Supplementary Materials for:

**Title:** The maternal X chromosome impairs cognition and accelerates brain aging through epigenetic modulation in female mice

**Authors:** Samira Abdulai-Saiku¹, Shweta Gupta¹, Dan Wang¹, Arturo J. Moreno¹, Yu Huang², Deepak Srivastava², Barbara Panning³,⁴, Dena B. Dubal¹,⁴,⁵*
Supplementary Figure 1. Parent-of-X mosaicism compared with paternal X silencing in maternal X skew in the hippocampus of a female mouse.

a, Left, diagram of parent-of-X composition of cells in Xm+Xp mice. Right, Representative image of immunohistochemistry showing cells that express Xp (tagged with GFP) and all NeuN+ cells (RFP) in the dentate gyrus region of the hippocampus in a female mouse. Scale Bar=60\(\mu\)m.

b, Left, diagram of cellular composition of cells in which the paternal X is silenced and skewed toward Xm (due to Xist deletion on Xm). Right, Representative image of immunohistochemistry showing maternal X skew, via paternal silencing of X (Xp, tagged with GFP) cells in the dentate gyrus region of the female hippocampus. All neurons are tagged with NeuN (red). Scale Bar=60\(\mu\)m.
Supplementary Figure 2. Additional measures in the body including cardiac, % fat, and V02 and VCO2 did not differ between experimental groups.

a. Cardiac echo measurements showed equivalent measures between Xm+Xp and Xm mice in fractional shortening (age=14-17 months, n=10-18 per experimental group). Unpaired two-tailed t-test, \( P > 0.1 \).
b. Body fat percentage did not differ between Xm+Xp and Xm mice (age=14-17 months, n=9-17 per experimental group). Unpaired two-tailed t-test, $P>0.05$.

c, d. The CLAMS metabolic cages were used to measure different metabolic parameters including oxygen consumption (VO₂), and carbon dioxide production (VCO₂) (age=14-17 months, n=10-18 per experimental group).

c, VO₂ consumption did not differ between the groups. Two-way ANOVA: genotype $P>0.05$

d, CO₂ consumption did not differ between the groups. Two-way ANOVA: genotype $P>0.05$
Supplementary Figure 3. Swim speed and latency to find visible platform did not differ between groups.

a, Swim speed did not differ between the experimental groups, measured during the visible platform trials (age=4-8 months, n=11-19 per experimental group). Unpaired two-tailed t-test, $P>0.05$.

b, Latency to find a visible platform did not differ between the experimental groups. (age=4-8 months, n=11-19 per experimental group). Mixed model ANOVA: genotype $P>0.05$. 