**Supporting Information**

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Fig. S1. Schematic summary of prior findings. Kmt2d^+/βGeo mice on a mixed C57BL/6J and 129SvEv background demonstrated a global deficiency of the open chromatin mark H3K4me3 in association with decreased neurogenesis in the GCL of the DG (Middle) compared with littermate Kmt2d^+/+ mice (Left). These defects were rescued with AR-42 (Right) (6), a class 1 and 2 histone deacetylase inhibitor (24), which has recently been shown to inhibit HDAC5 in liver cells (49).

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Fig. S2. Kmt2d^+/βGeo mice demonstrate a generalized tendency toward down-regulation of gene expression. Even when data were explored below the level of statistical significance for the top 1,000 most highly expressed genes and put into bins, there was a generalized tendency toward down-regulation of gene expression at all fold change (FC) bins (n = 6 per group).
Fig. S3. The Kmt2d probe-set that shows differential expression from microarray analysis is downstream of the SET domain. Schematic of the probe-set that overlaps the last exon of Kmt2d.

Fig. S4. The rationale describing how a KD could be used to counter the epigenetic defect in Kmt2d\textsuperscript{+/\betaGeo} mice. There are multiple ways to increase blood levels of BHB (direct injection, KD, and exercise). Because BHB is an endogenous HDACi, it may rescue the epigenetic abnormality seen in Kmt2d\textsuperscript{+/\betaGeo} mice, and thereby provide similar therapeutic benefits as AR-42 in Kmt2d\textsuperscript{+/\betaGeo} mice (Fig. S1).

Fig. S5. BHB is elevated in the serum and brain of Kmt2d\textsuperscript{+/\betaGeo} mice on a KD. (A) Serum BHB levels in Kmt2d\textsuperscript{+/\betaGeo} mice (n > 10) and littermate controls (n > 10) after 2 wk of the KD. (B) Brain BHB levels in Kmt2d\textsuperscript{+/\betaGeo} mice (n ≥ 5) and littermate controls (n ≥ 5) after 2 wk of the KD. *P < 0.05; ††P < 0.001.
Fig. S6. Two markers of renal function are normal in Kmt2d+/βGeo mice. (A) Creatinine levels in young mice (6 wk old) do not show a significant difference (Welch’s t test) between Kmt2d+/βGeo mice (n = 11) and littermate Kmt2d+/+ mice (n = 14), and all values are within the range of normal levels for mice of this age (dotted lines). (B) Blood urea nitrogen (BUN) levels show no significant difference (Welch’s t test) between Kmt2d+/βGeo mice (n = 11) and littermate Kmt2d+/+ mice (n = 14), and all values are within the range of normal levels for mice (dotted lines). N.S., not significant, P > 0.05.

