

**Table S1. Differentially bound H3K4me1 peaks from comparison of *Kmt2d*<sup>+/ $\beta$ Geo</sup> mice treated with vehicle versus *Kmt2d*<sup>+/ $\beta$</sup>  mice treated with vehicle**

Chr	Start	End	Distance to TSS	Fold change	P-value	Symbol
<b>Upregulated</b>						
chr1	24684051	24684350	5282	3.15	4.56E-08	<i>Lmbrd1</i>
chr17	13587351	13587750	-33456	3.04	3.73E-13	<i>2700054A10Rik</i>
chr11	31922601	31922900	-42883	2.98	4.82E-13	<i>4930524B15Rik</i>
chr1	85528851	85529150	69810	2.57	3.05E-06	<i>Sp110</i>
<b>Downregulated</b>						
chr3	75492601	75492950	64077	0.22	1.71E-07	<i>Pdcd10</i>
chr7	83179601	83179950	31305	0.29	1.04E-08	<i>A530021J07Rik</i>
chr4	1.46E+08	1.46E+08	16203	0.29	1.98E-05	<i>Zfp980</i>
chr2	1.62E+08	1.62E+08	-275288	0.30	3.48E-07	<i>Ptprtos</i>
chr16	67016151	67016500	359207	0.32	1.64E-11	<i>1700010K23Rik</i>
chr1	85180451	85180750	-19011	0.32	1.72E-06	<i>Gm7609</i>
chr2	1.34E+08	1.34E+08	128852	0.33	2.81E-06	<i>Hao1</i>
chr3	69799701	69800050	60019	0.34	2.1E-08	<i>Sptssb</i>
chr12	44648151	44648500	319440	0.34	6.68E-10	<i>Nrcam</i>
chr2	1.77E+08	1.77E+08	-25325	0.34	6.84E-06	<i>Gm14295</i>
chr11	1.1E+08	1.1E+08	-9049	0.35	1.48E-14	<i>Abca6</i>
chr16	39393901	39394250	491730	0.36	8.15E-09	<i>Igsf11</i>
chr18	19039551	19039850	962397	0.36	3.8E-06	<i>Dsc3</i>
chr15	36567701	36568000	-12278	0.38	9.4E-08	<i>Snx31</i>
chr2	1.24E+08	1.24E+08	-269444	0.39	4.97E-10	<i>Sema6d</i>
chr4	1.48E+08	1.48E+08	3533	0.39	0.000696	<i>Zfp979</i>
chr11	39221751	39222050	168325	0.39	2.27E-08	<i>4930553C11Rik</i>
chr1	85238501	85238800	31916	0.39	0.000908	<i>C130026I21Rik</i>
chr7	1.23E+08	1.23E+08	55509	0.39	3.19E-05	<i>4930413G21Rik</i>
chr12	1.06E+08	1.06E+08	-43909	0.40	1.8E-12	<i>1700121N20Rik</i>
chr19	53964301	53964650	19599	0.40	8.38E-07	<i>Shoc2</i>
chr17	16379951	16380250	-553514	0.40	8.38E-10	<i>Rgmb</i>
chr11	46955651	46956000	145026	0.40	2.37E-05	<i>Timd4</i>
chr2	82344951	82345300	291467	0.41	6.32E-14	<i>Zfp804a</i>

**Table S2. Differentially bound H3K4me1 peaks upon comparing *Kmt2d*<sup>+/βGeo</sup> mutant mice treated with TAK-418 versus *Kmt2d*<sup>+/+</sup> mice treated with vehicle**

