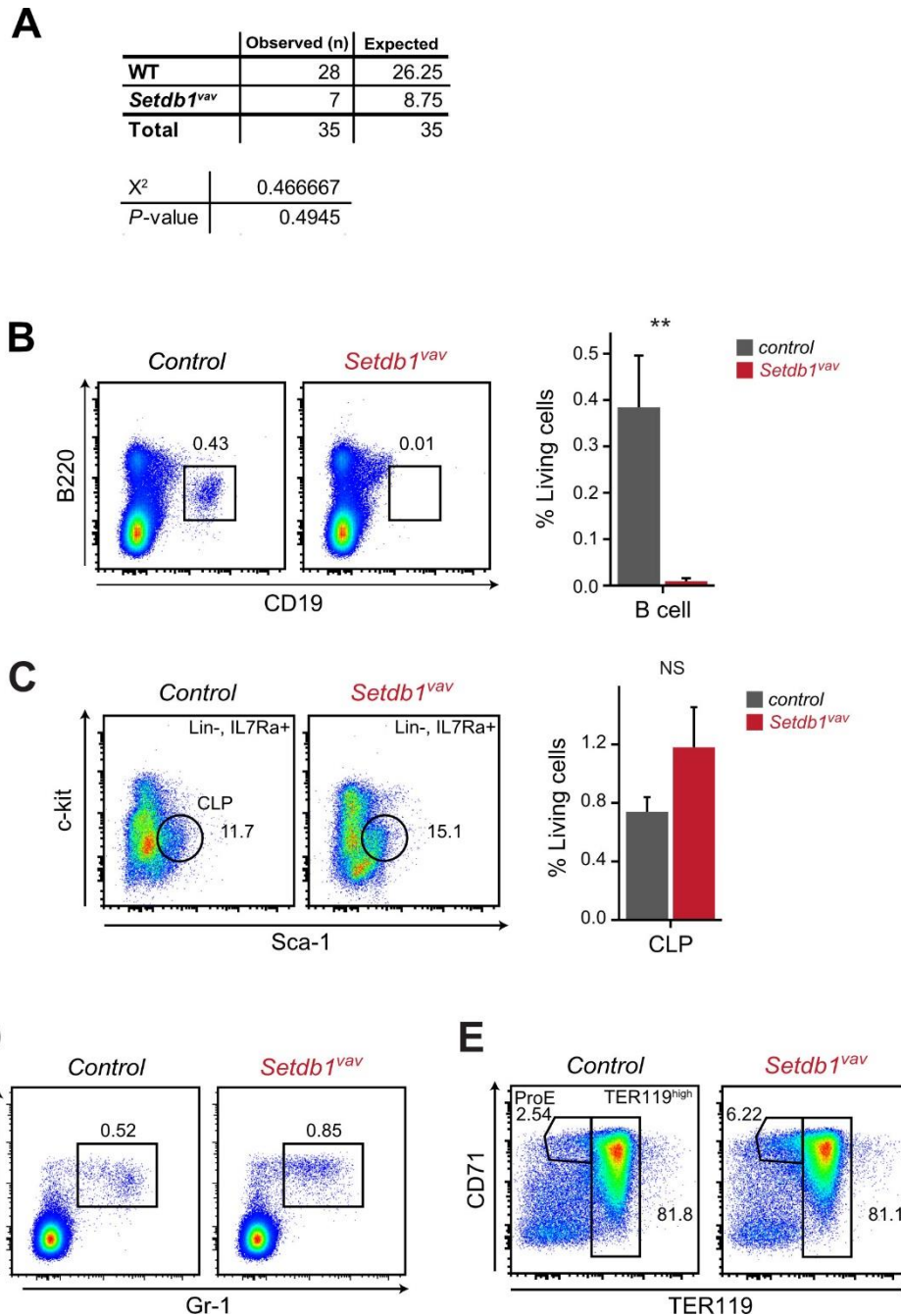
To isolate total RNA, E13.5 *Setdb1*<sup>va</sup> and control fetal liver LT-HSCs and MPPs were sorted directly into the 100 µl extraction buffer, provided by PicoPure RNA Isolation Kit (Thermo Fischer Scientific). Total RNA isolation was carried out according to the manufacturer's instructions. DNase treatment was performed on column using RNase-Free DNase Set (Qiagen). RNA quantity and quality were assessed on an Agilent 2100 Bioanalyzer by the Agilent RNA 6000 Pico Kit (Agilent Technologies). High-quality RNA samples with RNA Integrity Number (RIN) > 8 were used for cDNA synthesis with SMART-Seq v4 Ultra Low Input RNA Kit (Clontech) according to the manufacturer's instruction. Before proceeding to library preparation, cDNA was sheared in a Covaris S220 device

(PP 175; DF 10; CB 200; 5 min; 4°C) to the size range of 200–500 bp and subjected to library preparation with MicroPlex Library Preparation Kit v2 (Diagenode). The quantity of the libraries was assessed in a Qubit 3.0 Fluorometer with Qubit dsDNA HS Assay kit (Thermo Fischer Scientific). Libraries were further quantified by the Agilent High Sensitivity DNA Kit (Agilent Technologies). Libraries were sequenced using Illumina's HiSeq 1500 sequencer for 50 bp paired end (PE) reads at the Laboratory for Functional Genome Analysis (LAFUGA) within the Gene Center (LMU Munich).



**Fig. S1. Impaired hematopoietic lineage differentiation in postnatal *Setdb1<sup>va/v</sup>* mice**

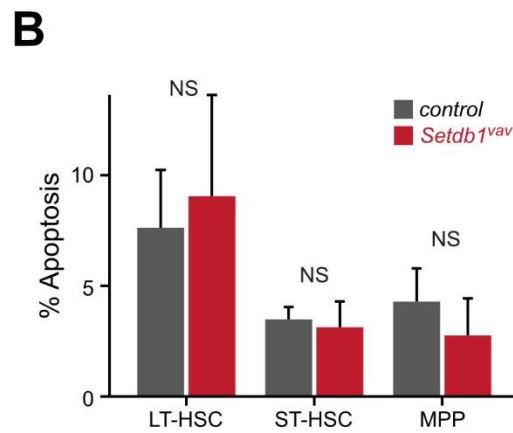
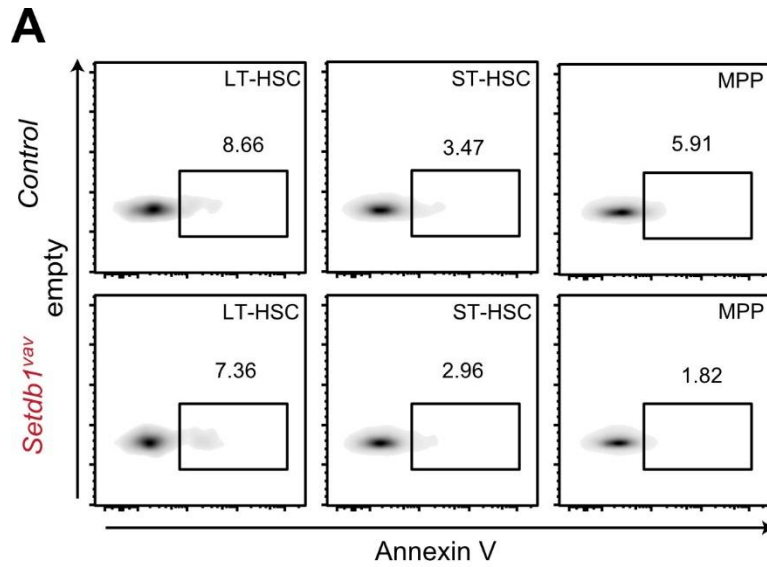
**(A)** Schematic of hematopoietic differentiation and cell types analyzed in this study. **(B)** Kaplan Meier plot showing survival of control and *Setdb1<sup>va/v</sup>* mice. **(C)** Representative FACS plots and bar graphs showing percentages of CD4<sup>+</sup> and CD8<sup>+</sup> T cells in the spleen of 2-week-old control and *Setdb1<sup>va/v</sup>* mice (n = 3). **(D)** Representative FACS plots showing B cells in the spleen of control and *Setdb1<sup>va/v</sup>* mice. **(E)** Representative FACS plots and bar graphs showing percentages of CLP cells in the bone marrow of 2-week-old control and *Setdb1<sup>va/v</sup>* mice (n = 7). **(F)** Representative FACS plots showing Gr-1<sup>+</sup> Mac-1<sup>+</sup> cells in the spleen of control and *Setdb1<sup>va/v</sup>* mice. **(G)** Representative FACS plots and bar graphs showing percentages of CMP, GMP, and MEP cells in the bone marrow of 2-week-old control and *Setdb1<sup>va/v</sup>* mice (n = 3). **(H)** Representative FACS plots showing ProE, and TER119<sup>+</sup> cells in the bone marrow of control and *Setdb1<sup>va/v</sup>* mice. **(I)** Absolute numbers of hematopoietic stem and progenitor cell populations in postnatal control and *Setdb1<sup>va/v</sup>* mice. Data are shown as mean ± SD. \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001 (unpaired two-tailed Student's t-test); CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte-monocyte progenitor; MEP, megakaryocyte–erythroid progenitor; NS, not significant.



**Fig. S2. Myeloerythroid differentiation bias in *Setdb1<sup>vav</sup>* Fetal Livers**

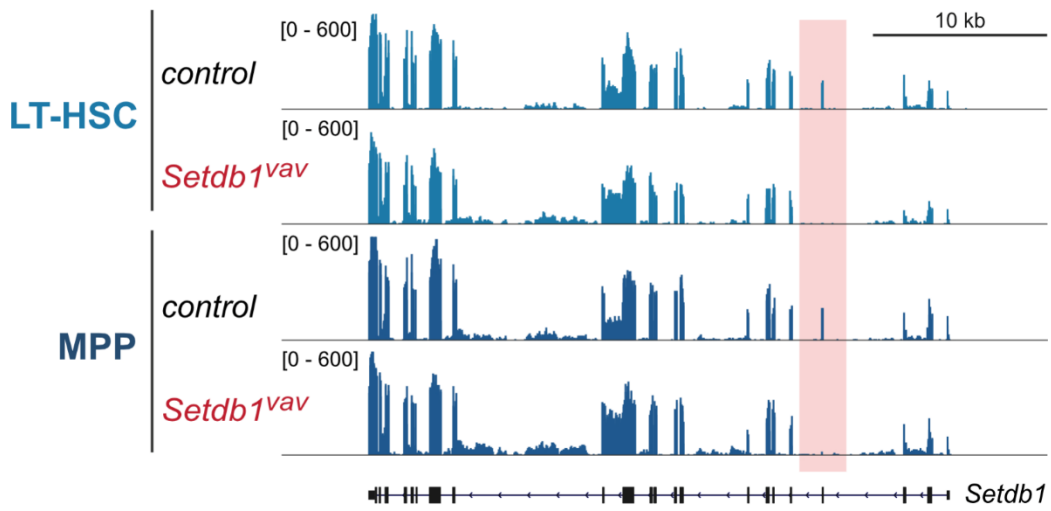
(A) Expected and observed Mendelian inheritance in embryos at E13.5. *P*-value was calculated with the Chi-square test. High *P* value indicates no significant deviation from the expected Mendelian Ratio. (B) Representative FACS plots and bar graph showing percentages of B cells in control and *Setdb1<sup>vav</sup>* E13.5 fetal livers (*n* = 3). (C) Representative FACS plots and bar graph showing percentages of CLP cells in control and *Setdb1<sup>vav</sup>* E13.5 fetal livers (*n* = 3). (D) Representative FACS plots showing Gr-1+ Mac-1+ cells and (E) ProE as well as TER119+ erythroblasts in control and *Setdb1<sup>vav</sup>* E13.5 fetal livers. Data are shown as mean  $\pm$  SD. \*\**P* < 0.01, (unpaired two-tailed Student's *t*-test); NS, not significant.





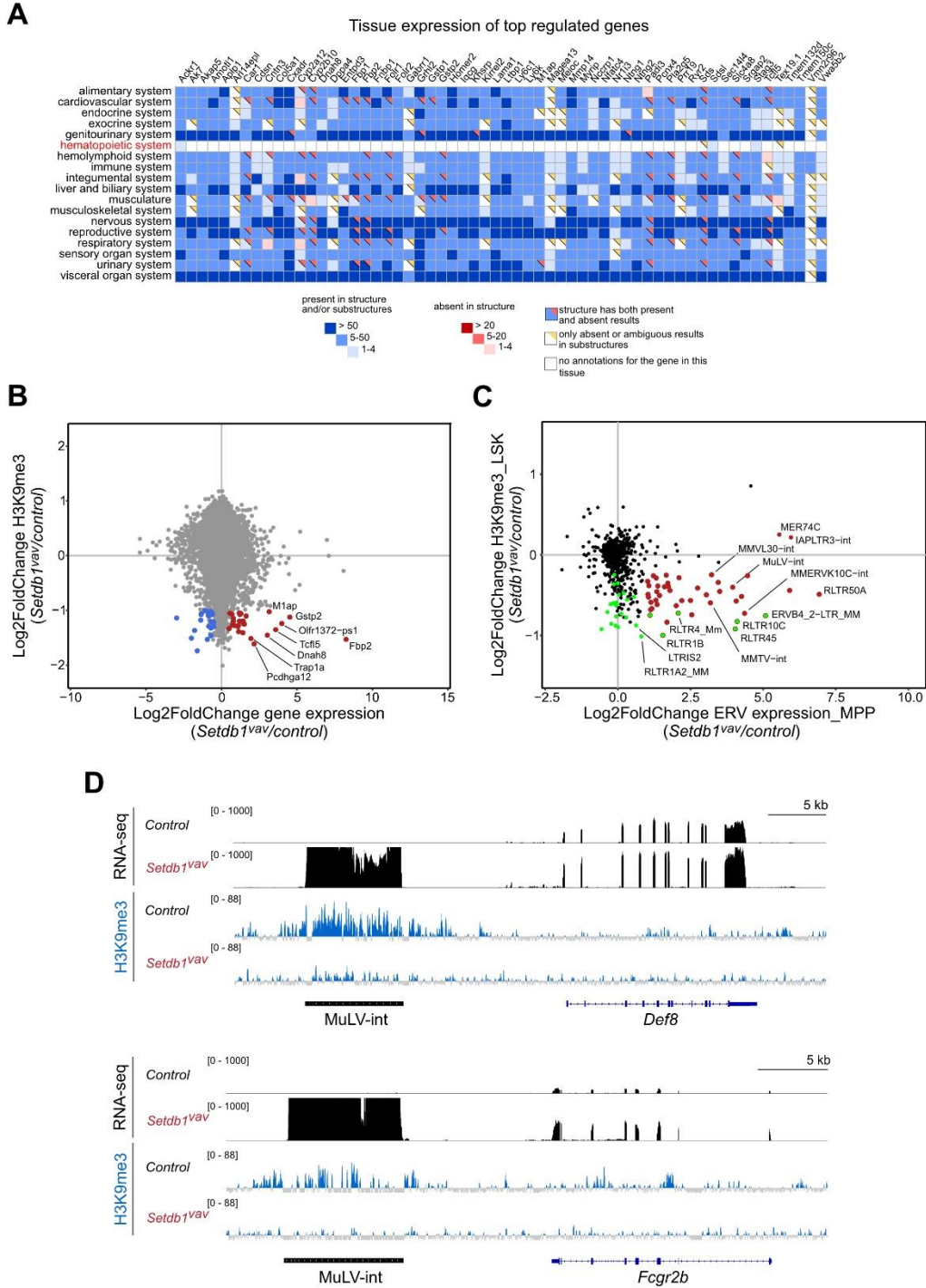
**Fig. S3. Normal survival of *Setdb1<sup>vav</sup>* FL HSPCs**

**(A)** Representative FACS plots and **(B)** bar graph showing percentages of apoptotic cells (Annexin V+) in LT-HSC, ST-HSC, and MPP cells in control and *Setdb1<sup>vav</sup>* E13.5 fetal livers (n = 4). Data are shown as mean  $\pm$  SD. unpaired two-tailed Student's t-test; NS, not significant.

