Supporting Information

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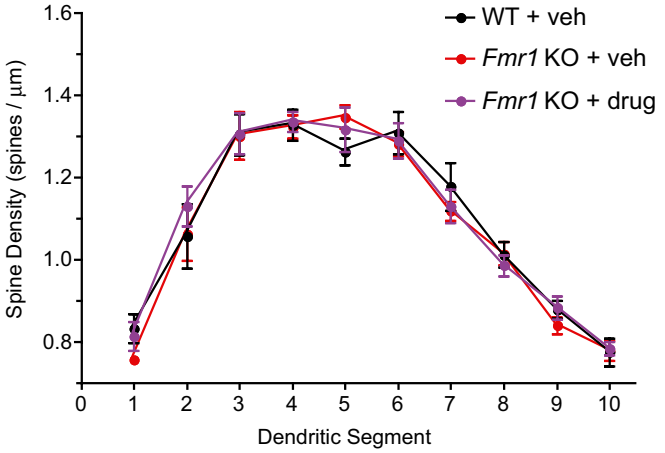

Fig. S1. Basal spine density was not abnormal in fragile X mental retardation 1 (*Fmr1*) KO mice. Basal dendritic segments of layer II/III pyramidal neurons from WT + vehicle (veh), *Fmr1* KO + vehicle, and *Fmr1* KO + drug, where FRAX486 was administered via a single s.c. injection 8 h before tissue collection. Dendrites were divided into 10 segments of 10 µm each based on distance from the soma (proximal to distal, left to right). Statistical analysis showed no difference between genotype and treatment groups. Values are mean ± SEM (WT + vehicle, $n = 40$ neurons, four mice; *Fmr1* KO + vehicle, $n = 60$ neurons, six mice; *Fmr1* KO + drug, $n = 60$ neurons, six mice). One-way ANOVA comparing all groups for each segment: $P > 0.05$.