Chr	Start	End	Distance to TSS	Fold change	P-value	Description
<b>Upregulated</b>						
chr15	38308451	38308800	-7914	4.580961	1.09E-13	<i>Klf10</i>
chr6	47757851	47758150	-5075	4.23132	2.01E-08	<i>Rn4.5s</i>
chr1	24684051	24684350	5282	3.949866	6.11E-09	<i>Lmbrd1</i>
chr6	47672201	47672550	24	3.767908	2.43E-10	<i>Rn4.5s</i>
chr6	1.16E+08	1.16E+08	-27345	3.241102	3.45E-10	<i>Plxnd1</i>
chr6	4923851	4924250	20730	3.084724	1.32E-08	<i>Ppp1r9a</i>
chr8	39152901	39153300	-144880	2.902813	1.98E-07	<i>Gm6213</i>
chr1	1.71E+08	1.71E+08	602	2.835173	2.93E-08	<i>Mir6546</i>
chrX	1.7E+08	1.7E+08	-17458	2.834468	8.93E-17	<i>G530011O06Rik</i>
chr1	69456651	69457000	229135	2.756085	5.28E-08	<i>Ikzf2</i>
chr1	88257601	88258050	11583	2.689857	3.49E-07	<i>6430706D22Rik</i>
chr14	1.23E+08	1.23E+08	34747	2.478949	5.06E-05	<i>Pcca</i>
chr17	13305901	13306450	-48397	2.451861	1.63E-51	<i>Tcp10c</i>
chrX	1.7E+08	1.7E+08	-26258	2.40602	5.48E-33	<i>G530011O06Rik</i>
chr1	1E+08	1E+08	407535	2.316954	6.16E-05	<i>Cntnap5b</i>
chrX	1.7E+08	1.7E+08	-15508	2.311163	9.46E-27	<i>G530011O06Rik</i>
chr4	3176851	3177150	4917	2.299987	2.06E-06	<i>Vmn1r2</i>
chr1	88286301	88287250	-9196	2.294952	1.11E-10	<i>Hjrp</i>
chr18	82170301	82170950	-178545	2.293223	8.63E-15	<i>Mir5127</i>
chr4	1.47E+08	1.47E+08	99559	2.250408	3.67E-06	<i>Zfp982</i>
chr16	3239551	3239950	-352648	2.226777	6.48E-06	<i>Olfr161</i>
chr4	1.22E+08	1.22E+08	-500850	2.217059	2.41E-05	<i>Gm12887</i>
chr17	57855901	57856300	86530	2.144734	8.81E-11	<i>Cntnap5c</i>
<b>Downregulated</b>						
chr1	85463551	85463850	135110	0.462643	4.47E-05	<i>Sp110</i>
chr4	1.47E+08	1.47E+08	-128525	0.444317	0.000501	<i>Rex2</i>
chr1	85010801	85011150	-75892	0.436585	6.64E-05	<i>Slc16a14</i>
chrX	1.27E+08	1.27E+08	140604	0.425518	2.04E-09	<i>4932411N23Rik</i>
chr1	85312151	85312500	-41759	0.419504	0.000288	<i>C130026I21Rik</i>
chr8	95117501	95117800	-4308	0.413902	2.52E-05	<i>Kifc3</i>
chr8	20382251	20382600	-19223	0.398451	1.19E-05	<i>Gm15319</i>

**Table S3. Differentially bound H3K4me3 peaks upon comparison of *Kmt2d*<sup>+/ $\beta$ Geo</sup> on vehicle versus *Kmt2d*<sup>+/<sup>+</sup></sup> mice treated with vehicle.**