**A**

**Fig. S4. Efficient deletion of *Setdb1* in *Setdb1*<sup>vav</sup> LT-HSC and MPP**

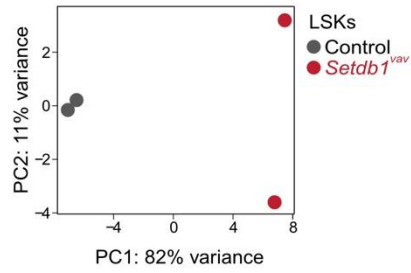
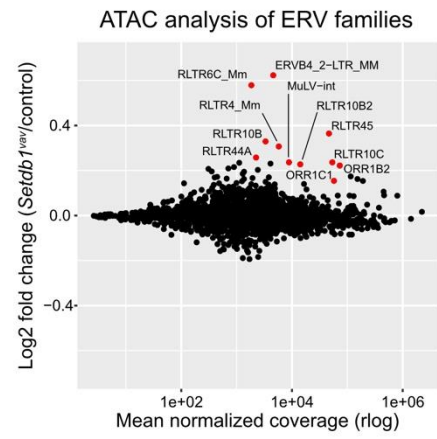
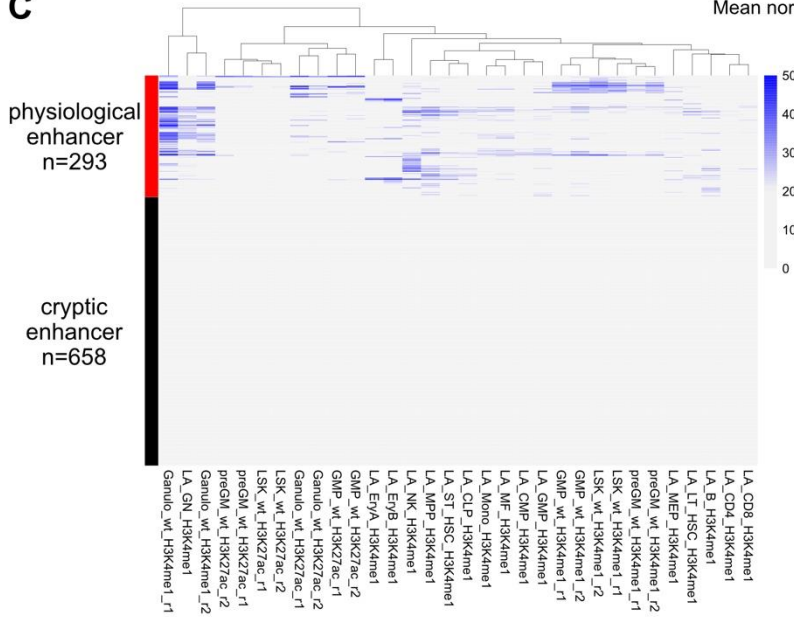
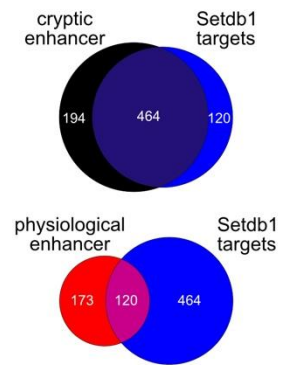
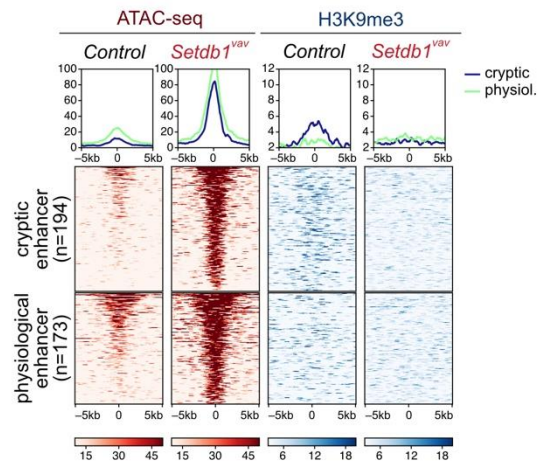
**(A)** Genome browser view showing RNA-seq tracks in the *Setdb1* locus. Red-colored box indicates exon 4 which is efficiently deleted in *Setdb1*<sup>vav</sup> LT-HSC and MPP cells.



**Fig. S5. Non-hematopoietic genes and retrotransposons lose H3K9me3 and are derepressed in *Setdb1<sup>vav</sup>* HSPCs**

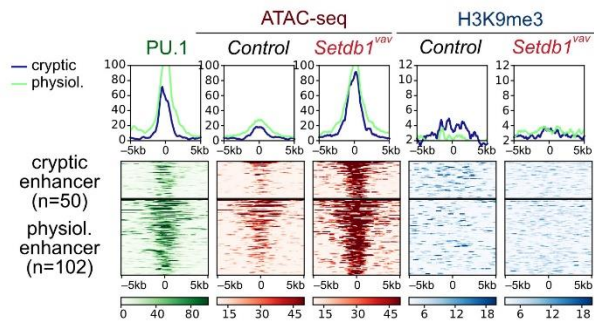
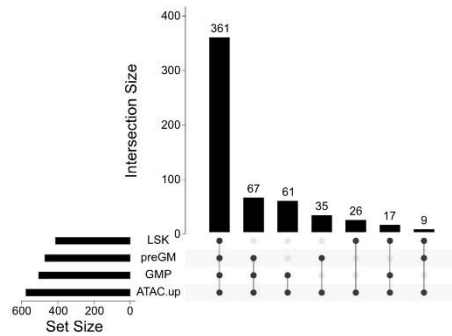
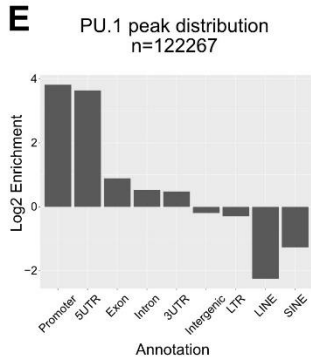
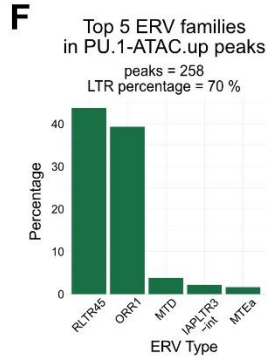
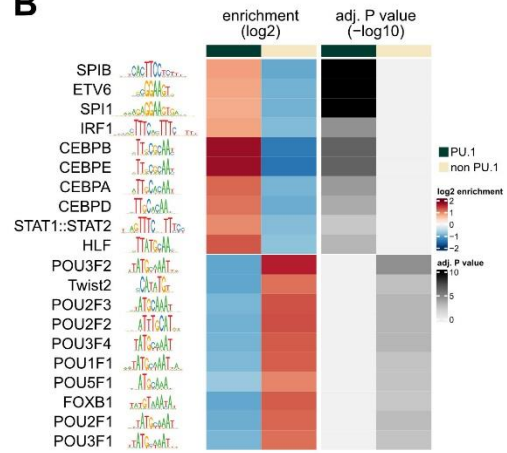
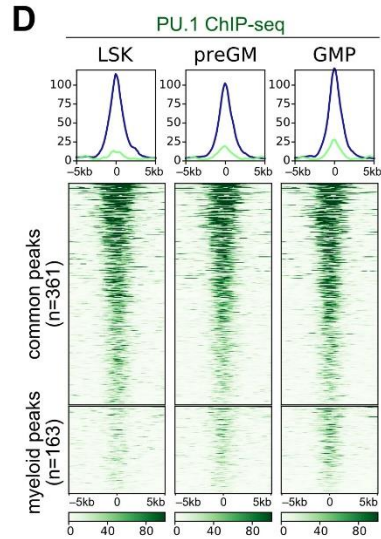
(A) Tissue expression of top 60 up-regulated genes in *Setdb1<sup>vav</sup>* MPPs (<https://www.informatics.jax.org/expression.shtml>). (B) Scatter plot showing gene expression changes vs. changes in promoter H3K9me3 (-4kb - +1kb relative to TSS) of genes. Highlighted are significantly upregulated (red) or downregulated (blue) genes in *Setdb1<sup>vav</sup>* MPPs (Padj < 0.05, abs log2 fold change > 0.5) with reduced H3K9me3 (log2 fold change < -1). (C) Scatter plot showing

changes in expression of ERV families vs. changes in ERV family H3K9me3 occupancy. Highlighted in red are significantly upregulated ERV families in *Setdb1<sup>vaV</sup>* MPPs (Padj < 0.01, log2 fold change > 1). ERV families with significantly reduced H3K9me3 (Padj < 0.05) are marked in green. **(D)** Genome browser view showing expression (RNA-seq) and H3K9me3 on two genomic regions with derepressed MuLV elements in *Setdb1<sup>vaV</sup>* MPPs. Genes in the vicinity of MuLVs (*Def8*, *Fcgr2b*) display increased expression in *Setdb1<sup>vaV</sup>* MPPs.

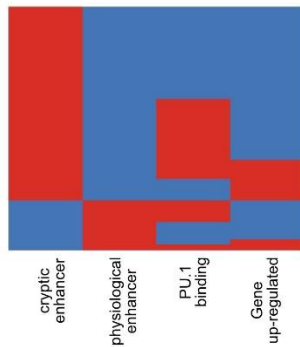
**A****B****C****D****E**

**Fig. S6. Enhanced chromatin accessibility on ERVs and enhancer regions in *Setdb1<sup>va</sup>* LSK cells**

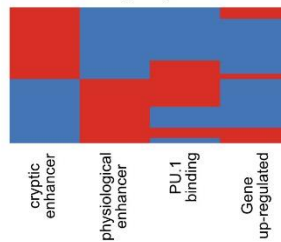
**(A)** PCA of ATAC-seq peaks coverage in control vs. *Setdb1<sup>va</sup>* LSK cells. **(B)** Association of *Setdb1<sup>va</sup>* upregulated ATAC peaks with ERV families. Bar plot shows the proportion of ATAC\_up peaks overlapping with ERVs. **(C)** Clustered heatmap showing normalized read coverage for enhancer chromatin modifications H3K4me1 or H3K27ac on ATAC\_up peaks using Lara-Astiaso et al. 2014 and Pundhir et al., 2018 data. ATAC\_up peaks with detectable levels of either histone modification in any cell state were assigned physiological enhancers, while ATAC\_up peaks without detectable enrichment of enhancer modifications were assigned cryptic enhancers. **(D)** Venn diagrams showing overlaps between cryptic and physiological enhancers with H3K9me3 enrichment (SETDB1 targets). **(E)** Heatmap and cumulative coverage plots showing ATAC and H3K9me3 coverage for ATAC\_up peaks without H3K9me3 enrichment corresponding to cryptic and physiological enhancers. Distance from the peak center is given in bp.

**A****C****E****F****B****D****G**

Setdb1 targets (H3K9me3 pos.)



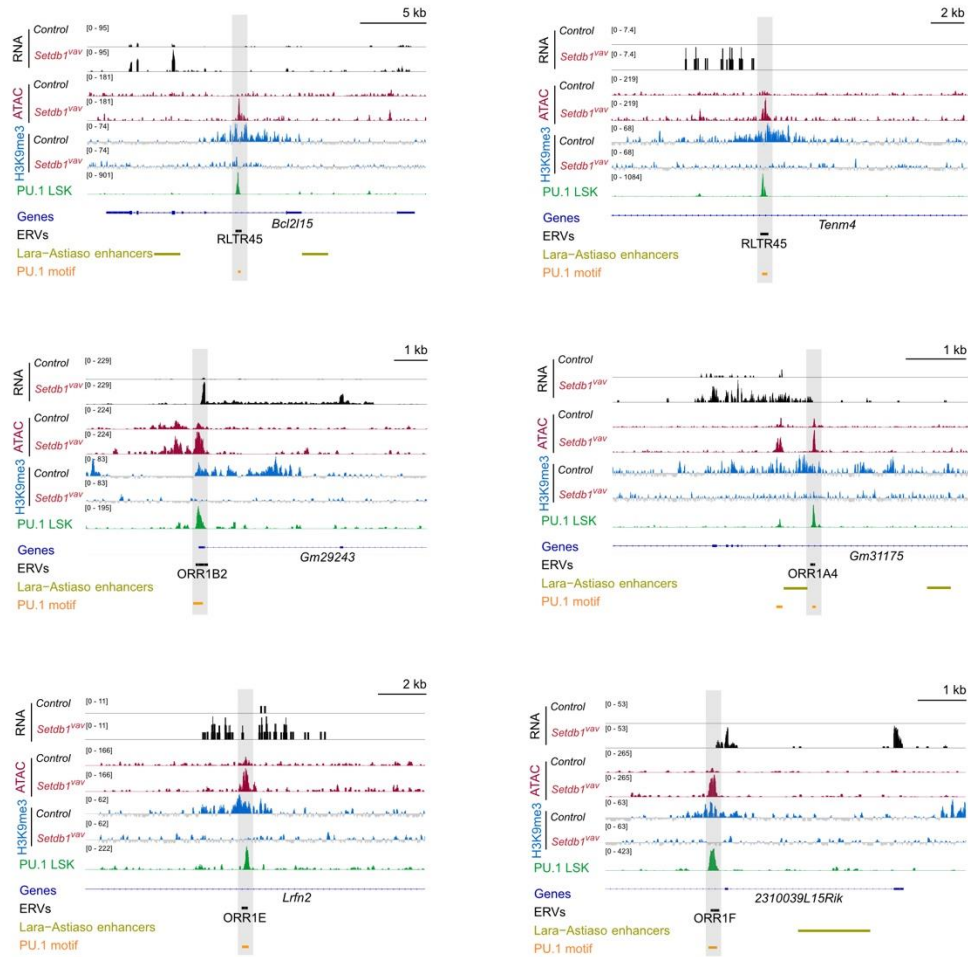
non Setdb1 targets (H3K9me3 neg.)



**Fig. S7. Connections between ATAC\_up peaks and PU.1 binding**

**(A)** Heatmap and cumulative coverage plots of ATAC\_up peaks without H3K9me3 enrichment overlapping with PU.1 peaks in LSK cells (3) showing PU.1 binding, ATAC-seq, and H3K9me3 ChIP-seq coverage. Distance from the peak center is given in bp. **(B)** monaLisa analysis of PU.1 enriched vs. non-PU.1 enriched ATAC\_up peaks. Heatmap displays motifs, motif enrichment, and adjusted p-value. **(C)** UpSet plot showing overlaps between ATAC\_up peaks and PU.1 binding in LSK, preGM, and GMP cells. **(D)** Heatmap and cumulative coverage plots of PU.1 binding in ATAC\_up peaks that are common or myeloid-specific as defined in (C). **(E)** Enrichment of genomic features in PU.1 peaks. **(F)** Association of ATAC\_up peaks overlapping with PU.1 binding with ERV families. Bar plot shows the proportion of ATAC\_up peaks overlapping with ERVs. **(G)** Heatmaps showing connections between cryptic and physiological enhancers, PU.1 binding, and up-regulated genes in the vicinity of these regions. Red – feature present; Blue – feature absent.



**A****Fig. S8. SETDB1-dependent expression changes**

(A) Genome browser view of SETDB1-dependent expression changes on genes along with ATAC-seq and H3K9me3 coverage. PU.1 binding profile is based on (3).