Fig. S7. Crebbp+/- mice do not share metabolic alterations found in Kmt2d+/βGeo mice. Rubinstein-Taybi syndrome is another Mendelian disorder of the epigenetic machinery, caused by deficiency of a histone acetyltransferase (CREBBP), which secondarily leads to a global deficiency of histone acetylation (14). The histone tails have previously been suggested to act as a potential acetyl-CoA sink (15). Furthermore, other studies have linked NAD+ and histone acetylation (16). A global deficiency of histone acetylation could therefore potentially lead to chronic acetyl-CoA elevation, thereby driving beta-oxidation and secondarily increasing NADH/NAD+ ratio in both KS and Rubinstein-Taybi syndrome. BHB levels from urine show a significant (P < 0.05) elevation in Kmt2d+/βGeo mice compared with Kmt2d+/+ and Crebbp+/- mice (13) (n = 6–8 per group). However, no significant differences were seen between Kmt2d+/+ and Crebbp+/- mice (P = 0.36). *P < 0.05.
Fig. 5B. Lactate/pyruvate ratio is abnormal in Kmt2d<sup>+/βGeo</sup> mice. (A) Both BHB/AcAc and lactate/pyruvate ratios are controlled by the NADH/NAD<sup>+</sup> ratio. (B) In addition to the increased BHB/AcAc ratio, serum analysis from KD-treated animals shows Kmt2d<sup>+/βGeo</sup> mice had a significant increase in the lactate/pyruvate (Lac/Pyr) ratio compared with KD-treated Kmt2d<sup>+/+</sup> littermates (n = 12–15 per group). *P < 0.05.
Fig. S9. Exogenous BHB treatment rescues the neurogenesis defect in Kmt2d<sup>+/βGeo</sup> mice. (A) Several distinct doses (0, 2.5, 5, 10 mM/kg) of BHB were injected i.p., followed by urine collection 1.5 h later (approximate time of BHB peak levels) (19). The 5 mM/kg dose shows a BHB level that resembles the urine BHB profile (approximated in this figure with dashed lines) from KD-treated mice (n = 22 total). (B) A single 5 mM/kg BHB injection (9 AM) of BHB per day (for 2 wk) yielded comparable peak levels as mice on a KD but less total daily exposure, as seen from a urine time course (12 h; n = 4–5 per group). Also shown is the saline vehicle group. (C) Kmt2d<sup>+/βGeo</sup> mice injected with a once-daily dose of 5 mM/kg BHB (for 2 wk) show a significant increase in the EdU<sup>+</sup> cell numbers in the GCL of the DG of the mice compared with Kmt2d<sup>+/βGeo</sup> mice injected with saline vehicle. However, this rescue did not show the same magnitude of rescue compared with the EdU<sup>+</sup> cell numbers from KD treatment (n = 5–12). (D) Mice implanted with a 2-wk BHB pump that provided 2.5 mg/mL BHB at a rate of 0.25 μL/h showed a significant (P < 0.05) increase in BHB measured from urine (n = 10–12 per group). However, although the pump provided a constant stream of BHB, the urine BHB did not reach comparable levels to what was seen in mice on a KD (1–2 mM BHB). (E) The combination of osmotic pumps and three injections of 5 mM/kg BHB at 9 AM, 1 AM, and 5 AM showed a more similar BHB profile to KD-treated mice when treated for 2 wk (n = 4–5 per group). (F) When treated with this higher daily dose of BHB for 2 wk, we saw a more pronounced rescue of EdU<sup>+</sup> cell numbers in the DG GCL in Kmt2d<sup>+/βGeo</sup> mice, which more closely mirrors the rescue seen after KD treatment. (G and H) We further confirmed the neurogenesis rescue at both low and high doses of BHB (treated for 2 wk) by looking at the fraction of DCX<sup>+</sup> cells in the DG GCL and found that this measure showed similar neurogenesis rescues compared with EdU analysis (n = 7–10 per group). *P < 0.05; **P < 0.01; †P < 0.001. N.S., not significant, P > 0.05.
Fig. S10. Control experiments for behavioral testing. (A) The latencies to find the hidden platform during the 5 d of training showed a significant interaction ($P < 0.05$) between genotypes, but no significant effect from treatment ($P = 0.204$), as examined by a repeated-measures ANOVA. (B) The latencies to find the platform during the flag training did not show a significant interaction for either genotype or treatment ($P = 0.142$), as examined by a repeated-measures ANOVA ($n = 19–32$ per group). (C) Kmt2d+/βGeo mice did not show a significant difference from Kmt2d+/+ mice on the regular diet, and did not demonstrate decreased activity on the KD in an open-field test, whereas Kmt2d++ mice did show an increase ($P < 0.05$) in activity compared with Kmt2d+/βGeo mice only when both were treated with the KD. There were no differences for grip strength for either genotype or treatment ($n = 5–15$ per group). (D) Kmt2d+/βGeo mice did not show a significant difference from Kmt2d+/+ mice on the regular diet, and did not have decreased activity on the KD, as measured by an open field test, whereas Kmt2d++ mice did show an increase ($P < 0.001$) in activity compared with Kmt2d+/βGeo mice only when both were treated with the KD ($n = 13–26$ per group). The increased activity seen in wild-type animals on KD has been previously described (50). *$P < 0.05$; ††$P < 0.001$. 

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