Symbol	Chr	Start	End	P-value	Fold change	Description
<b>Upregulated</b>						
<i>Cnot9</i>	chr1	74506301	74506800	5.83E-06	2.750	CCR4-NOT transcription complex, subunit 9
<i>Zfp800</i>	chr6	28261001	28261350	5.95E-04	2.500	zinc finger protein 800
<b>Downregulated</b>						
<i>Tspan2</i>	chr3	1.03E+08	1.03E+08	1.73E-07	0.258	tetraspanin 2
<i>B3gnt5</i>	chr16	19761051	19761400	1.83E-06	0.264	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5
<i>Zbtb18</i>	chr1	1.77E+08	1.77E+08	4.31E-07	0.271	zinc finger and BTB domain containing 18
<i>4833420G17Rik</i>	chr13	1.19E+08	1.19E+08	2.53E-02	0.280	RIKEN cDNA 4833420G17 gene
<i>Ddx3x</i>	chrX	13281151	13281800	2.54E-12	0.299	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 3, X-linked
<i>Zfp503</i>	chr14	21987651	21987750	1.23E-02	0.315	zinc finger protein 503
<i>Asns</i>	chr6	7692901	7693200	1.05E-06	0.318	asparagine synthetase
<i>Mfap1b</i>	chr2	1.21E+08	1.21E+08	2.46E-05	0.319	microfibrillar-associated protein 1B
<i>Cfap36</i>	chr11	29247101	29247400	4.37E-05	0.321	cilia and flagella associated protein 36
<i>Nfkbiz</i>	chr16	55821701	55822050	9.65E-06	0.323	nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, zeta
<i>Osbp16</i>	chr2	76406201	76406400	2.10E-03	0.323	oxysterol binding protein-like 6
<i>Tubb4a</i>	chr17	57087351	57087500	3.21E-03	0.327	tubulin, beta 4A class IVA
<i>Rerg</i>	chr6	1.37E+08	1.37E+08	4.38E-04	0.327	RAS-like, estrogen-regulated, growth-inhibitor
<i>Pagr1a</i>	chr7	1.27E+08	1.27E+08	1.37E-04	0.332	PAXIP1 associated glutamate rich protein 1A
<i>Cacfd1</i>	chr2	27010051	27010400	3.73E-06	0.341	calcium channel flower domain containing 1
<i>Tmem151b</i>	chr17	45549251	45549650	1.60E-05	0.342	transmembrane protein 151B
<i>Hebp1</i>	chr6	1.35E+08	1.35E+08	2.36E-04	0.347	heme binding protein 1
<i>Tmem55a</i>	chr4	14864301	14864750	1.73E-07	0.348	transmembrane protein 55A
<i>Narf</i>	chr11	1.21E+08	1.21E+08	6.89E-06	0.348	nuclear prelamin A recognition factor
<i>BC055324</i>	chr1	1.64E+08	1.64E+08	7.22E-04	0.348	cDNA sequence BC055324
<i>Akap1</i>	chr11	88864201	88864600	1.06E-06	0.349	A kinase (PRKA) anchor protein 1
<i>Etv1</i>	chr12	38778801	38779250	2.76E-05	0.350	ets variant 1

**Table S4. Differentially bound H3K4me3 peaks upon comparison of *Kmt2d*<sup>+/βGeo</sup> mice on TAK-418 versus *Kmt2d*<sup>+/+</sup> mice treated with vehicle.**