**Table S1: Antibodies**

Antibody	Clone	Fluorochrome	Provider	Identifier		
Anti-mouse CD117	2B8	APC-Alexa Fluor 780	Thermo Fischer Scientific	Cat# 47-1171-80		
Anti-mouse CD127(IL7R $\alpha$ )	A7R34	PE-Cy5	Thermo Fischer Scientific	Cat# 15-1271-81		
Anti-mouse CD150	mShad150	APC	Thermo Fischer Scientific	Cat# 17-1502-80		
Anti-mouse CD150	mShad150	FITC	Thermo Fischer Scientific	Cat# 11-1502-80		
Anti-mouse CD16/32	93	PE-Cy7	Thermo Fischer Scientific	Cat# 25-0161-81		
Anti-mouse CD34	RAM34	eFluor 660	Thermo Fischer Scientific	Cat# 50-0341-82		
Anti-mouse CD3e	145-2C11	APC-eFluor 780	Thermo Fischer Scientific	Cat# 47-0031-80		
Anti-mouse CD45.1	A20	PE-Cy7	Thermo Fischer Scientific	Cat# 25-0453-81		
Anti-mouse CD45.2	104	FITC	Thermo Fischer Scientific	Cat# 11-0454-81		
Anti-mouse CD45R/B220	RA3-SB2	APC-Alexa-Fluor 750	Thermo Fischer Scientific	Cat# 27-0452-82		
Anti-mouse CD48	HM48-1	PE-Cy7	Thermo Fischer Scientific	Cat# 25-0481-80		
Anti-mouse CD62L	MEL-14	FITC	Thermo Fischer Scientific	Cat# 11-0621-82		
Anti-mouse CD71	R17217	PE	Thermo Fischer Scientific	Cat# 12-0711-81		
Anti-mouse CD8a	53-6.7	PE-Cy7	Thermo Fischer Scientific	Cat# 25-0081-81		
Anti-mouse Ki67	SolA15	eFluor 450	Thermo Fischer Scientific	Cat# 48-5698-80		
Anti-mouse Ly-6G(Gr-1)	RB6-8C5	PE	Thermo Fischer Scientific	Cat# 12-5931-81		
Anti-mouse Sca-1	D7	FITC	Thermo Fischer Scientific	Cat# 11-5981-81		
Anti-mouse Sca-1	D7	PerCP-Cyanine 5.5	Thermo Fischer Scientific	Cat# 45 5981-80		
Anti-mouse Ter119	TER119	APC-AlexaFluor 780	Thermo Fischer Scientific	Cat# 47-5921-80		
Anti-mouse Ter119	Ter-119	PE	Thermo Fischer Scientific	Cat# 12-5921-81		
Anti-mouse CD11b/Mac-1	M1/70	PE	BD Bioscience	Cat# 553311		
Anti-mouse CD11c	HL3	PE	BD Bioscience	Cat# 553802		
Anti-mouse CD127(IL7R $\alpha$ )	SB/199	BV421	BD Bioscience	Cat# 566300		
Anti-mouse CD19	1D3	PE	BD Bioscience	Cat# 553786		
Anti-mouse CD3e	145-2C11	PE	BD Bioscience	Cat# 553064		
Anti-mouse CD4	PM4-5	PE	BD Bioscience	Cat# 553049		
Anti-mouse CD45R/B220	RA3-6B2	PE	BD Bioscience	Cat# 561878		
Anti-mouse CD49d (VLA-4)	R1-2	BV786	BD Bioscience	Cat# 564397		
Anti-mouse CD8a	53-6.7	PE	BD Bioscience	Cat# 553033		
Mouse BD Fc Block	2.4G2	purified	BD Bioscience	Cat# 553142		
<b>ChIP antibody</b>						
Target	ID	Weight	Host	Type	Provider	Identifier
H3K9me3	249	17 kDa	rabbit	polyclonal	Active Motif	39161

**Table S2: Markers for cell definition**

Cell population	Gating strategy
LT-HSC	Living cells, Lin <sup>-</sup> , Sca-1 <sup>+</sup> , c-kit <sup>+</sup> , CD150 <sup>+</sup> , CD48 <sup>-</sup>
MPP	Living cells, Lin <sup>-</sup> , Sca-1 <sup>+</sup> , c-kit <sup>+</sup> , CD150 <sup>-</sup> , CD48 <sup>+</sup>
LSK	Living cells, Lin <sup>-</sup> , Sca-1 <sup>+</sup> , c-kit <sup>+</sup>
CLP	Living cells, Lin <sup>-</sup> , IL7R $\alpha$ <sup>+</sup> , Sca-1 <sup>low</sup> , c-kit <sup>low</sup>
CMP	Living cells, Lin <sup>-</sup> , c-kit <sup>high</sup> , Sca-1 <sup>-</sup> , CD34 <sup>+</sup> , CD16/32 <sup>-low</sup>
MEP	Living cells, Lin <sup>-</sup> , c-kit <sup>high</sup> , Sca-1 <sup>-</sup> , CD34 <sup>-</sup> , CD16/32 <sup>-</sup>
GMP	Living cells, Lin <sup>-</sup> , c-kit <sup>high</sup> , Sca-1 <sup>-</sup> , CD34 <sup>+</sup> , CD16/32 <sup>+</sup>
B cell	Living cells, Lymphocyte, CD19 <sup>+</sup> , B220 <sup>+</sup>
DN1	Living cells, CD44 <sup>+</sup> , CD25 <sup>-</sup>
DN2	Living cells, CD44 <sup>+</sup> , CD25 <sup>+</sup>
DN3	Living cells, CD44 <sup>+</sup> , CD25 <sup>+</sup>
DN4	Living cells, CD44 <sup>+</sup> , CD25 <sup>-</sup>
DP	Living cells, CD3 <sup>+</sup> , CD4 <sup>+</sup> , CD8 <sup>+</sup>
SP CD4	Living cells, CD3 <sup>+</sup> , CD4 <sup>+</sup> , CD8 <sup>-</sup>
SP CD8	Living cells, CD3 <sup>+</sup> , CD4 <sup>-</sup> , CD8 <sup>+</sup>
ProE	Living cells, CD71 <sup>+</sup> , TER119 <sup>-</sup>
TER119 erythroblasts	Living cells, CD71 <sup>+</sup> , TER119 <sup>+</sup>
Granulocyte/Macrophage/Monocyte	Living cells, Gr-1 <sup>+</sup> , Mac-1 <sup>+</sup>

**Table S3: Reagents and commercial assays**

Reagent/Commercial assay	Provider	Identifier
Agencourt AMPure XP	Beckman Coulter	Cat# A63882
Agilent High Sensitivity DNA Kit	Agilent	Cat# 5067-4626
Agilent RNA 6000 Pico Kit	Agilent	Cat# 5067-1513
Annexin V Apoptosis Detection Kit FITC	Thermo Fischer Scientific	Cat# 88-8005-72
Anti-PE MicroBeads	Miltenyi	Cat# 130-048-801
Arcturus® PicoPure® RNA Isolation Kit	Thermo Fischer Scientific	Cat# KIT0204
CellTrace CFSE Cell Proliferation Kit	Thermo Fischer Scientific	Cat# C34570
cOmplete, Mini, EDTA-free Protease Inhibitor Cocktail	Roche Diagnostics	Cat# 4693159001
Digitonin	Promega	Cat# G9441
Dynabeads Protein A/Protein G	Thermo Fischer Scientific	Cat# 10015D
Elution Buffer (EB)	Qiagen	Cat# 19086
Foxp3 / Transcription Factor Staining Buffer Set	Thermo Fischer Scientific	Cat# 00-5523-00
Methocult M3434	STEMCELL Technologies	Cat# 03434
Methocult M3630	STEMCELL Technologies	Cat# 03630
MicroPlex Library Preparation Kit v2	Diagenode	Cat# C05010012
MNase	Biolabs	Cat# M0247S
Nextera DNA Library Preparation Kit	Illumina	Cat# FC-121-1030
Nuclei Isolation Kit: Nuclei EZ Prep	Sigma	Cat# NUC-101
Osteosoft	Merck	Cat# 101728
PCR clean-up MinElute kit	Qiagen	Cat# 28006
Qubit dsDNA HS Assay kit	Thermo Fischer Scientific	Cat# Q33854
red blood cell lysis buffer	BD Bioscience	Cat# 555899
RNase-Free DNase Set	Qiagen	Cat# 79254
SMART-Seq v4 Ultra Low Input RNA Kit	Clontech	Cat# 634888
Zombie Aqua Fixable Viability Dye	BioLegend	Cat# 423101

**Table S4: NGS libraries**

Library Name	ID	Experiment	Sequencing mode	Index
LT-HSC_Con2	GS98	RNA-seq	50 bp paired-end	ATCACG
LT-HSC_Con3	GS99	RNA-seq	50 bp paired-end	CGATGT
LT-HSC_Con4	GS100	RNA-seq	50 bp paired-end	TTAGGC
LT-HSC_Mut-1	GS101	RNA-seq	50 bp paired-end	TGACCA
LT-HSC_Mut-3	GS102	RNA-seq	50 bp paired-end	ACAGTG
LT-HSC_Mut-4	GS103	RNA-seq	50 bp paired-end	GCCAAT
MPP_Con1	GS104	RNA-seq	50 bp paired-end	CAGATC
MPP_Con2	GS105	RNA-seq	50 bp paired-end	ACTTGA
MPP_Con3	GS106	RNA-seq	50 bp paired-end	GATCAG
MPP_Mut-1	GS107	RNA-seq	50 bp paired-end	TAGCTT
MPP_Mut-2	GS108	RNA-seq	50 bp paired-end	GGCTAC
MPP_Mut-4	GS109	RNA-seq	50 bp paired-end	CTTGTA
LSK_Input_con_1	GS353	ULI-NChIP-seq	50 bp single-end	ATCACG
LSK_H3K9me3_con_1	GS344	ULI-NChIP-seq	50 bp single-end	CGATGT
LSK_H3K9me3_con_2	GS229	ULI-NChIP-seq	50 bp single-end	CGATGT
LSK_H3K9me3_con_3	GS346	ULI-NChIP-seq	50 bp single-end	GCCAAT
LSK_H3K9me3_mut_1	GS345	ULI-NChIP-seq	50 bp single-end	TTAGGC
LSK_H3K9me3_mut_2	GS352	ULI-NChIP-seq	50 bp single-end	ACAGTG
LSK_H3K9me3_mut_3	GS347	ULI-NChIP-seq	50 bp single-end	CAGATC
FL_LSK_con1_Omni-ATAC	GS472	Omni-ATAC-seq	50 bp single-end	GCTACGCT
FL_LSK_con2_Omni-ATAC	GS444	Omni-ATAC-seq	50 bp single-end	AGGCAGAA
FL_LSK_mut1_Omni-ATAC	GS473	Omni-ATAC-seq	50 bp single-end	CGAGGCTG
FL_LSK_mut2_Omni-ATAC	GS445	Omni-ATAC-seq	50 bp single-end	CGAGGCTG

**Table S5: Genes significantly upregulated in *Setdb1*<sup>av</sup> LT-HSCs**

gene	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
Magea13	255.443892	3.91226304	0.19643763	14.321552	1.60E-46	5.81E-43
Iqcg	287.272926	3.05452084	0.18559501	15.868804	1.04E-56	5.03E-53
Stag3	1405.794399	2.96320513	0.14616343	20.180222	1.46E-90	2.11E-86
Dnah8	1156.891857	2.43437381	0.12855484	18.871677	1.95E-79	1.41E-75
Tmem150c	79.504009	2.3214372	0.20866722	7.200562	6.00E-13	3.94E-10
Akap5	151.113252	2.2954194	0.20506166	11.110825	1.11E-28	1.61E-25
M1ap	484.265603	2.25293503	0.18157802	12.381931	3.27E-35	7.90E-32
1700097N02Rik	366.951065	2.13473463	0.18728389	11.37589	5.51E-30	9.98E-27
Fcgr2b	330.552619	2.12454222	0.20874961	11.328495	9.48E-30	1.52E-26
2810474O19Rik	3390.548825	1.93852159	0.15016093	12.911049	3.90E-38	1.13E-34
Gstp2	160.178937	1.68153886	0.20842234	8.635023	5.87E-18	7.08E-15
Meioc	157.803667	1.65184762	0.20174505	7.675555	1.65E-14	1.40E-11
Car1	5570.616251	1.51888416	0.20014001	11.862318	1.86E-32	3.84E-29
Cldn10	75.734083	1.45283395	0.20865305	7.036914	1.97E-12	1.14E-09
Amot1	72.14265	1.43147296	0.20387799	7.666442	1.77E-14	1.42E-11
Gstp1	2152.671706	1.40856093	0.15182173	9.277802	1.73E-20	2.28E-17
Entpd3	40.988717	1.27476849	0.19673728	6.659554	2.75E-11	1.42E-08
Slc1a4	482.573921	1.23794086	0.19432793	6.386418	1.70E-10	7.45E-08
Ldoc1l	452.503309	1.23520375	0.17539496	7.039409	1.93E-12	1.14E-09
Def8	4929.919785	1.21784481	0.15543229	7.837245	4.61E-15	4.17E-12
Arl14epl	32.508212	1.14781722	0.19016589	6.491304	8.51E-11	3.85E-08
4930447C04Rik	382.551671	1.13766289	0.19646058	5.805384	6.42E-09	2.11E-06
Gapt	203.319914	1.1132987	0.18953193	5.871636	4.32E-09	1.45E-06
Klr1c	153.227214	1.09468584	0.20429564	5.382096	7.36E-08	1.97E-05
4930526115Rik	241.494179	1.08501191	0.20717535	5.29028	1.22E-07	2.98E-05
Ccdc36	112.457841	1.04715475	0.20532129	5.120434	3.05E-07	6.39E-05
Alyref2	180.660008	1.04393917	0.18457833	5.647978	1.62E-08	5.00E-06
Ryr2	75.216236	1.0355964	0.20873744	5.011592	5.40E-07	1.09E-04
Pkd1l3	68.589833	1.01737463	0.2081999	4.908146	9.19E-07	1.68E-04
C1rl	730.183064	1.01268793	0.16693859	6.065563	1.31E-09	4.88E-07
Zcwpw1	375.548056	1.00419496	0.16520607	6.074028	1.25E-09	4.75E-07
Dmc1	104.838371	0.98371019	0.20414146	4.826925	1.39E-06	2.45E-04
Dzip1	132.121506	0.97594868	0.20796499	4.734001	2.20E-06	3.62E-04
Slc16a3	1162.807003	0.97411192	0.18503253	5.270051	1.36E-07	3.14E-05
D330045A20Rik	92.206377	0.95352279	0.20870374	4.636378	3.55E-06	5.58E-04
Prr19	37.544232	0.93537032	0.20037275	4.909571	9.13E-07	1.68E-04
Tex15	74.889019	0.9319548	0.18949118	5.874347	4.25E-09	1.45E-06
Il1rl1	150.715209	0.92350896	0.2055335	4.509114	6.51E-06	9.24E-04
Nrg4	188.551232	0.92274335	0.20494394	4.520514	6.17E-06	8.84E-04
Ccbl2	541.191988	0.91384198	0.17344768	5.269568	1.37E-07	3.14E-05
Tmem132d	36.787472	0.90442472	0.18708119	5.594943	2.21E-08	6.52E-06
Slc25a31	22.63805	0.88531814	0.18979648	5.029432	4.92E-07	1.00E-04
4930539E08Rik	53.381508	0.88075998	0.20605221	4.372692	1.23E-05	1.54E-03
Al506816	199.747206	0.87295248	0.19608176	4.454109	8.42E-06	1.14E-03
Akr1c13	500.162217	0.8534203	0.15873709	5.375031	7.66E-08	2.01E-05
Rnf17	342.525776	0.84962577	0.20536135	4.156852	3.23E-05	3.62E-03
Crispld2	361.701669	0.82653131	0.18592153	4.446959	8.71E-06	1.17E-03
Gal3st3	43.084192	0.82035737	0.19040549	4.778267	1.77E-06	3.05E-04
Akap2	34.753933	0.80739374	0.20497151	4.006668	6.16E-05	6.23E-03
Zfp709	216.664257	0.80374616	0.1809703	4.438546	9.06E-06	1.20E-03
1700001L05Rik	168.440655	0.80027346	0.2028753	3.951596	7.76E-05	7.34E-03
Pcdhga12	77.556453	0.7909819	0.20878042	3.81509	1.36E-04	1.10E-02
Espnl	51.866306	0.78770911	0.2037334	3.971345	7.15E-05	6.90E-03
Hsh2d	391.530922	0.78424511	0.17299579	4.532843	5.82E-06	8.51E-04
Ly6c1	36.512204	0.77958271	0.19869699	4.090409	4.31E-05	4.72E-03
Mical2	194.215177	0.77913449	0.19425818	4.013209	5.99E-05	6.11E-03
Afap1	74.85081	0.77826478	0.20432842	3.8092	1.39E-04	1.11E-02
Gpc2	251.915388	0.77243878	0.16343089	4.72341	2.32E-06	3.73E-04
Setx	1744.23535	0.77002243	0.14561667	5.287996	1.24E-07	2.98E-05
1700030C10Rik	99.581071	0.76140523	0.20872912	3.672047	2.41E-04	1.70E-02
Skint3	79.464851	0.75893565	0.20756442	3.710488	2.07E-04	1.51E-02
Pla2g5	18.915604	0.75783223	0.17068315	5.580133	2.40E-08	6.96E-06
Ahsa2	886.628337	0.74579887	0.14029963	5.314843	1.07E-07	2.66E-05
Ttc39b	681.499997	0.72498535	0.15566518	4.656681	3.21E-06	5.11E-04
Erdr1	280.126236	0.72139105	0.20452258	3.629982	2.83E-04	1.93E-02
Alpl	92.145693	0.7137502	0.20720178	3.502408	4.61E-04	2.84E-02
Gm13154	63.290205	0.71267247	0.20842036	3.428791	6.06E-04	3.50E-02
Catsperg1	106.002561	0.70364025	0.19680271	3.574283	3.51E-04	2.26E-02