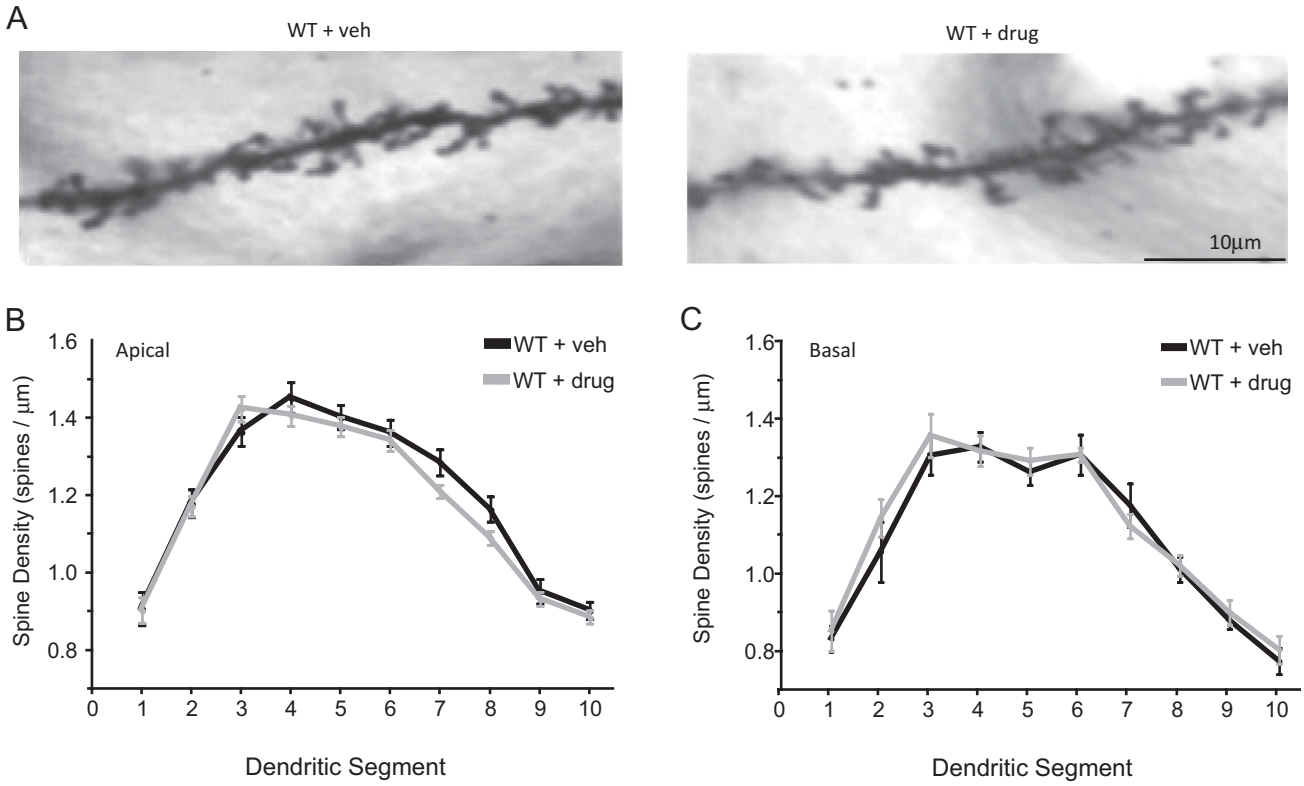

Fig. S2. FRAX486 had no effect on spine density in control mice. (*A*) Representative apical dendritic segments of layer II/III pyramidal neurons from WT mice treated with vehicle (veh) control or FRAX486, where drug was administered daily for 21 d. (*B* and *C*) Dendrites were divided into 10 segments of 10 µm each based on distance from the soma (proximal to distal, left to right). Statistical analysis showed no difference in spine density in any of the 10 apical dendritic segments (*B*). Statistical analysis showed no difference in spine density in any of the 10 basal dendritic segments (*C*). Values are mean ± SEM [WT + vehicle (1 d), $n = 40$ neurons, four mice; WT + drug (21 d), $n = 50$ neurons, five mice].

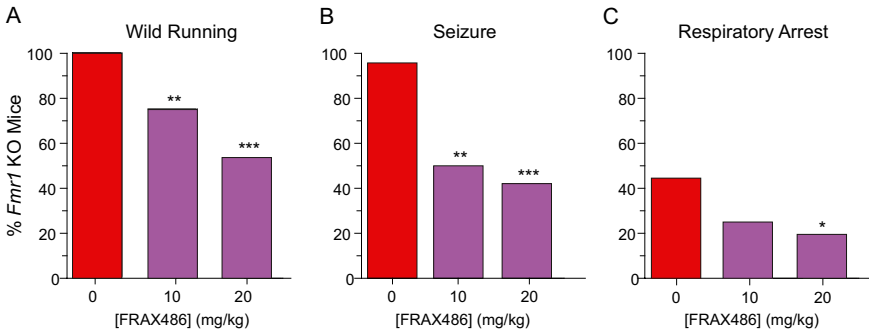

Fig. S3. Daily administration of FRAX486 reduced audiogenic seizures susceptibility. Five daily injections of 0, 10, or 20 mg/kg FRAX486 were administered, the last of which was given to *Fmr1* KO mice 8 h before assay. Incidences of wild running (*A*) and seizure (*B*) were reduced by both doses. Incidences of respiratory arrest and death (*C*) were reduced by 20 mg/kg but not 10 mg/kg. Values are mean ± SEM (*Fmr1* KO + vehicle, $n = 27$; *Fmr1* KO + 10 mg/kg, $n = 4$ mice; *Fmr1* KO + 20 mg/kg, $n = 26$ mice). The effect of the lower dose on survival did not reach statistical significance, in part because it was only administered to only a few mice ($P = 0.231$). χ^2 test was used to compare incidence in drug treated mice to that of vehicle control: $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