Symbol	Chr	Start	End	P-value	Fold change	Gene.Description
<b>Upregulated</b>						
<i>Col19a1</i>	chr1	24613301	24613950	4.99E-17	4.091	collagen, type XIX, alpha 1
<i>Ajap1</i>	chr4	1.53E+08	1.53E+08	2.81E-14	4.050	adherens junction associated protein 1
<i>6820431F2</i> <i>ORik</i>	chr8	20150551	20150950	4.31E-08	3.538	cadherin 11 pseudogene
<b>Downregulated</b>						
<i>Ddx6</i>	chr9	44605601	44606000	3.11E-07	0.172	DEAD (Asp-Glu-Ala-Asp) box polypeptide 6
<i>B430212C0</i> <i>6Rik</i>	chr18	67343651	67344100	9.01E-10	0.188	RIKEN cDNA B430212C06 gene
<i>2310022B0</i> <i>5Rik</i>	chr8	1.25E+08	1.25E+08	9.21E-11	0.200	RIKEN cDNA 2310022B05 gene
<i>1810014B0</i> <i>1Rik</i>	chr10	86685501	86685950	9.46E-09	0.202	RIKEN cDNA 1810014B01 gene
<i>Smad7</i>	chr18	75342701	75343050	4.97E-07	0.207	SMAD family member 7
<i>Mri1</i>	chr8	84256851	84257250	1.57E-07	0.208	methylthioribose-1-phosphate isomerase 1
<i>Rela</i>	chr19	5637651	5638050	1.89E-07	0.211	v-rel reticuloendotheliosis viral oncogene homolog A (avian)
<i>Trim59</i>	chr3	69044301	69044800	5.31E-11	0.212	tripartite motif-containing 59
<i>Lca5l</i>	chr16	96191901	96192300	7.84E-07	0.221	Leber congenital amaurosis 5-like
<i>Vapb</i>	chr2	1.74E+08	1.74E+08	6.89E-09	0.229	vesicle-associated membrane protein, associated protein B and C
<i>Pskh1</i>	chr8	1.06E+08	1.06E+08	2.49E-06	0.232	protein serine kinase H1
<i>Parp4</i>	chr14	56575501	56575850	6.95E-05	0.238	poly (ADP-ribose) polymerase family, member 4
<i>Suclg2</i>	chr6	95718501	95718850	1.37E-06	0.239	succinate-Coenzyme A ligase, GDP-forming, beta subunit
<i>Mfap3l</i>	chr8	60632351	60632700	1.92E-05	0.239	microfibrillar-associated protein 3-like
<i>Patl1</i>	chr19	11912601	11913150	3.19E-07	0.241	protein associated with topoisomerase II homolog 1 (yeast)
<i>Tmem120b</i>	chr5	1.23E+08	1.23E+08	1.96E-05	0.242	transmembrane protein 120B
<i>Them6</i>	chr15	74721351	74721800	5.89E-07	0.247	thioesterase superfamily member 6
<i>Ptov1</i>	chr7	44869301	44869700	4.36E-06	0.253	prostate tumor over expressed gene 1
<i>Zfp334</i>	chr2	1.65E+08	1.65E+08	5.89E-06	0.255	zinc finger protein 334
<i>Mir6921</i>	chr11	60176651	60177250	5.64E-07	0.255	microRNA 6921
<i>Dcaf5</i>	chr12	80434951	80435350	8.47E-08	0.256	DDB1 and CUL4 associated factor 5
<i>Slc1a2</i>	chr2	1.03E+08	1.03E+08	6.06E-06	0.257	solute carrier family 1 (glial high affinity glutamate transporter), member 2
<i>Zbtb43</i>	chr2	33468101	33468500	2.43E-06	0.258	zinc finger and BTB domain containing 43
<i>Exosc9</i>	chr3	36552651	36553000	6.43E-05	0.259	exosome component 9

**Table S5. Differentially expressed genes upon comparison of *Kmt2d*<sup>+/βGeo</sup> mice on vehicle versus *Kmt2d*<sup>+/+</sup> mice on vehicle.**

Symbol	Description	Fold change	P value
<b>Upregulated</b>			
<i>Nlrp5-ps</i>	NLR family, pyrin domain containing 5, pseudogene	2.319	7.69E-05
<i>Onecut1</i>	one cut domain, family member 1	2.095	4.82E-04
<i>Fmod</i>	Fibromodulin	1.734	1.75E-04
<i>A4galt</i>	alpha 1,4-galactosyltransferase	1.722	2.41E-02
<i>Clec3b</i>	C-type lectin domain family 3, member b	1.719	7.90E-03
<i>Ptx3</i>	pentraxin related gene	1.642	1.83E-02
<i>Mlph</i>	Melanophilin	1.638	2.10E-02
<i>Xdh</i>	xanthine dehydrogenase	1.636	1.23E-02
<i>Kcnh6</i>	potassium voltage-gated channel, subfamily H (eag-related), member 6	1.601	4.75E-10
<i>Eln</i>	Elastin	1.587	1.71E-07
<i>F13a1</i>	coagulation factor XIII, A1 subunit	1.575	2.59E-02
<b>Downregulated</b>			
<i>Trh</i>	thyrotropin releasing hormone	0.112	1.85E-02
<i>Rxfp1</i>	relaxin/insulin-like family peptide receptor 1	0.448	5.10E-08
<i>Nxph3</i>	neurexophilin 3	0.469	3.92E-06
<i>Tshz2</i>	teashirt zinc finger family member 2	0.484	1.94E-04
<i>Plcz1</i>	phospholipase C, zeta 1	0.500	8.14E-04
<i>Fos</i>	FBJ osteosarcoma oncogene	0.535	4.39E-02
<i>Egr2</i>	early growth response 2	0.563	8.96E-03
<i>Olfir287</i>	olfactory receptor 28	0.567	1.79E-05
<i>Susd2</i>	sushi domain containing 2	0.577	3.78E-03
<i>Nts</i>	Neurotensin	0.577	1.48E-02
<i>Nhlh1</i>	nescient helix loop helix 1	0.607	1.24E-02
<i>Cbln1</i>	cerebellin 1 precursor protein	0.625	8.97E-03
<i>Otof</i>	Otoferlin	0.627	2.46E-04
<i>Olfir55</i>	olfactory receptor 55	0.668	4.30E-02
<i>Ntn5</i>	netrin 5	0.683	1.34E-02
<i>Bub1b</i>	mitotic checkpoint serine/threonine kinase	0.683	3.62E-03
<i>Nov</i>	nephroblastoma overexpressed gene	0.685	1.12E-02
<i>Igfbp6</i>	insulin-like growth factor binding protein 6	0.688	2.46E-03
<i>Met</i>	met proto-oncogene	0.690	2.67E-03
<i>Fosb</i>	FBJ osteosarcoma oncogene B	0.696	4.73E-03
<i>Arc</i>	activity regulated cytoskeletal-associated protein	0.730	3.76E-02
<i>Junb</i>	jun B proto-oncogene	0.737	2.82E-04
<i>Kcnf1</i>	potassium voltage-gated channel, subfamily F, member 1	0.755	9.99E-09