B3gnt7	405.739699	0.70266079	0.16122981	4.357118	1.32E-05	1.60E-03
Vmn2r96	24.159363	0.69160109	0.16564514	5.711345	1.12E-08	3.53E-06
Zfp110	1121.151946	0.68804101	0.1294443	5.314812	1.07E-07	2.66E-05
Pcdhgb4	88.708836	0.68505956	0.20541956	3.397567	6.80E-04	3.80E-02
Fbp1	43.254192	0.6781096	0.19547288	3.636825	2.76E-04	1.89E-02
Ltbp1	139.342763	0.6746406	0.2014961	3.458683	5.43E-04	3.17E-02
Sdsl	76.13298	0.67177386	0.20287425	3.393298	6.91E-04	3.84E-02
Kirrel2	15.774965	0.6618209	0.16367434	5.280192	1.29E-07	3.06E-05
Zc3hav1l	314.784676	0.65717529	0.17340558	3.788624	1.51E-04	1.20E-02
Fam208a	619.876027	0.65195806	0.16895591	3.858411	1.14E-04	9.95E-03
Mtl5	63.694551	0.64635484	0.19530953	3.464246	5.32E-04	3.12E-02
Pxt1	28.988235	0.64588508	0.19908316	3.31969	9.01E-04	4.71E-02
Ecm1	1049.563095	0.64537822	0.16825535	3.836173	1.25E-04	1.05E-02
Zfp808	321.693253	0.64277975	0.15963417	4.025207	5.69E-05	5.86E-03
Gdf3	266.059556	0.64211678	0.17785653	3.610295	3.06E-04	2.04E-02
Hyou1	759.320218	0.64155368	0.16191474	3.962428	7.42E-05	7.11E-03
Scml4	384.776296	0.63985857	0.19347652	3.308621	9.38E-04	4.83E-02
Tdrkh	554.084503	0.63865777	0.16451983	3.881931	1.04E-04	9.24E-03
2610305D13Rik	356.043352	0.63320556	0.19227102	3.295655	9.82E-04	4.99E-02
Plcd3	32.704786	0.63313914	0.19481719	3.379692	7.26E-04	4.02E-02
Frdm6	492.023553	0.63275438	0.17050529	3.710743	2.07E-04	1.51E-02
Ept1	573.026286	0.6299149	0.1594849	3.949316	7.84E-05	7.37E-03
Aim2	552.331834	0.62619114	0.17138168	3.653999	2.58E-04	1.79E-02
Sema4f	50.977002	0.62066967	0.19549825	3.300122	9.66E-04	4.94E-02
Fbp2	202.17511	0.61379998	0.15920801	7.160053	8.06E-13	5.07E-10
Gadd45g	235.319201	0.61311868	0.1792034	3.420641	6.25E-04	3.57E-02
Cnr2	559.245883	0.60904949	0.15692885	3.880914	1.04E-04	9.24E-03
Adad2	12.715649	0.60027951	0.16053591	4.345901	1.39E-05	1.67E-03
Ncf1	675.588019	0.59481666	0.17861582	3.331103	8.65E-04	4.57E-02
Macrod2	346.529623	0.58665848	0.15381247	3.813437	1.37E-04	1.10E-02
Epha2	24.572881	0.58236394	0.1758981	3.678915	2.34E-04	1.68E-02
Sh2d5	215.64213	0.57825578	0.1730108	3.340995	8.35E-04	4.46E-02
Tex19.1	546.048641	0.57550772	0.15563464	8.186358	2.69E-16	2.78E-13
Cep70	691.712079	0.56873458	0.13793961	4.122658	3.75E-05	4.14E-03
Morc2a	905.086842	0.56428549	0.15363233	3.672653	2.40E-04	1.70E-02
Smc5	3572.585429	0.54859882	0.10729779	5.112802	3.17E-07	6.56E-05
Uqcc2	1326.123245	0.5434979	0.13369201	4.065244	4.80E-05	5.09E-03
Gm13157	535.60155	0.54324844	0.13959749	3.891165	9.98E-05	9.07E-03
Tex19.2	15.378277	0.53885116	0.15691992	4.16912	3.06E-05	3.48E-03
H2-T23	2307.497992	0.53685487	0.14674943	3.658395	2.54E-04	1.77E-02
Trap1a	1097.053648	0.52944868	0.15164413	8.131168	4.25E-16	4.10E-13
Ly6k	19.390029	0.52356629	0.15217831	4.584245	4.56E-06	6.94E-04
Olfir1372-ps1	18.969776	0.52195242	0.15080716	5.185252	2.16E-07	4.59E-05
Tmem184b	628.485714	0.51894215	0.13885906	3.736731	1.86E-04	1.40E-02
Sync	14.67601	0.51766985	0.1625647	3.692288	2.22E-04	1.60E-02
Chrb4	31.227441	0.51325263	0.16872671	3.47007	5.20E-04	3.07E-02
Vill	2335.577876	0.50953625	0.11823148	4.309519	1.64E-05	1.96E-03
Clstn3	2056.573937	0.5071999	0.14432647	3.514227	4.41E-04	2.74E-02
Arhgap30	2243.379433	0.50497001	0.14036584	3.597585	3.21E-04	2.11E-02
Nccrp1	10.61331	0.50112984	0.15092135	4.024524	5.71E-05	5.86E-03
Pfkl	989.025056	0.50012056	0.13314498	3.756083	1.73E-04	1.31E-02
Sfn4	16.253304	0.49968218	0.14854267	4.996294	5.84E-07	1.16E-04
F11r	1326.354052	0.49427955	0.14934877	3.309591	9.34E-04	4.83E-02
St6galnac3	477.429939	0.49404679	0.13858878	3.564528	3.65E-04	2.33E-02
Padi3	220.787559	0.47657343	0.15831296	3.844068	1.21E-04	1.04E-02
Klh6	2728.955394	0.47395349	0.12608981	3.758852	1.71E-04	1.31E-02
Ethel	962.827767	0.46944334	0.12529242	3.746578	1.79E-04	1.36E-02
Ppa1	1828.979226	0.45154397	0.13637817	3.311004	9.30E-04	4.83E-02
Gabbr1	11.001119	0.43916735	0.14177783	4.530549	5.88E-06	8.51E-04
Ppef1	14.552503	0.41006352	0.14108345	3.820551	1.33E-04	1.10E-02
Ankrd36	9.834425	0.40929274	0.14215315	3.479822	5.02E-04	3.00E-02
Cyp2b10	13.131999	0.39875897	0.13660528	4.565828	4.98E-06	7.42E-04
Fmr1nb	15.659048	0.39526754	0.14181825	3.668574	2.44E-04	1.71E-02
1700029P11Rik	7.900071	0.36261379	0.13173963	4.053408	5.05E-05	5.26E-03
Ntnq1	7.055213	0.34009188	0.13135398	3.338586	8.42E-04	4.46E-02
Dppa4	13.899712	0.33673336	0.13392516	3.339528	8.39E-04	4.46E-02
Tuba3a	11.756002	0.32301932	0.12726473	3.677581	2.35E-04	1.68E-02
2310043L19Rik	7.927234	0.31033314	0.12621337	3.342659	8.30E-04	4.45E-02
Ccl12	14.377147	0.30487065	0.12418268	3.771932	1.62E-04	1.25E-02
Fcrib	7.460955	0.29110436	0.12052145	3.765698	1.66E-04	1.28E-02

Cdsn	6.136405	0.29059951	0.12044486	3.619434	2.95E-04	1.99E-02
Capn11	11.410019	0.2707337	0.11857808	3.477275	5.07E-04	3.02E-02
Tcfl5	9.384256	0.26929407	0.11865486	3.328959	8.72E-04	4.59E-02
Ak7	98.237383	0.26917523	0.11818644	4.377602	1.20E-05	1.52E-03
Prss42	7.648234	0.21011662	0.10495761	3.413385	6.42E-04	3.63E-02
Mmp13	15.365767	0.03603977	0.04608085	5.335055	9.55E-08	2.47E-05

**Table S6:** Genes significantly downregulated in *Setdb1*<sup>Δvav</sup> LT-HSCs

gene	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
Igf1	425.941256	-1.5556759	0.1851376	-8.40225	4.38E-17	4.88E-14
Muc6	95.659654	-1.513428	0.2071867	-7.318294	2.51E-13	1.73E-10
Igf2	1393.824195	-1.4714635	0.1949422	-7.590994	3.17E-14	2.42E-11
Ces2b	100.011713	-1.4415444	0.2047328	-7.024418	2.15E-12	1.20E-09
Plbd1	83.170428	-1.3334879	0.2075579	-6.715387	1.88E-11	1.01E-08
H19	1598.410735	-1.3284269	0.1782038	-7.46223	8.51E-14	6.16E-11
Clec1b	101.21703	-1.3049536	0.2082363	-6.51708	7.17E-11	3.46E-08
Cd36	108.654841	-1.3009417	0.2087819	-6.378119	1.79E-10	7.63E-08
Meg3	357.778493	-1.298693	0.1978024	-6.582702	4.62E-11	2.31E-08
C6	35.216139	-1.2898255	0.1959837	-6.499298	8.07E-11	3.77E-08
Tmem26	118.322552	-1.2517557	0.2070247	-6.091788	1.12E-09	4.49E-07
Il18bp	289.299225	-1.2217478	0.2028804	-6.060889	1.35E-09	4.90E-07
Gfra2	52.208587	-1.2099955	0.2077384	-5.952224	2.65E-09	9.34E-07
Fcgrt	525.126826	-1.0745087	0.1692687	-6.34481	2.23E-10	9.21E-08
Vldlr	38.902298	-1.0373061	0.2047597	-5.204119	1.95E-07	4.27E-05
Pitx2	74.818756	-1.014036	0.2079789	-4.982615	6.27E-07	1.23E-04
Plxna4os1	131.328724	-1.0111203	0.2078564	-4.910071	9.10E-07	1.68E-04
Gimap3	182.090816	-0.9962522	0.2049205	-4.880551	1.06E-06	1.91E-04
Cyp4b1	134.302033	-0.9857281	0.1995577	-4.935902	7.98E-07	1.52E-04
Wfdc18	31.272367	-0.9832358	0.1986185	-5.206372	1.93E-07	4.27E-05
S100a16	165.35317	-0.9723587	0.2044095	-4.768407	1.86E-06	3.16E-04
Wfdc17	180.298103	-0.9707684	0.2064128	-4.734748	2.19E-06	3.62E-04
Kcna2	22.307133	-0.9521371	0.1834438	-5.795422	6.81E-09	2.19E-06
Syne4	108.535891	-0.9516352	0.200373	-4.743624	2.10E-06	3.53E-04
Tac2	23.309428	-0.9468217	0.1905944	-5.221686	1.77E-07	4.01E-05
Postn	295.938217	-0.9452318	0.2005636	-4.727118	2.28E-06	3.70E-04
Plekhhg1	422.860269	-0.9319419	0.1670245	-5.574498	2.48E-08	7.04E-06
Dhrs3	239.673433	-0.9276352	0.1922848	-4.8269	1.39E-06	2.45E-04
Flt3	1464.376128	-0.9075568	0.149377	-6.074097	1.25E-09	4.75E-07
Epb4.113	199.132192	-0.9038017	0.1990437	-4.548619	5.40E-06	7.97E-04
Fxyd1	70.793994	-0.8904782	0.2084212	-4.284387	1.83E-05	2.16E-03
Ctsh	510.597795	-0.8705468	0.1980324	-4.406782	1.05E-05	1.36E-03
3632451O06Rik	83.792661	-0.8443961	0.2016569	-4.180864	2.90E-05	3.36E-03
Jun	429.56836	-0.8413209	0.15301	-5.493238	3.95E-08	1.10E-05
Fam132a	1061.373919	-0.8324807	0.1864542	-4.467428	7.92E-06	1.10E-03
Efna1	252.099538	-0.8314191	0.1938361	-4.289321	1.79E-05	2.13E-03
Aqp1	654.537921	-0.8283186	0.1809568	-4.578147	4.69E-06	7.07E-04
Fpr1	35.991362	-0.8249161	0.1871858	-4.973822	6.56E-07	1.27E-04
Lama3	24.344749	-0.8202546	0.1928618	-4.489535	7.14E-06	1.00E-03
Nrk	184.358521	-0.8192814	0.2065871	-3.980772	6.87E-05	6.75E-03
Mrap	106.844329	-0.8179833	0.205948	-4.083859	4.43E-05	4.78E-03
Car3	69.516105	-0.8137523	0.1858012	-5.186138	2.15E-07	4.59E-05
Epha7	62.36513	-0.8125505	0.207659	-3.97488	7.04E-05	6.84E-03
Armcx4	161.063427	-0.7958166	0.199852	-3.981581	6.85E-05	6.75E-03
Sqrdl	100.674422	-0.7957601	0.205234	-3.877921	1.05E-04	9.30E-03
Lancl3	75.802869	-0.7955882	0.2075572	-3.837758	1.24E-04	1.05E-02
Gem	1265.246778	-0.7936787	0.1415986	-5.603963	2.10E-08	6.32E-06
Ndnf	54.19703	-0.7655982	0.2022556	-3.904467	9.44E-05	8.76E-03
Bex2	109.902323	-0.7482612	0.2059221	-3.640114	2.73E-04	1.88E-02
Trf	3178.874402	-0.748031	0.2010852	-3.901669	9.55E-05	8.81E-03
Serpinf1	1217.870776	-0.7460152	0.169078	-4.41222	1.02E-05	1.33E-03
Dkk1	88.423944	-0.7417883	0.2020352	-3.818911	1.34E-04	1.10E-02
Sh2d4a	237.846297	-0.7403581	0.2085354	-3.575617	3.49E-04	2.26E-02
Gpc3	178.154229	-0.7333674	0.2078016	-3.592066	3.28E-04	2.15E-02
Gjb2	43.859642	-0.7297818	0.1735191	-5.453643	4.93E-08	1.35E-05
Scd1	251.220966	-0.7266717	0.2024402	-3.59766	3.21E-04	2.11E-02
Dlk1	827.548923	-0.7258604	0.1962065	-3.957765	7.57E-05	7.20E-03
Cyp26b1	116.393815	-0.7250747	0.1992633	-3.634491	2.79E-04	1.90E-02