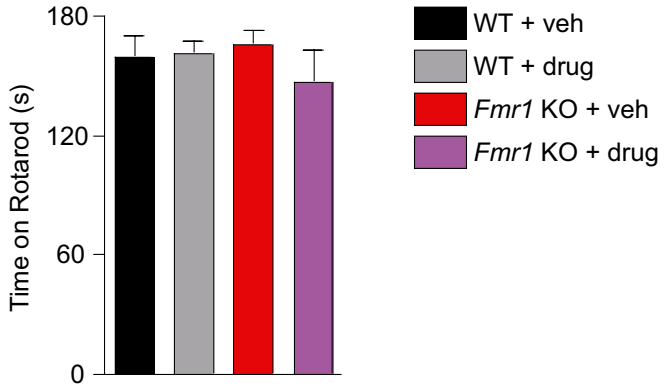

Fig. S4. Treatment with FRAX486 did not impair motor coordination. The rotarod performance test was used to assay balance and motor coordination in mice treated with 20 mg/kg FRAX486. WT and *Fmr1* KO mice were administered a single dose of FRAX486 or vehicle, and 4 h, 4.5 h, and 5.25 h later, the mice participated in three trials on the accelerating rotarod. Rodents naturally try to stay on the rotating cylinder. Latency to fall off was measured in each of three trials. Each trial lasted a maximum of 180 s, and the average for each animal used for the statistics. Values are mean ± SEM (WT + vehicle, $n = 7$; WT + drug, $n = 11$; *Fmr1* KO + vehicle, $n = 12$; *Fmr1* KO + drug, $n = 9$). Two-way ANOVA: interaction, $P = 0.3298$; genotype, $P = 0.7437$; treatment, $P = 0.4290$; Bonferroni post hoc tests show no effect of genotype or drug treatment.

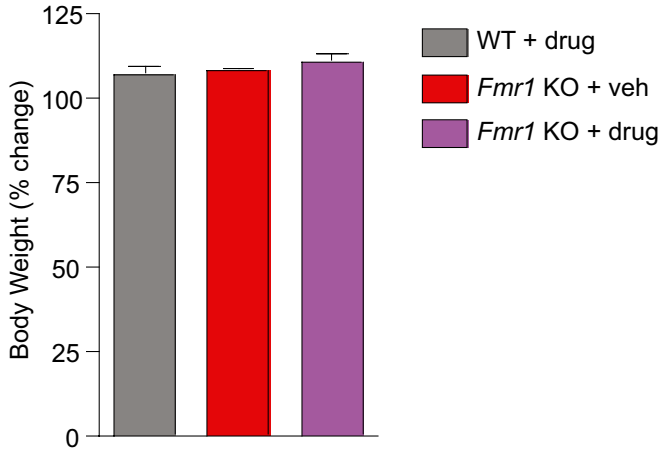

Fig. S5. Treatment with FRAX486 did not affect body weight. Daily administration of 20 mg/kg FRAX486 for 21 d did not impact normal increases in body weight, one indication of good health. Mice were 8 wk old at the start of drug treatment. Values are mean ± SEM (*Fmr1* KO + vehicle, $n = 5$; *Fmr1* KO + drug, $n = 6$; WT + drug, $n = 5$).

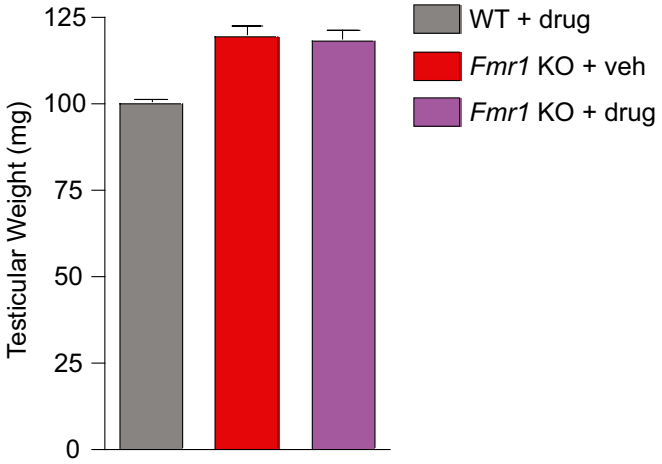

Fig. S6. Macroorchidism in *Fmr1* KO mice was not rescued by FRAX486. Mice were administered daily s.c. injections of 20 mg/kg FRAX486 or vehicle alone for 21 d. One (in the case of WT) or both (in the case of KO) testes were collected and weighed. Consistent with the literature of human and murine males without *Fmr1* KO, *Fmr1* KO + vehicle had enlarged testes compared with WT + drug. Treatment of *Fmr1* KO with FRAX486 did not rescue this abnormality. Values are mean ± SEM (*Fmr1* KO + vehicle, 119.7 ± 2.6, $n = 12$ testes from six mice; *Fmr1* KO + drug, 118.3 ± 3.3, $n = 11$ testes from six mice; WT + drug, 100.2 ± 0.88, $n = 6$ testes from six mice). Two-way ANOVA: interaction, $P = 0.8197$; genotype, $P < 0.0001$; treatment, $P = 0.8197$; Bonferroni post hoc tests show significant effect of genotype but not drug treatment.