**Table S6. Differentially expressed genes upon comparison of *Kmt2d*<sup>+/βGeo</sup> mice on TAK-418 versus *Kmt2d*<sup>+/+</sup> mice on vehicle control.**

Symbol	Description	Fold change	P-value
<b>Upregulated</b>			
<i>Prph</i>	Peripherin	3.040	7.04E-05
<i>Atp4a</i>	ATPase, H+/K+ exchanging, gastric, alpha polypeptide	2.226	6.27E-04
<i>Lefty2</i>	left-right determination factor 2	2.131	3.16E-05
<i>Nlrp5-ps</i>	NLR family, pyrin domain containing 5, pseudogene	1.953	1.51E-03
<i>Gipc3</i>	GIPC PDZ domain containing family, member 3	1.865	1.02E-04
<i>Espn</i>	Espin	1.863	4.17E-10
<i>Arsi</i>	arylsulfatase i	1.788	4.62E-03
<i>Onecut1</i>	one cut domain, family member 1	1.740	5.63E-03
<i>Samd11</i>	sterile alpha motif domain containing 11	1.710	2.11E-02
<i>Ppp1r32</i>	protein phosphatase 1, regulatory subunit 32	1.692	6.83E-03
<i>Slc16a3</i>	solute carrier family 16 (monocarboxylic acid transporters), member 3	1.674	1.55E-03
<i>Tnxb</i>	tenascin XB	1.658	3.26E-14
<i>Duxbl3</i>	double homeobox B-like 3	1.636	1.84E-02
<i>Arhgap36</i>	Rho GTPase activating protein 36	1.630	8.82E-04
<i>Rps6kc1</i>	ribosomal protein S6 kinase polypeptide 1	1.617	4.43E-04
<i>Plp2</i>	proteolipid protein 2	1.615	2.60E-03
<i>Lrrn4</i>	leucine rich repeat neuronal 4	1.613	1.72E-02
<b>Downregulated</b>			
<i>Trh</i>	thyrotropin releasing hormone	0.167	4.40E-02
<i>Baiap2l1</i>	BAI1-associated protein 2-like 1	0.362	6.94E-04
<i>Egr2</i>	early growth response 2	0.550	1.02E-03
<i>Cd59a</i>	CD59a antigen	0.612	1.65E-03
<i>Otof</i>	Otoferlin	0.627	3.62E-04
<i>Ppfibp2</i>	PTPRF interacting protein, binding protein 2 (liprin beta 2)	0.628	4.86E-02
<i>Mir129-1</i>	microRNA 129-1	0.636	1.66E-03
<i>Rxfp1</i>	relaxin/insulin-like family peptide receptor 1	0.660	1.86E-03
<i>Satb2</i>	special AT-rich sequence binding protein 2	0.669	1.74E-05
<i>Iqub</i>	IQ motif and ubiquitin domain containing	0.676	4.76E-02
<i>Fam46c</i>	family with sequence similarity 46, member C	0.678	2.25E-02