S1pr3	34.553057	-0.7128973	0.1797903	-4.616943	3.89E-06	6.00E-04
Col11a2	239.035725	-0.712395	0.1787753	-3.982808	6.81E-05	6.75E-03
Fxyd7	53.034754	-0.7084429	0.2085922	-3.399425	6.75E-04	3.79E-02
Hoxa3	177.516428	-0.7075926	0.1852637	-3.814417	1.37E-04	1.10E-02
Ccl6	124.607259	-0.707321	0.2074918	-3.466312	5.28E-04	3.10E-02
Hid1	880.096927	-0.7061947	0.18728	-3.772385	1.62E-04	1.25E-02
Ecscr	405.559422	-0.7032363	0.1763328	-3.987458	6.68E-05	6.71E-03
Angptl3	51.897242	-0.6909535	0.1873129	-4.057749	4.95E-05	5.20E-03
Itih4	70.212194	-0.6901982	0.1788433	-4.62263	3.79E-06	5.90E-04
Zfp354c	257.498857	-0.6899704	0.1822516	-3.782947	1.55E-04	1.23E-02
Sepp1	4396.032413	-0.6867481	0.1554893	-4.417085	1.00E-05	1.32E-03
Gsta4	165.158002	-0.6860896	0.1852658	-3.698846	2.17E-04	1.57E-02
Pde2a	1032.802806	-0.6777887	0.1552155	-4.365773	1.27E-05	1.58E-03
Sox18	330.878521	-0.675221	0.1869066	-3.611193	3.05E-04	2.04E-02
Ikbke	588.79895	-0.6737371	0.1751544	-3.846612	1.20E-04	1.04E-02
Acox2	27.787547	-0.6727887	0.1928802	-3.660984	2.51E-04	1.76E-02
Spon2	24.14373	-0.6720432	0.1790074	-4.255121	2.09E-05	2.44E-03
Folr2	66.101804	-0.6699711	0.1848569	-4.064355	4.82E-05	5.09E-03
Mafb	71.108701	-0.6646306	0.1915939	-3.716339	2.02E-04	1.49E-02
Hpgd	243.375507	-0.6636823	0.2033778	-3.358521	7.84E-04	4.26E-02
Trib2	30.32784	-0.6589709	0.1962204	-3.475335	5.10E-04	3.03E-02
Tox	182.79478	-0.6547175	0.1978662	-3.308374	9.38E-04	4.83E-02
Enpp2	19.831381	-0.6539077	0.1673476	-4.459628	8.21E-06	1.12E-03
Serpina1c	30.753348	-0.6534966	0.1694613	-4.821449	1.43E-06	2.49E-04
F2	137.985609	-0.6519707	0.1899692	-3.717411	2.01E-04	1.49E-02
Hmgcs2	66.286961	-0.6517076	0.1866867	-3.821031	1.33E-04	1.10E-02
Irf6	419.737162	-0.6478002	0.1799602	-3.598377	3.20E-04	2.11E-02
Btdb3	756.60238	-0.6476678	0.1736222	-3.730424	1.91E-04	1.43E-02
Rdh12	335.366089	-0.6476189	0.1687313	-3.836034	1.25E-04	1.05E-02
Sgsm1	599.945445	-0.646276	0.1851816	-3.49018	4.83E-04	2.94E-02
Clec7a	43.489634	-0.6440714	0.1854043	-3.819564	1.34E-04	1.10E-02
Pid1	19.555739	-0.6414378	0.1669674	-4.462714	8.09E-06	1.12E-03
Snhg11	18.557363	-0.6402921	0.1796922	-3.889808	1.00E-04	9.07E-03
Ccr5	48.258203	-0.6379448	0.191622	-3.535126	4.08E-04	2.59E-02
Cd22	16.154108	-0.6312287	0.1719102	-4.12767	3.66E-05	4.08E-03
Vdr	355.640531	-0.6228348	0.1766514	-3.524409	4.24E-04	2.66E-02
Serpina1e	38.051433	-0.6218423	0.1719765	-4.363863	1.28E-05	1.58E-03
Stab2	95.478434	-0.6149588	0.1821083	-3.779788	1.57E-04	1.23E-02
Prdm5	236.726949	-0.6025731	0.1716197	-3.507992	4.52E-04	2.79E-02
Itgb5	55.029079	-0.602156	0.1905149	-3.359244	7.82E-04	4.26E-02
Pld2	212.289872	-0.6013125	0.1778686	-3.377957	7.30E-04	4.03E-02
Prodh2	25.066926	-0.5940125	0.1835575	-3.487032	4.88E-04	2.95E-02
Cacna2d1	28.897228	-0.5851662	0.1839661	-3.400841	6.72E-04	3.78E-02
Pparg	12.513595	-0.584916	0.1613196	-4.159281	3.19E-05	3.61E-03
Zfp870	261.261655	-0.5832662	0.1690622	-3.448174	5.64E-04	3.27E-02
Sema6d	70.021048	-0.5759463	0.1819205	-3.489483	4.84E-04	2.94E-02
Ccr2	31.482134	-0.5749633	0.1641945	-4.394651	1.11E-05	1.42E-03
Cd82	1163.312019	-0.5728482	0.1479962	-3.869963	1.09E-04	9.55E-03
Sdc1	625.090596	-0.5686102	0.1428271	-3.979631	6.90E-05	6.75E-03
Pld3	1009.029419	-0.568319	0.1303116	-4.360325	1.30E-05	1.59E-03
Itm2a	948.230117	-0.557254	0.1457528	-3.822664	1.32E-04	1.10E-02
Emcn	431.602261	-0.5399243	0.163472	-3.30217	9.59E-04	4.92E-02
Cfi	73.177378	-0.5364755	0.1737537	-3.524603	4.24E-04	2.66E-02
Tmem154	462.333986	-0.5295636	0.1567916	-3.376429	7.34E-04	4.04E-02
Dsp	12.416632	-0.5261037	0.1664281	-3.487072	4.88E-04	2.95E-02
Serinc5	905.106993	-0.5241273	0.1402261	-3.737005	1.86E-04	1.40E-02
Tsc22d1	1756.658565	-0.5239202	0.128265	-4.084252	4.42E-05	4.78E-03
Paqr9	19.762757	-0.5238419	0.1722254	-3.365295	7.65E-04	4.19E-02
Cyp2c44	13.133108	-0.5053779	0.1528904	-4.065872	4.79E-05	5.09E-03
Slc1a2	10.738583	-0.5002941	0.1525938	-3.886403	1.02E-04	9.15E-03
Otc	34.423774	-0.4956555	0.1652013	-3.524145	4.25E-04	2.66E-02
Cnn3	1250.912753	-0.4943356	0.1444976	-3.420833	6.24E-04	3.57E-02
Atg14	552.507554	-0.4829064	0.13574	-3.556533	3.76E-04	2.40E-02
Chga	22.222837	-0.4801615	0.1611564	-3.499253	4.67E-04	2.86E-02
Hoxa9	1422.726811	-0.4741318	0.1388621	-3.414089	6.40E-04	3.63E-02
Spp2	60.405342	-0.4711199	0.1644517	-3.35148	8.04E-04	4.32E-02
Pcsk5	10.148476	-0.4652567	0.1547821	-3.420067	6.26E-04	3.57E-02
Ugt2b34	35.343813	-0.4594334	0.1615809	-3.353415	7.98E-04	4.31E-02
Mat1a	35.064494	-0.4594317	0.1502972	-4.172481	3.01E-05	3.46E-03
Serpina1d	49.183127	-0.45479	0.1616428	-3.324749	8.85E-04	4.64E-02

F13b	10.685743	-0.4425091	0.1492807	-3.481149	4.99E-04	3.00E-02
Hmga2	1778.826852	-0.4272461	0.1190899	-3.587401	3.34E-04	2.18E-02
Crp	22.172264	-0.4202027	0.1473542	-3.707476	2.09E-04	1.52E-02
Pipox	17.931882	-0.4137955	0.1470158	-3.578772	3.45E-04	2.24E-02
Glul	1361.034326	-0.3975756	0.1205139	-3.298679	9.71E-04	4.95E-02
Abhd4	1432.976703	-0.3939315	0.1118116	-3.522871	4.27E-04	2.66E-02
Itm2b	9587.609004	-0.3855565	0.1116817	-3.452241	5.56E-04	3.23E-02
Adra2b	13.911228	-0.3563666	0.1335481	-3.774865	1.60E-04	1.25E-02
Vsig4	8.387361	-0.3463763	0.1305705	-3.915673	9.02E-05	8.42E-03
D10Bwg1379e	7.762445	-0.3404254	0.1297482	-3.840029	1.23E-04	1.05E-02
Ugt2b36	10.539274	-0.2922276	0.1214889	-3.895086	9.82E-05	8.99E-03
BC024386	8.984557	-0.255519	0.1149079	-3.624912	2.89E-04	1.95E-02
Vcam1	729.652925	-0.2278482	0.1127439	-3.353215	7.99E-04	4.31E-02

**Table S7:** Genes significantly upregulated in *Setdb1*<sup>Δ</sup> MPPs (top 200)

gene	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
Fbp2	1.58E+03	8.2541579	0.24438549	20.60665	2.39E-94	3.44E-91
Tex19.1	1.08E+03	8.083226	0.28192239	11.457578	2.15E-30	3.60E-28
Tmem150c	4.67E+02	7.1041668	0.2860165	9.649715	4.93E-22	4.40E-20
Car1	9.42E+03	6.982836	0.15262235	45.185125	0.00E+00	0.00E+00
Meioc	2.08E+02	5.2794679	0.32981941	9.781682	1.35E-22	1.27E-20
Ak7	1.62E+02	5.2075651	0.31248955	11.046507	2.28E-28	3.45E-26
Amotl1	1.54E+02	5.1732828	0.29920875	12.118374	8.44E-34	1.78E-31
Magea13	2.09E+02	4.8787257	0.2666422	15.846501	1.49E-56	7.91E-54
Gstp2	2.48E+02	4.5292684	0.25200899	16.681776	1.78E-62	1.16E-59
Fbp1	4.29E+02	4.4745765	0.18136385	23.763939	7.89E-125	1.89E-121
Vmn2r96	6.50E+01	4.4481598	0.34529664	7.839606	4.52E-15	2.00E-13
Arl14epl	6.43E+01	4.2773757	0.3400137	7.19541	6.23E-13	2.08E-11
Ryr2	1.40E+02	4.1225307	0.26760501	14.011934	1.32E-44	5.12E-42
Olfrl1372-ps1	4.36E+01	3.9968248	0.35344406	7.328812	2.32E-13	8.36E-12
Sec14l4	4.66E+01	3.9206038	0.34595845	6.73355	1.66E-11	4.45E-10
Ntnq1	9.60E+01	3.8200288	0.27801616	12.368047	3.89E-35	9.32E-33
Tcf15	3.38E+01	3.5923296	0.36272554	6.935883	4.04E-12	1.20E-10
Akap5	2.94E+02	3.4304792	0.18153778	18.56288	6.42E-77	5.76E-74
Pla2g5	3.04E+01	3.3887289	0.36248962	6.024304	1.70E-09	3.32E-08
Stag3	1.61E+03	3.344433	0.13921801	23.967611	6.06E-127	1.74E-123
Sdsl	6.30E+01	3.3285062	0.30508122	9.916427	3.53E-23	3.45E-21
Grhl2	2.90E+01	3.2989723	0.35949484	5.979455	2.24E-09	4.27E-08
lqcg	2.30E+02	3.2480146	0.18828823	16.923842	3.00E-64	2.16E-61
Aplp1	4.41E+01	3.2396361	0.32816101	8.573795	1.00E-17	5.80E-16
M1ap	5.83E+02	3.1619179	0.14407853	21.811953	1.79E-105	2.85E-102
Cyp2b10	2.82E+01	3.1547991	0.37208061	6.559276	5.41E-11	1.35E-09
Mmp14	1.05E+02	3.1159403	0.26237901	11.434653	2.81E-30	4.63E-28
Slc4a8	1.19E+02	3.1105676	0.23038539	13.050133	6.34E-39	2.03E-36
Ltbp1	2.45E+02	3.0817303	0.20722643	14.668696	1.02E-48	4.59E-46
Homer2	2.16E+02	3.0658014	0.34542929	8.881049	6.62E-19	4.47E-17
Dnah8	1.42E+03	3.0363132	0.11592375	26.140477	1.26E-150	9.08E-147
Cdsn	2.05E+01	3.0092211	0.37226303	6.253657	4.01E-10	8.83E-09
Ly6k	4.23E+01	3.001536	0.36433733	7.177866	7.08E-13	2.35E-11
Padi3	2.56E+02	2.977548	0.18555072	15.855746	1.28E-56	7.09E-54
Kirrel2	2.44E+01	2.9753266	0.36264435	6.110809	9.91E-10	2.05E-08
Cyp2a12	1.95E+01	2.9560387	0.37297182	6.187053	6.13E-10	1.30E-08
Myrip	2.56E+01	2.9076802	0.36671585	6.065094	1.32E-09	2.65E-08
Ackr1	8.61E+01	2.8773135	0.26332001	10.547203	5.23E-26	6.26E-24
Gabbr1	2.07E+01	2.870101	0.37208456	5.469914	4.50E-08	6.80E-07
Vwa5b2	4.08E+01	2.8574232	0.32468856	8.072025	6.91E-16	3.31E-14
Col5a1	9.25E+02	2.8514505	0.17159252	16.5788	9.92E-62	6.20E-59
Lama1	1.82E+01	2.8369186	0.37479207	6.063762	1.33E-09	2.66E-08
Nfatc4	1.82E+01	2.8278286	0.37495495	6.057338	1.38E-09	2.76E-08
Cntn3	4.21E+01	2.7769376	0.32963023	7.834128	4.72E-15	2.08E-13
Entpd3	3.28E+01	2.7663237	0.3598698	6.860813	6.85E-12	1.96E-10
Tmem132d	2.68E+01	2.7449186	0.35642945	6.67772	2.43E-11	6.42E-10
Nccrp1	2.86E+01	2.743152	0.35427774	6.818235	9.22E-12	2.58E-10
Ly6c1	1.77E+01	2.6979353	0.37420186	5.259703	1.44E-07	1.99E-06
Prr19	3.79E+01	2.6942456	0.34999997	7.141996	9.20E-13	3.01E-11
Dppa4	1.76E+01	2.6789908	0.37707019	5.937862	2.89E-09	5.37E-08
Ahsa2	1.66E+03	2.632368	0.11423269	23.020153	2.93E-117	6.01E-114



Il1r1	2.96E+02	2.6204741	0.21618071	12.04907	1.96E-33	4.03E-31
Pcsk9	1.04E+02	2.6153912	0.23716617	10.801604	3.38E-27	4.65E-25
2410076I21Rik	7.70E+01	2.6104434	0.30745884	8.279124	1.24E-16	6.37E-15
1700029P11Rik	1.49E+01	2.5787021	0.37757459	5.762687	8.28E-09	1.42E-07
Vmn2r24	1.52E+01	2.5766322	0.37765178	5.770258	7.92E-09	1.36E-07
1700097N02Rik	4.29E+02	2.5743662	0.3351893	7.722739	1.14E-14	4.85E-13
Col4a3	3.93E+01	2.571029	0.33847733	7.176444	7.15E-13	2.37E-11
2810474O19Rik	3.30E+03	2.5670461	0.10242141	25.051977	1.66E-138	7.96E-135
Ankrd36	2.08E+01	2.5257113	0.36766677	5.88643	3.95E-09	7.14E-08
Adad2	1.77E+01	2.4764895	0.37319994	5.361957	8.23E-08	1.19E-06
Sptb	1.35E+03	2.4566872	0.15061662	16.29497	1.07E-59	6.41E-57
Xlr3a	2.31E+01	2.4307363	0.36640856	5.980374	2.23E-09	6.45E-08
BC051019	1.65E+01	2.4271703	0.37331679	5.262914	1.42E-07	1.96E-06
Epcam	5.27E+01	2.4271036	0.29943945	7.84435	4.35E-15	1.94E-13
Ndufa4l2	5.94E+02	2.4244287	0.31992395	7.598859	2.99E-14	1.23E-12
Ano1	4.60E+01	2.4012748	0.3078289	7.515032	5.69E-14	2.23E-12
Tex19.2	1.44E+01	2.3893618	0.37787824	4.929744	8.23E-07	9.79E-06
Amigo2	9.92E+01	2.3524958	0.24923359	9.301851	1.38E-20	1.06E-18
Pxt1	3.66E+01	2.332726	0.32156663	6.942113	3.86E-12	1.15E-10
Gtsf1	1.59E+01	2.3087368	0.37580444	5.102801	3.35E-07	4.29E-06
Upk1b	2.45E+01	2.2966229	0.35447098	6.04418	1.50E-09	2.97E-08
Tdrd5	2.36E+01	2.2917469	0.3618248	5.892723	3.80E-09	6.90E-08
Dmc1	7.41E+01	2.2666426	0.27267926	8.166755	3.17E-16	1.57E-14
Mt2	2.10E+03	2.2587531	0.15696362	14.383432	6.58E-47	2.78E-44
Gypa	7.37E+02	2.2565957	0.18243251	12.352005	4.75E-35	1.10E-32
Wbp2nl	1.18E+01	2.244762	0.37899335	5.367012	8.01E-08	1.16E-06
Serpnb9g	1.16E+01	2.2413306	0.37899351	5.356585	8.48E-08	1.22E-06
Penk	3.03E+01	2.2370209	0.36826337	5.845052	5.06E-09	9.01E-08
Popdc2	6.65E+01	2.2248377	0.28895163	7.559147	4.06E-14	1.61E-12
Sgcz	1.13E+01	2.1990749	0.37894313	5.302462	1.14E-07	1.60E-06
Cbr3	2.10E+01	2.1823257	0.35769163	5.689323	1.28E-08	2.10E-07
4930433N12Rik	1.56E+01	2.1705249	0.37882052	4.704372	2.55E-06	2.71E-05
Tspo2	6.90E+02	2.1641035	0.16758155	12.895819	4.75E-38	1.42E-35
Pcdhga12	5.06E+01	2.1629848	0.28982032	7.287607	3.16E-13	1.11E-11
Ank2	4.30E+01	2.1504115	0.32294262	6.487961	8.70E-11	2.09E-09
Gal3st3	2.65E+01	2.1444144	0.35130444	5.829809	5.55E-09	9.83E-08
Amn	1.61E+01	2.1425722	0.3769106	5.048975	4.44E-07	5.55E-06
Boll	2.96E+01	2.1321832	0.34097267	6.011172	1.84E-09	3.59E-08
Tmod1	1.43E+02	2.1304337	0.24505362	8.634574	5.89E-18	3.47E-16
Cbr2	1.89E+01	2.1233983	0.36996244	5.333892	9.61E-08	1.38E-06
Apol8	7.51E+01	2.115492	0.29226115	7.144207	9.05E-13	2.97E-11
Epb4.2	5.99E+02	2.1015449	0.16074989	13.05361	6.06E-39	1.98E-36
Grtp1	5.78E+01	2.0952139	0.28483933	7.221951	5.12E-13	1.73E-11
D330045A20Rik	1.40E+02	2.0940183	0.23196378	8.963982	3.13E-19	2.19E-17
Sowaha	8.93E+01	2.0936704	0.25665094	8.066341	7.24E-16	3.45E-14
Horrad2	8.87E+01	2.0871257	0.27599417	7.483542	7.23E-14	2.79E-12
5730507C01Rik	3.88E+01	2.072165	0.3071122	6.561114	5.34E-11	1.34E-09
Cebpe	1.23E+02	2.0714911	0.24886287	8.261228	1.44E-16	7.34E-15
Dzip1	1.46E+02	2.0662841	0.20935162	9.803614	1.09E-22	1.03E-20
4930447C04Rik	2.72E+02	2.063864	0.19053148	10.796215	3.59E-27	4.86E-25
Smarca5-ps	3.68E+01	2.0600335	0.32338929	6.198111	5.71E-10	1.22E-08
Vangl1	3.21E+02	2.0567091	0.17820156	11.50894	1.19E-30	2.03E-28
Slc7a15	1.07E+01	2.0521509	0.37897587	4.50194	6.73E-06	6.50E-05
Redrum	4.80E+02	2.0423822	0.16072623	12.684269	7.23E-37	1.96E-34
Snca	3.96E+02	2.0400194	0.19436385	10.473953	1.14E-25	1.34E-23
Slc30a10	2.92E+02	2.0361654	0.19624331	10.34534	4.39E-25	4.85E-23
D10Bwg1379e	3.22E+01	2.0150673	0.33196491	5.893414	3.78E-09	6.88E-08
Mt1	4.41E+03	2.0136056	0.14051912	14.327448	1.47E-46	6.05E-44
Gm10532	1.26E+01	2.0102036	0.3789976	4.425531	9.62E-06	8.99E-05
Plcd3	6.98E+01	2.0062575	0.27996756	7.077194	1.47E-12	4.62E-11
1700112E06Rik	3.52E+01	1.9883581	0.32162862	6.020759	1.74E-09	3.39E-08
Stk32b	2.96E+01	1.9739019	0.33112361	5.775883	7.66E-09	1.32E-07
Optn	2.50E+02	1.9674104	0.19523599	10.045178	9.65E-24	9.69E-22
Slc1a4	4.12E+02	1.9630441	0.17766528	11.028837	2.77E-28	4.15E-26
Gstp1	2.60E+03	1.9605183	0.1120568	17.490958	1.68E-68	1.27E-65
Tuba8	1.36E+02	1.9585726	0.20858646	9.330734	1.05E-20	8.12E-19
Acacb	6.63E+01	1.9553998	0.25574239	7.542733	4.60E-14	1.82E-12
Trap1a	1.16E+03	1.9540155	0.37261897	8.957164	3.33E-19	2.32E-17
Nfx1	5.64E+02	1.9495015	0.14093272	13.813961	2.10E-43	7.94E-41
Klf5	8.05E+01	1.9464011	0.25624007	7.517698	5.57E-14	2.19E-12

Fech	2.69E+03	1.9415137	0.14453862	13.429242	4.08E-41	1.46E-38
Tdrd9	1.22E+01	1.9391623	0.37769286	4.591633	4.40E-06	4.44E-05
Gsdma3	1.07E+01	1.9379318	0.37671399	5.058685	4.22E-07	5.30E-06
Atp6ap1l	9.95E+00	1.9309149	0.37855964	4.36595	1.27E-05	1.15E-04
Fcgr2b	2.62E+02	1.9230629	0.17738093	10.809547	3.10E-27	4.33E-25
Acox1	9.61E+00	1.9169993	0.37853477	4.332432	1.47E-05	1.32E-04
Prss42	1.33E+01	1.9152947	0.37721834	4.65955	3.17E-06	3.30E-05
2310043L19Rik	9.08E+00	1.9062002	0.37678334	4.927773	8.32E-07	9.84E-06
Podxl	5.64E+02	1.9029792	0.15912148	11.944381	6.95E-33	1.41E-30
Hvcn1	1.21E+02	1.8994078	0.21318079	8.85126	8.65E-19	5.73E-17
2210417A02Rik	1.50E+01	1.8992132	0.37186007	4.788962	1.68E-06	1.87E-05
Add2	1.75E+03	1.899148	0.16138124	11.76389	5.99E-32	1.09E-29
Vwce	2.57E+01	1.8902033	0.3477712	5.271153	1.36E-07	1.89E-06
Il1bos	1.20E+01	1.889921	0.37821979	4.510582	6.47E-06	6.28E-05
Eif5a2	1.97E+02	1.8824409	0.18218032	10.292988	7.58E-25	8.25E-23
1700030C10Rik	8.08E+01	1.8733156	0.27241749	6.817067	9.29E-12	2.59E-10
Abcg4	2.72E+02	1.8675217	0.17312577	10.758813	5.39E-27	7.23E-25
Cpne7	3.47E+01	1.8635477	0.32763337	5.569335	2.56E-08	4.05E-07
Ank1	8.26E+02	1.8525289	0.14680183	12.609505	1.87E-36	4.89E-34
Rragd	1.45E+01	1.8515074	0.37279034	4.676028	2.92E-06	3.07E-05
Rnf17	3.87E+02	1.8453956	0.36339271	5.151091	2.59E-07	3.41E-06
Cnm1	2.77E+01	1.8435696	0.34391923	5.228558	1.71E-07	2.32E-06
Trim10	3.19E+02	1.8393796	0.19583773	9.374018	6.98E-21	5.48E-19
Ank3	2.63E+01	1.8343701	0.34533591	5.17026	2.34E-07	3.10E-06
Rgcc	9.13E+02	1.8282528	0.15335036	11.914362	9.96E-33	1.96E-30
Itgb2l	4.42E+01	1.8263005	0.31995682	5.624701	1.86E-08	3.00E-07
Ccln2	4.71E+02	1.8090039	0.1744751	10.355095	3.97E-25	4.42E-23
1300017J02Rik	9.66E+01	1.8084013	0.22951985	7.821863	5.20E-15	2.29E-13
St6galnac5	3.73E+01	1.7994762	0.32405846	5.457667	4.82E-08	7.23E-07
Slc6a9	2.34E+02	1.7981928	0.19361983	9.262268	2.00E-20	1.51E-18
Rhox5	2.29E+01	1.7972429	0.37487027	4.719689	2.36E-06	2.53E-05
Prkd1	2.59E+01	1.7891198	0.34175806	5.101486	3.37E-07	4.31E-06
Trim24	6.65E+02	1.7841554	0.14478288	12.312184	7.79E-35	1.75E-32
Sh3d19	1.42E+02	1.780313	0.21482112	8.250458	1.58E-16	7.98E-15
Tex15	1.22E+02	1.7748523	0.37478047	5.705069	1.16E-08	1.92E-07
Fam83g	1.09E+02	1.7733599	0.22563604	7.812588	5.60E-15	2.44E-13
Rhag	2.55E+03	1.7696599	0.28906694	6.126993	8.96E-10	1.87E-08
Irs2	1.90E+02	1.7587364	0.2019191	8.682935	3.86E-18	2.28E-16
Trem3	7.91E+01	1.7576669	0.27024601	6.454857	1.08E-10	2.59E-09
Adam8	1.32E+02	1.7559211	0.21489626	8.132031	4.22E-16	2.07E-14
Arhgef12	9.93E+01	1.7542993	0.24328562	7.166975	7.67E-13	2.53E-11
Slc41a3	7.54E+02	1.7519053	0.16899152	10.359446	3.79E-25	4.26E-23
Sdk1	2.14E+01	1.7485105	0.35713452	4.762848	1.91E-06	2.10E-05
Slc16a3	1.37E+03	1.7450623	0.14662717	11.896841	1.23E-32	2.38E-30
Arsg	1.01E+02	1.7428601	0.25010653	6.928161	4.26E-12	1.26E-10
Bmp7	1.98E+01	1.7318167	0.36600178	4.607125	4.08E-06	4.14E-05
Msrb3	8.45E+02	1.7301374	0.15843142	10.913954	9.89E-28	1.43E-25
1700001L05Rik	2.07E+02	1.7282591	0.19253148	8.951137	3.52E-19	2.44E-17
Spats2	2.06E+02	1.7270595	0.18042072	9.544908	1.36E-21	1.15E-19
Ccl2	4.43E+01	1.726626	0.32467141	5.25478	1.48E-07	2.04E-06
Pak6	2.60E+01	1.7219666	0.3467813	4.857082	1.19E-06	1.37E-05
Tspan33	4.62E+02	1.7174177	0.19021571	9.019235	1.89E-19	1.35E-17
Aldh1l2	1.15E+01	1.7161724	0.3774673	4.264996	2.00E-05	1.73E-04
Akap2	5.96E+01	1.7146673	0.2958471	5.74384	9.26E-09	1.57E-07
Hesx1	1.68E+02	1.7135531	0.21570412	7.917612	2.42E-15	1.10E-13
Cpox	4.03E+03	1.7084151	0.1432706	11.92307	8.97E-33	1.79E-30
Ccdc36	1.08E+02	1.7040506	0.24567178	6.901606	5.14E-12	1.50E-10
Asns	4.17E+03	1.7006954	0.14832721	11.464606	1.99E-30	3.36E-28
Endod1	6.06E+02	1.6951126	0.16004222	10.582936	3.58E-26	4.43E-24
Topaz1	8.57E+00	1.6852439	0.37203864	4.695433	2.66E-06	2.82E-05
Nipa1	1.01E+02	1.6814922	0.23888885	7.000687	2.55E-12	7.72E-11
Garem	3.17E+02	1.6790166	0.17210148	9.740019	2.04E-22	1.87E-20
Pnma5	7.29E+00	1.6762174	0.37261055	4.585052	4.54E-06	4.55E-05
Gpat2	2.92E+01	1.664523	0.34356771	4.764981	1.89E-06	2.09E-05
Syce1	2.48E+01	1.6634882	0.36858931	4.454438	8.41E-06	7.94E-05
Plkr	1.42E+03	1.662053	0.16003003	10.3826	2.98E-25	3.39E-23
Socs2	3.03E+02	1.6568173	0.19767477	8.368816	5.82E-17	3.11E-15
Abcb10	1.48E+03	1.6509062	0.13643081	12.097008	1.10E-33	2.28E-31
Fgl1	8.82E+00	1.6505894	0.37454591	4.07219	4.66E-05	3.63E-04
Fbxl2	1.28E+02	1.6486457	0.22321685	7.355764	1.90E-13	6.97E-12

Ache	7.13E+01	1.6460253	0.2758719	5.925142	3.12E-09	5.75E-08
Fam210b	5.51E+02	1.6452739	0.17284593	9.51093	1.89E-21	1.57E-19
LOC100503676	1.63E+01	1.6445516	0.36858571	4.327371	1.51E-05	1.34E-04
Gal3st1	6.43E+01	1.6435764	0.27818269	5.862843	4.55E-09	8.14E-08
Lmna	1.12E+03	1.642653	0.14726075	11.150278	7.14E-29	1.10E-26
Gm364	8.46E+00	1.6325516	0.37718667	3.8102	1.39E-04	9.64E-04
Spta1	5.14E+02	1.6276725	0.16588143	9.803417	1.09E-22	1.03E-20
Pkhd11l	6.99E+01	1.6273659	0.26486748	6.099877	1.06E-09	2.18E-08
Icam4	5.39E+02	1.6265693	0.16921394	9.604373	7.66E-22	6.75E-20

**Table S8:** Genes significantly downregulated in *Setdb1*<sup>va</sup> MPPs (top 200)

gene	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
Pcmt1	259.461109	-0.4149673	0.15265721	-2.71788	6.57E-03	2.57E-02
Stau2	94.001797	-0.8126577	0.23887946	-3.39753	6.80E-04	3.82E-03
Ly96	77.646431	-0.681469	0.23406031	-2.907893	3.64E-03	1.57E-02
Jph1	5.812483	-1.4105675	0.36537442	-4.122636	3.75E-05	2.99E-04
Bend6	4.76038	-1.0029569	0.35992232	-2.702846	6.87E-03	2.67E-02
Arid5a	788.548212	-0.7710534	0.14979253	-5.146777	2.65E-07	3.48E-06
Kansl3	1136.77299	-0.3277806	0.12227354	-2.680649	7.35E-03	2.82E-02
Lman2l	642.047384	-0.4913136	0.13580279	-3.617597	2.97E-04	1.86E-03
Cnm4	264.515439	-0.5642653	0.15058264	-3.7462	1.80E-04	1.21E-03
Sema4c	141.092519	-1.5714217	0.21445763	-7.298457	2.91E-13	1.03E-11
Inpp4a	156.856103	-0.5159228	0.17885481	-2.883514	3.93E-03	1.68E-02
2010300C02Rik	11.502283	-1.0684195	0.37743572	-2.799482	5.12E-03	2.09E-02
Il18rap	534.470406	-0.4412928	0.13925104	-3.168803	1.53E-03	7.60E-03
Fhl2	3.188195	-0.7616386	0.33188367	-2.474872	1.33E-02	4.58E-02
Slc40a1	1492.34733	-0.8855074	0.13353628	-6.630541	3.34E-11	8.59E-10
Sdpr	34.754133	-3.1150944	0.34716129	-7.291983	3.05E-13	1.07E-11
Nabp1	376.915639	-0.6220399	0.13543957	-4.591731	4.40E-06	4.44E-05
Myo1b	50.560413	-1.1412251	0.28029017	-4.050389	5.11E-05	3.94E-04
Stat4	1057.97101	-0.382895	0.12398623	-3.088119	2.01E-03	9.66E-03
Stat1	1225.38643	-0.9441332	0.15262202	-6.185383	6.20E-10	1.31E-08
Pgap1	36.169685	-1.3545791	0.31984774	-4.192934	2.75E-05	2.29E-04
Ankrd44	561.870478	-0.6479016	0.12884948	-5.027611	4.97E-07	6.13E-06
Clk1	2185.18145	-0.6903021	0.11518644	-5.992662	2.06E-09	3.98E-08
Cflar	465.712518	-0.3464866	0.13729051	-2.523603	1.16E-02	4.11E-02
Raph1	77.038384	-1.1795257	0.23808161	-4.934756	8.03E-07	9.55E-06
Cd28	39.579292	-1.8931908	0.30662667	-6.024879	1.69E-09	3.32E-08
Icos	79.789007	-2.1144106	0.25710427	-8.092248	5.86E-16	2.83E-14
Pard3b	106.863035	-0.8221206	0.20786255	-3.949846	7.82E-05	5.73E-04
Klf7	49.676084	-0.8582828	0.27503384	-3.111534	1.86E-03	9.02E-03
Plekhm3	265.312809	-0.5556024	0.14890062	-3.730418	1.91E-04	1.27E-03
ldh1	621.115756	-0.567858	0.12036147	-4.717403	2.39E-06	2.56E-05
Ikzf2	465.995697	-0.7642567	0.14010883	-5.453365	4.94E-08	7.39E-07
Fn1	161.838603	-2.2215622	0.19054898	-11.550504	7.34E-31	1.27E-28
Igfbp5	9.031992	-1.7044485	0.37660478	-4.063464	4.83E-05	3.75E-04
Tns1	988.781827	-0.4702976	0.12704468	-3.701645	2.14E-04	1.40E-03
Cxcr2	84.999467	-0.5756822	0.23076496	-2.492567	1.27E-02	4.40E-02
Aamp	3883.03981	-0.2938244	0.09821668	-2.991578	2.78E-03	1.26E-02
Slc11a1	209.721792	-1.8826082	0.20583033	-9.109243	8.30E-20	6.14E-18
Ctdsp1	321.762893	-0.3836821	0.14219937	-2.697916	6.98E-03	2.70E-02
Cyp27a1	206.341002	-0.8542764	0.18303303	-4.663938	3.10E-06	3.24E-05
Prkag3	9.391356	-1.0946195	0.37899768	-2.849877	4.37E-03	1.83E-02
Glb1l	177.387095	-0.5256631	0.17681203	-2.971991	2.96E-03	1.33E-02
Dnpep	734.760163	-0.3748064	0.11825264	-3.169398	1.53E-03	7.59E-03
Spep	30.995259	-0.7784761	0.31438098	-2.467813	1.36E-02	4.65E-02
Obsl1	165.050039	-1.0410637	0.21223951	-4.899023	9.63E-07	1.13E-05
Stk11ip	964.532855	-0.2807838	0.10770398	-2.606947	9.14E-03	3.37E-02
Dock10	2229.53262	-0.6782504	0.12088418	-5.610539	2.02E-08	3.24E-07
Pid1	83.529174	-3.0992277	0.28652566	-10.228214	1.48E-24	1.59E-22
Sp110	1395.68846	-0.9055007	0.13498342	-6.707538	1.98E-11	5.28E-10
Sp140	244.052945	-1.0219332	0.15475787	-6.597299	4.19E-11	1.06E-09
Sp100	630.925317	-1.0147197	0.17764112	-5.71057	1.13E-08	1.87E-07
A630001G21Rik	277.933277	-0.7979153	0.16046569	-4.970186	6.69E-07	8.09E-06
Itn2c	559.284404	-0.5405304	0.12863206	-4.201683	2.65E-05	2.21E-04
Inpp5d	3809.72048	-0.3462573	0.1209231	-2.86343	4.19E-03	1.77E-02
Usp40	555.023057	-0.4410936	0.13755729	-3.206375	1.34E-03	6.79E-03
Arl4c	63.898342	-0.8368909	0.25299337	-3.30081	9.64E-04	5.10E-03
Lrrfip1	2688.75928	-0.2575479	0.10340735	-2.490602	1.28E-02	4.42E-02
Ramp1	1740.5401	-0.4046702	0.14096085	-2.870753	4.09E-03	1.74E-02

Kihl30	10.438771	-1.7236675	0.37899004	-4.077769	4.55E-05	3.55E-04
Hes6	657.59604	-0.7117092	0.14454546	-4.923068	8.52E-07	1.01E-05
Gpr35	75.548047	-2.6579691	0.26928699	-9.521067	1.71E-21	1.44E-19
Bok	145.826576	-0.8572717	0.22587354	-3.791868	1.50E-04	1.03E-03
D2hgdh	312.255834	-0.4622314	0.14539	-3.17877	1.48E-03	7.38E-03
Pdcd1	11.846205	-1.1254029	0.37830662	-2.945894	3.22E-03	1.43E-02
Fam174a	227.833723	-1.0399944	0.1787549	-5.812391	6.16E-09	1.08E-07
St8sia4	1229.60682	-0.914202	0.12088816	-7.561426	3.99E-14	1.59E-12
Bcl2	335.7952	-0.5202049	0.15396108	-3.378278	7.29E-04	4.06E-03
Dsel	40.957952	-0.9362896	0.29281242	-3.184415	1.45E-03	7.27E-03
Tmem37	79.283409	-1.5418866	0.26287148	-5.82677	5.65E-09	9.98E-08
Marco	303.566612	-1.210284	0.37099779	-3.608306	3.08E-04	1.92E-03
Slc35f5	163.687264	-0.6326214	0.1826424	-3.461983	5.36E-04	3.11E-03
Cxcr4	296.481738	-0.7523913	0.15024659	-5.005716	5.57E-07	6.81E-06
Rassf5	2512.70681	-0.762445	0.11137203	-6.845639	7.61E-12	2.15E-10
Ikike	364.943589	-0.8022793	0.15087829	-5.315429	1.06E-07	1.51E-06
5430435G22Rik	46.127929	-1.4679953	0.28417663	-5.110225	3.22E-07	4.13E-06
Nuak2	112.451221	-0.6742043	0.2264541	-2.974732	2.93E-03	1.32E-02
Tmcc2	566.118565	-0.5816193	0.17526495	-3.318172	9.06E-04	4.85E-03
Sox13	211.509101	-0.6335615	0.18493382	-3.424664	6.16E-04	3.50E-03
Lax1	960.690148	-0.6859249	0.14782402	-4.639748	3.49E-06	3.60E-05
Btg2	511.237304	-0.6661118	0.13273164	-5.017544	5.23E-07	6.45E-06
Ppfa4	253.569979	-2.0444201	0.180834	-11.256607	2.15E-29	3.47E-27
Ptpn7	3893.6767	-0.253718	0.09654598	-2.627941	8.59E-03	3.21E-02
Csrp1	2282.44358	-0.3264794	0.10068447	-3.242562	1.18E-03	6.10E-03
Tnni1	36.160524	-0.9385977	0.30992186	-3.015163	2.57E-03	1.18E-02
Kif21b	668.820449	-0.4904754	0.12799453	-3.83173	1.27E-04	8.92E-04
Ptprc	3125.17661	-0.5464297	0.11892359	-4.594717	4.33E-06	4.38E-05
Cfh	172.66379	-2.2164097	0.22604616	-9.729227	2.26E-22	2.07E-20
Rgs2	882.952554	-1.2516032	0.11845865	-10.56197	4.47E-26	5.40E-24
Rgs1	63.608561	-0.8669807	0.26265788	-3.293074	9.91E-04	5.23E-03
Hmcn1	35.573347	-0.8976248	0.32293435	-2.768363	5.63E-03	2.27E-02
Fam129a	272.810647	-1.754933	0.17555184	-9.969993	2.06E-23	2.04E-21
1700025G04Rik	401.511563	-0.527638	0.16237166	-3.249178	1.16E-03	5.98E-03
Rgl1	444.389792	-0.9531637	0.15618891	-6.100276	1.06E-09	2.18E-08
Ncf2	1435.8091	-0.5079398	0.11296933	-4.496094	6.92E-06	6.65E-05
Npl	569.452877	-0.4099069	0.12352098	-3.318298	9.06E-04	4.85E-03
Rgs8	18.873552	-0.9691661	0.35726132	-2.691136	7.12E-03	2.74E-02
Rnasel	697.562043	-0.4295345	0.12639249	-3.398227	6.78E-04	3.81E-03
Glul	680.388305	-0.3198336	0.11679599	-2.738286	6.18E-03	2.44E-02
Tor1aip1	803.870847	-0.397085	0.11071232	-3.586479	3.35E-04	2.07E-03
Soat1	413.71809	-0.4946359	0.1467466	-3.370241	7.51E-04	4.16E-03
Tor3a	493.381777	-0.8544601	0.13940159	-6.127696	8.92E-10	1.86E-08
2810025M15Rik	489.679253	-0.3921703	0.13286685	-2.951395	3.16E-03	1.40E-02
BC026585	244.891701	-0.4156782	0.15881208	-2.616976	8.87E-03	3.30E-02
Serpinc1	23.516913	-0.974412	0.36975618	-2.630689	8.52E-03	3.19E-02
Fmo1	4.540749	-1.0260376	0.35275543	-3.000271	2.70E-03	1.23E-02
Sell	737.28846	-1.2818703	0.18220015	-7.032564	2.03E-12	6.21E-11
Selp	52.2761	-1.8499318	0.30036602	-6.061877	1.35E-09	2.69E-08
Rcsd1	2287.84024	-0.4595483	0.10815882	-4.248755	2.15E-05	1.84E-04
Pbx1	154.506397	-0.6868547	0.18209917	-3.769366	1.64E-04	1.11E-03
Sh2d1b1	21.700767	-0.8867068	0.35858345	-2.462257	1.38E-02	4.71E-02
Gm7694	73.501315	-1.2868877	0.25534411	-5.01601	5.28E-07	6.49E-06
1700015E13Rik	9.877991	-0.9498365	0.37870763	-2.487452	1.29E-02	4.45E-02
Nos1ap	57.755601	-1.2209646	0.28223407	-4.304212	1.68E-05	1.48E-04
Fcgr4	44.046175	-1.9398975	0.31932958	-5.944861	2.77E-09	5.16E-08
Fcgr3	503.932696	-0.5344401	0.15358316	-3.479348	5.03E-04	2.94E-03
Fcer1g	1088.97105	-1.1609871	0.13731421	-8.45292	2.84E-17	1.56E-15
Arhgap30	3314.74068	-0.3700518	0.11855299	-3.12138	1.80E-03	8.77E-03
Usf1	879.153928	-0.5358572	0.11974974	-4.474521	7.66E-06	7.31E-05
Slamf7	4.11154	-0.865089	0.35124923	-2.442988	1.46E-02	4.92E-02
Cd48	2475.78232	-0.3984236	0.11826424	-3.368885	7.55E-04	4.18E-03
Cd84	631.892239	-0.4629575	0.13094738	-3.535172	4.08E-04	2.45E-03
Vangl2	174.71839	-0.7289031	0.20440625	-3.563875	3.65E-04	2.23E-03
Pea15a	174.545511	-0.7460543	0.18377353	-4.056993	4.97E-05	3.85E-04
Slamf8	5.618738	-1.3242757	0.36116551	-4.009018	6.10E-05	4.61E-04
Pydc4	19.837732	-1.4962093	0.36780788	-3.995414	6.46E-05	4.83E-04
Pyhin1	222.403333	-2.4976351	0.24355165	-10.176268	2.53E-24	2.67E-22
Pydc3	65.84181	-1.6189354	0.30605387	-5.250938	1.51E-07	2.08E-06
Al607873	164.864536	-2.1542661	0.24140903	-8.859791	8.02E-19	5.35E-17

Ifi204	148.949477	-3.3529713	0.25522937	-12.644185	1.20E-36	3.20E-34
Mndal	1030.2928	-1.197516	0.13405034	-8.930951	4.22E-19	2.88E-17
Mnda	31.551614	-2.6707619	0.35770123	-6.651123	9.12E-11	7.56E-10
Ifi203	1313.22066	-1.0716611	0.12094456	-8.859311	8.05E-19	5.35E-17
Ifi205	19.522026	-2.758035	0.37244694	-5.29139	1.21E-07	1.70E-06
Olfr433	13.406425	-1.4134381	0.37504312	-3.667089	2.45E-04	1.58E-03
Kmo	108.338369	-2.5182755	0.23149145	-10.657355	1.61E-26	2.07E-24
Sdcccag8	385.401283	-0.4017657	0.13802561	-2.910504	3.61E-03	1.56E-02
Hmga2-ps1	53.181314	-0.9527233	0.28639246	-3.315959	9.13E-04	4.88E-03
Akt3	120.580774	-0.4862513	0.19809132	-2.453674	1.41E-02	4.81E-02
Zbtb18	226.523113	-0.7433715	0.16898621	-4.396858	1.10E-05	1.01E-04
Adck3	402.718742	-0.7615315	0.14639851	-5.200282	1.99E-07	2.69E-06
Ephx1	22.982992	-1.2085894	0.34136209	-3.49825	4.68E-04	2.77E-03
Dusp10	54.491066	-0.7787984	0.2754115	-2.821677	4.78E-03	1.98E-02
Hlx	90.809409	-1.6823443	0.23478455	-7.110372	1.16E-12	3.72E-11
Lyplal1	104.380248	-0.7871481	0.21854276	-3.597603	3.21E-04	1.99E-03
Vash2	38.922426	-0.8772787	0.30315188	-2.883386	3.93E-03	1.68E-02
Batf3	19.54319	-2.1823704	0.36353594	-5.468684	4.53E-08	6.83E-07
Atf3	23.917815	-1.9239394	0.34567051	-5.327007	9.98E-08	1.42E-06
Tmem206	871.593819	-0.4501069	0.12380272	-3.635497	2.77E-04	1.76E-03
Traf5	122.489507	-0.8198342	0.2093856	-3.911035	9.19E-05	6.65E-04
Irf6	61.922869	-0.7805568	0.26291401	-2.963354	3.04E-03	1.36E-02
Traf3ip3	1731.45163	-0.7179701	0.11020298	-6.514615	7.29E-11	1.78E-09
Cd34	9683.69267	-0.4213118	0.10258039	-4.107124	4.01E-05	3.17E-04
Gm16897	73.113509	-0.7525301	0.23454047	-3.203273	1.36E-03	6.85E-03
Plekhg1	40.318898	-1.1036259	0.29728326	-3.689482	2.25E-04	1.46E-03
Ipcef1	264.194271	-0.4518361	0.14942761	-3.023248	2.50E-03	1.16E-02
Cnksr3	226.423297	-0.7091858	0.16816995	-4.215002	2.50E-05	2.10E-04
Zc3h12d	27.619494	-1.5089608	0.32926164	-4.49895	6.83E-06	6.58E-05
Tab2	983.102248	-0.313235	0.10703087	-2.926516	3.43E-03	1.50E-02
Sash1	33.925176	-0.8159274	0.30489433	-2.666207	7.67E-03	2.92E-02
Adgb	25.036134	-1.2569654	0.33635258	-3.692187	2.22E-04	1.45E-03
Rab32	825.630546	-0.9159217	0.12483705	-7.335504	2.21E-13	7.99E-12
Utrn	1102.60761	-0.3661087	0.11082579	-3.303369	9.55E-04	5.07E-03
Phactr2	506.266342	-0.8636041	0.13812844	-6.250358	4.10E-10	8.99E-09
Hivep2	88.105779	-0.9535841	0.27207284	-3.499251	4.67E-04	2.76E-03
Abracl	1109.08142	-0.2611058	0.10252667	-2.546669	1.09E-02	3.89E-02
Ccdc28a	145.02032	-0.5449366	0.18435135	-2.954623	3.13E-03	1.39E-02
Nhs1	51.249466	-0.6680974	0.26657909	-2.501816	1.24E-02	4.32E-02
Ifngr1	2038.15528	-0.3126654	0.10061382	-3.107539	1.89E-03	9.13E-03
Slc35d3	378.600119	-1.0760163	0.15660624	-6.8667	6.57E-12	1.89E-10
Map3k5	211.165384	-0.6608633	0.17655591	-3.741587	1.83E-04	1.22E-03
Stx7	915.15172	-0.4010245	0.10834961	-3.701062	2.15E-04	1.41E-03
Epb4.1i2	900.702449	-0.5414762	0.1229326	-4.404395	1.06E-05	9.81E-05
L3mbtl3	239.06999	-0.4000933	0.16047261	-2.492882	1.27E-02	4.40E-02
Arhgap18	1279.51019	-0.521925	0.12583358	-4.147567	3.36E-05	2.72E-04
Ptprk	97.097929	-1.5947029	0.25610456	-6.192181	5.93E-10	1.26E-08
Zufsp	303.793749	-0.4872755	0.14712091	-3.311498	9.28E-04	4.95E-03
Fam26f	66.130268	-1.0251919	0.24746146	-4.128769	3.65E-05	2.92E-04
Dse	160.58509	-1.882562	0.19703034	-9.499996	2.10E-21	1.72E-19
Tspyl4	125.005512	-0.5565277	0.20811415	-2.672842	7.52E-03	2.87E-02
Marcks	477.468113	-1.0593661	0.15558925	-6.805686	1.01E-11	2.78E-10
Cdk19	1191.54737	-0.53179	0.10536004	-5.047116	4.49E-07	5.59E-06
Smpd2	284.425191	-0.6278466	0.1536188	-4.085897	4.39E-05	3.45E-04
Aim1	83.006095	-1.2576876	0.2414318	-5.187602	2.13E-07	2.86E-06
Prdm1	19.661104	-1.2648871	0.35276042	-3.532646	4.11E-04	2.47E-03
Lilrb4	108.783534	-1.3057967	0.21598523	-6.024373	1.70E-09	3.32E-08
Dcbld1	43.042288	-1.0702131	0.28937889	-3.678934	2.34E-04	1.51E-03
Msl3l2	70.297085	-0.6994979	0.24053942	-2.90377	3.69E-03	1.59E-02
Gja1	301.619259	-0.9238585	0.15548312	-5.938391	2.88E-09	5.36E-08
Fabp7	2.352255	-0.6709716	0.30413738	-2.622255	8.74E-03	3.25E-02
Smpdl3a	606.363415	-0.4271123	0.13757494	-3.104401	1.91E-03	9.21E-03
Sowahc	24.061948	-1.4055449	0.33975066	-4.067135	4.76E-05	3.70E-04
Ddit4	122.972592	-1.2462708	0.20942901	-5.934305	2.95E-09	5.48E-08
Psap	7838.36342	-1.1323748	0.1079819	-10.486398	9.98E-26	1.18E-23
4632428N05Rik	675.63337	-1.1212519	0.1341911	-8.352488	6.68E-17	3.53E-15
Slc29a3	781.110505	-0.8241945	0.12225192	-6.740596	1.58E-11	4.28E-10
Pcbd1	68.689596	-0.9155501	0.24745178	-3.690484	2.24E-04	1.46E-03
Sgpl1	821.477675	-0.4260845	0.11231673	-3.793408	1.49E-04	1.02E-03
Pald1	76.465361	-0.8155813	0.24007551	-3.390962	6.96E-04	3.90E-03

Tet1	864.980979	-0.4194313	0.12117189	-3.461308	5.38E-04	3.11E-03
Arid5b	155.894161	-0.760917	0.18360318	-4.141127	3.46E-05	2.79E-04

**Table S9:** ERV families significantly upregulated in *Setdb1<sup>Δvav</sup>* LT-HSCs

ERV family	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
RLTR50A LTR ERVK	115.3087637	4.533159221	0.435083149	9.561292439	1.16E-21	1.76E-19
MER74C LTR ERVL	60.86860916	3.872425015	0.444044979	8.040695305	8.93E-16	5.42E-14
IAPLTR3-int LTR ERVK	424.1192674	3.533401388	0.327992663	10.72363884	7.88E-27	2.39E-24
ERVB4_1-I_MM-int LTR ERVK	315.9321202	3.4898036	0.36392553	9.53538359	1.49E-21	1.81E-19
MuLV-int LTR ERV1	22922.2934	3.039734155	0.233035461	13.04413417	6.86E-39	4.17E-36
ERVB4_2-I_MM-int LTR ERVK	356.5933941	2.968110392	0.453625471	6.573314453	4.92E-11	2.30E-09
RLTR6C_Mm LTR ERV1	60.72438053	2.69618733	0.313394163	8.451187	2.88E-17	2.19E-15
RLTR45 LTR ERVK	288.6002807	2.493699688	0.307778932	8.084902775	6.22E-16	4.20E-14
IAPLTR4 LTR ERVK	88.5827766	2.422171983	0.337590193	7.121798244	1.07E-12	5.39E-11
MMERVK10C-int LTR ERVK	4211.197678	2.330897416	0.303676898	7.676101582	1.64E-14	9.05E-13
RLTR10C LTR ERVK	1004.051256	2.300374391	0.429998961	5.362872898	8.19E-08	3.31E-06
MMVL30-int LTR ERV1	1625.49848	2.271243474	0.25075945	9.055488101	1.36E-19	1.38E-17
MMTV-int LTR ERVK	2346.616032	2.177523161	0.519621572	4.343993242	1.40E-05	0.000404423
RLTR3_Mm LTR ERVK	151.4994152	2.009509415	0.38034619	5.274264254	1.33E-07	5.06E-06
MMERVK9C_I-int LTR ERVK	777.712505	1.813424411	0.430303418	4.220603425	2.44E-05	0.000643022
RLTR45-int LTR ERVK	1171.273351	1.537845251	0.152967061	10.05209711	8.99E-24	1.82E-21
RLTR4_Mm LTR ERV1	1552.67623	1.431960201	0.166509462	8.599135905	8.03E-18	6.96E-16
RMER17A-int LTR ERVK	112.8897621	1.378754235	0.309312048	4.45188001	8.51E-06	0.000287049
IAP1-MM_LTR LTR ERVK	71.95243687	1.344447962	0.280063154	4.790628455	1.66E-06	5.94E-05
IAP-d-int LTR ERVK	83.46731214	1.171041168	0.27241038	4.293984673	1.75E-05	0.000484206
RLTR27 LTR ERVK	142.9454108	1.014595359	0.233136987	4.350011722	1.36E-05	0.000404423

**Table S10:** ERV families significantly upregulated in *Setdb1<sup>Δvav</sup>* MPPs

ERV family	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
RLTR50A LTR ERVK	112.7377492	6.929567457	0.582665062	10.07538056	7.10E-24	1.48E-22
IAPLTR3-int LTR ERVK	1322.760671	5.957725342	0.157610998	37.62674776	0	0
ERVB4_2-I_MM-int LTR ERVK	897.0974631	5.910899848	0.234652904	25.04700266	1.88E-138	3.26E-136
MER74C LTR ERVL	86.60942973	5.554551083	0.443789845	11.79587217	4.10E-32	1.07E-30
ERVB4_2-LTR_MM LTR ERVK	13.59193799	5.082019253	0.853016671	5.094731889	3.49E-07	3.78E-06
MURVY-int LTR ERV1	91.12981362	4.575814994	0.377260772	11.88992911	1.34E-32	3.65E-31
ERVB4_1-I_MM-int LTR ERVK	470.7609106	4.463654539	0.235284245	18.91930749	7.91E-80	4.11E-78
RLTR6C_Mm LTR ERV1	173.4371546	4.36015532	0.284265451	15.21781907	2.69E-52	1.00E-50
IAPLTR4 LTR ERVK	190.9319203	4.255906444	0.217054451	19.46185888	2.31E-84	1.34E-82
RLTR10C LTR ERVK	1821.47028	4.104850424	0.186450461	22.00638463	2.50E-107	1.86E-105
MMERVK10C-int LTR ERVK	6983.174981	4.072903087	0.169537979	24.02112512	1.67E-127	2.17E-125
RLTR45 LTR ERVK	566.3067057	4.04025705	0.196402788	20.54051038	9.36E-94	6.08E-92
MuLV-int LTR ERV1	49020.75262	3.952581031	0.08330411	47.44701156	0	0
RLTR45-int LTR ERVK	3108.836542	3.505584294	0.148604976	23.58676223	5.27E-123	5.48E-121
RMER17A-int LTR ERVK	201.7851635	3.468191276	0.200183696	17.275576	7.19E-67	2.87E-65
MMERVK9C_I-int LTR ERVK	1325.062329	3.4538709	0.186990354	18.46522903	3.93E-76	1.86E-74
MMVL30-int LTR ERV1	3233.052446	3.225050534	0.181720952	17.74557956	1.86E-70	8.08E-69
RLTR44E LTR ERVK	27.28419614	3.184298209	0.464966709	6.735763031	1.63E-11	2.42E-10
MMTV-int LTR ERVK	2191.701474	3.045928684	0.209597331	14.53065152	7.75E-48	2.52E-46
ERVB3_1-I_MM-int LTR ERVK	75.54907149	2.745359668	0.257769033	10.61163017	2.63E-26	5.70E-25
RLTR10B2 LTR ERVK	108.4660333	2.543976306	0.262208818	9.685157987	3.49E-22	6.97E-21
IAP-d-int LTR ERVK	86.40761865	2.4991614	0.220819874	11.28977001	1.47E-29	3.65E-28
ERVB7_3-LTR_MM LTR ERVK	43.23376955	2.105487905	0.298962955	7.02196083	2.19E-12	3.56E-11
RLTR4_Mm LTR ERV1	2450.483703	2.078628927	0.090289422	23.02102007	2.87E-117	2.49E-115
MMERVK10D3_I-int LTR ERVK	123.6100053	2.007497073	0.178466267	11.23856713	2.64E-29	6.23E-28
RLTR44D LTR ERVK	12.13499142	1.792437478	0.463831404	3.835949484	0.00012508	0.001084028
RLTR1B-int LTR ERV1	528.99291	1.740523579	0.136122299	12.78500076	1.99E-37	6.08E-36
RLTR44B LTR ERVK	13.01648345	1.720522959	0.462942944	3.694239318	0.000220546	0.001791936
IAPLTR1a_Mm LTR ERVK	551.2716564	1.690250188	0.139320805	12.13087356	7.25E-34	2.09E-32
RLTR13D6 LTR ERVK	106.922081	1.66631935	0.182631626	9.118213844	7.64E-20	1.47E-18
RLTR3_Mm LTR ERVK	146.8750921	1.647747567	0.241466415	6.821636068	9.00E-12	1.42E-10
MMERGLN-int LTR ERV1	4888.177287	1.605707858	0.212633343	7.551467244	4.30E-14	7.99E-13
RLTR1B LTR ERV1	198.8568471	1.546579957	0.14474028	10.68237573	1.23E-26	2.78E-25
RLTR10B LTR ERVK	35.11920961	1.434639777	0.285223944	5.022919307	5.09E-07	5.29E-06

IAPEY4_I-int LTR ERVK	1699.292889	1.375984536	0.091758534	14.99543491	7.86E-51	2.73E-49
RLTR10D2 LTR ERVK	16.07381209	1.351069369	0.39536102	3.408108323	0.000654149	0.004535435
RLTR6-int LTR ERV1	1545.361106	1.342205529	0.180814296	7.422980167	1.15E-13	2.05E-12
ERVb7_2-LTR_MM LTR ERVK	277.7063945	1.320835098	0.186214205	7.092319668	1.32E-12	2.21E-11
ETnERV3-int LTR ERVK	216.0890444	1.22415767	0.183588255	6.667117705	2.61E-11	3.57E-10
IAP1-MM_LTR LTR ERVK	29.65836329	1.171322935	0.309980158	3.774939659	0.000160046	0.00136433
RLTR6_Mm LTR ERV1	177.0688217	1.137927028	0.185855389	6.121885718	9.25E-10	1.17E-08
IAPEz-int LTR ERVK	6025.906718	1.127922157	0.158440591	7.118875564	1.09E-12	1.89E-11
ETnERV-int LTR ERVK	352.3709473	1.06976194	0.161177729	6.636797323	3.21E-11	4.27E-10
RLTR10F LTR ERVK	68.98179147	1.053555807	0.209099229	5.036930087	4.73E-07	5.02E-06
ERVb4_1B-I_MM-int LTR ERVK	85.78410188	1.03679133	0.181763355	5.702631437	1.18E-08	1.36E-07
RMER16A3 LTR ERVK	30.77697187	1.026735636	0.292468527	3.508177612	0.000451188	0.003301675

**Table S11:** ERV families with significantly increased chromatin accessibility in *Setdb1<sup>val</sup>* MPPs

ERV family	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
ERVb4_2-LTR_MM	4579.73425703304	0.623163500748701	0.0758881708118468	8.32854275837693	8.1843511083208e-17	1.01813327787511e-13
RLTR6C_Mm	1846.54614192159	0.578992689651464	0.0763890561374721	7.61577095343994	2.62122151058355e-14	1.63039977958297e-11
RLTR45	46523.5385922518	0.364362719187501	0.0644538212359918	5.93950721014413	2.85880104194219e-09	1.18544949872536e-06
RLTR10B	3327.37366274259	0.329236891830772	0.0726745629106498	4.5325581952792	5.82736143430936e-06	0.00122685699227536
RLTR4_Mm	5769.20617268126	0.306861495195111	0.0764487231671018	4.02184009302607	5.77452563184084e-05	0.0102621569800143
RLTR44A	2243.27133827018	0.257756118032041	0.071905198614013	3.58581678955108	0.000336024814958508	0.0380013518007622
RLTR10C	53526.3487713016	0.236416744670636	0.0547547907800018	4.61557734081547	3.92004019059855e-06	0.00121913249927615
MuLV-int	8835.0461121663	0.236410256622205	0.0649536622708368	3.64007064044257	0.000272563254332021	0.0348982233588489
RLTR10B2	14100.9341017979	0.227545021695776	0.0592072914994421	3.98160943415245	6.84501924459093e-05	0.0106440049253389
ORR1B2	73031.3612633982	0.222184091566354	0.0490551840842682	4.52932233626524	5.91731668300015e-06	0.00122685699227536
ORR1C1	57251.7284189947	0.154299573476277	0.0424761562203273	3.63264362118272	0.000280532342112934	0.0348982233588489

## SI References

1. J. Brind'Amour, *et al.*, An ultra-low-input native ChIP-seq protocol for genome-wide profiling of rare cell populations. *Nat. Commun.* **6**, 6033 (2015).
2. M. R. Corces, *et al.*, An improved ATAC-seq protocol reduces background and enables interrogation of frozen tissues. *Nat. Methods* **14**, 959–962 (2017).
3. S. Pundhir, *et al.*, Enhancer and Transcription Factor Dynamics during Myeloid Differentiation Reveal an Early Differentiation Block in *Cebpa* null Progenitors. *Cell Rep.* **23**, 2744–2757 (2018).