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**Supplemental Information**

**RNAi-Based Gene Therapy Rescues  
Developmental and Epileptic Encephalopathy  
in a Genetic Mouse Model**

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Figure S1. *miDnm1a* improves survival in a dose dependent manner (C57BL/6J strain background pilot experiment; related to Figure 2A-C).

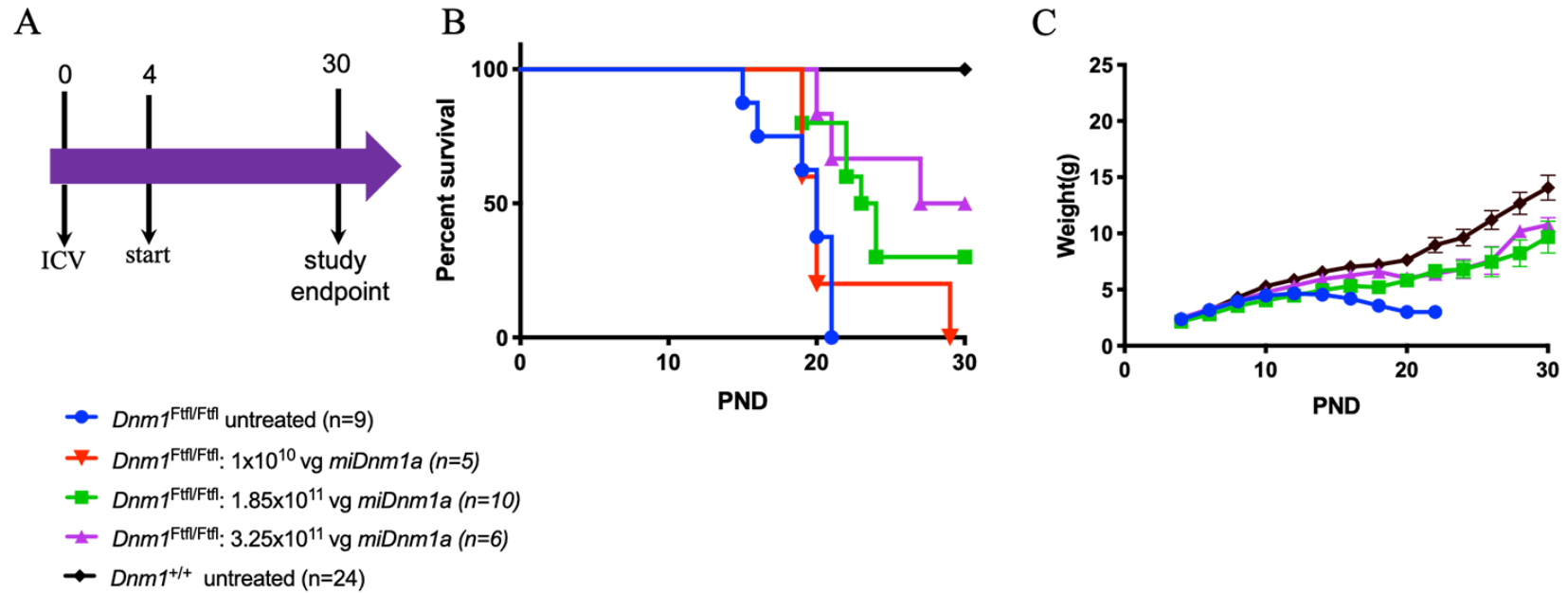
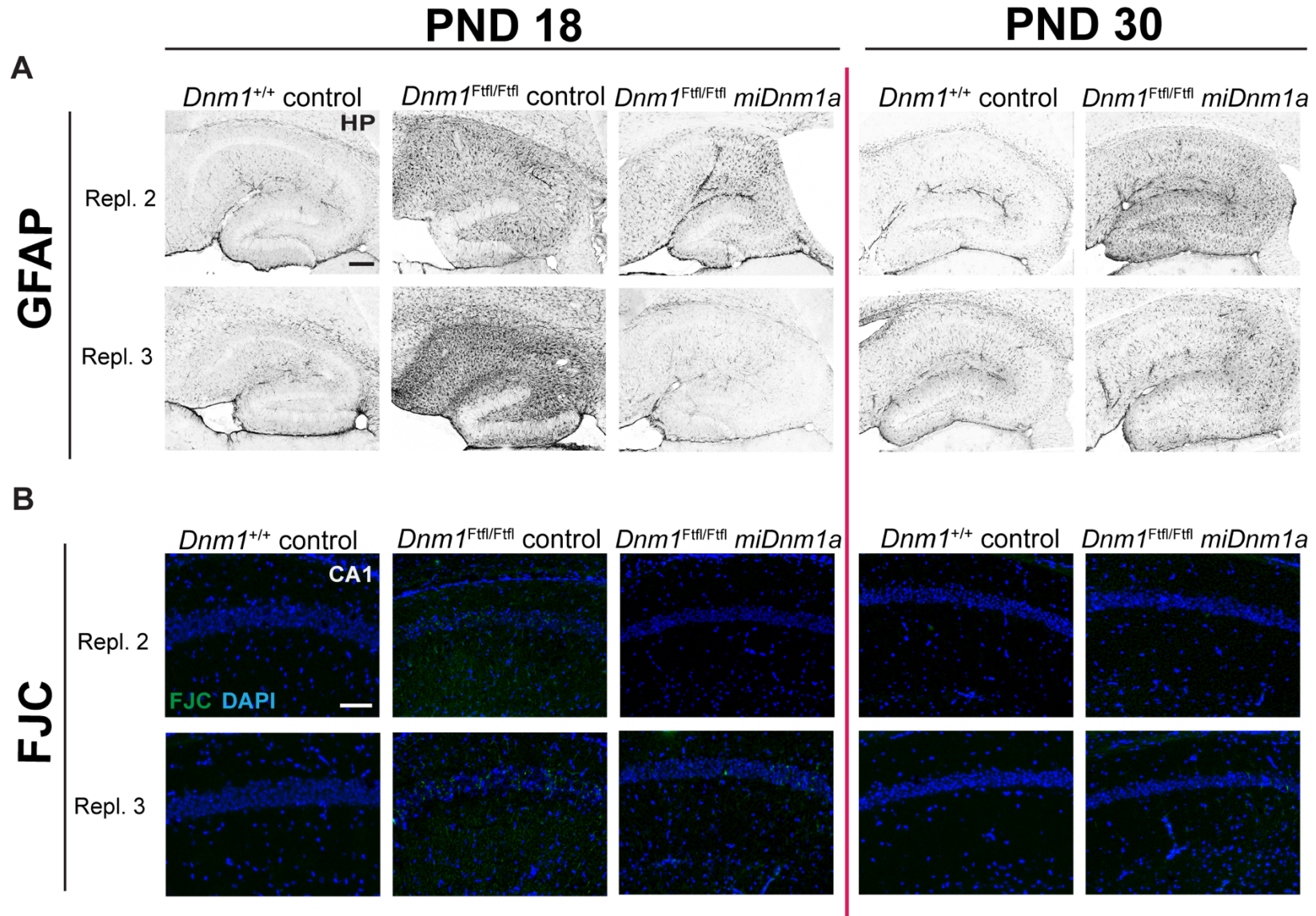


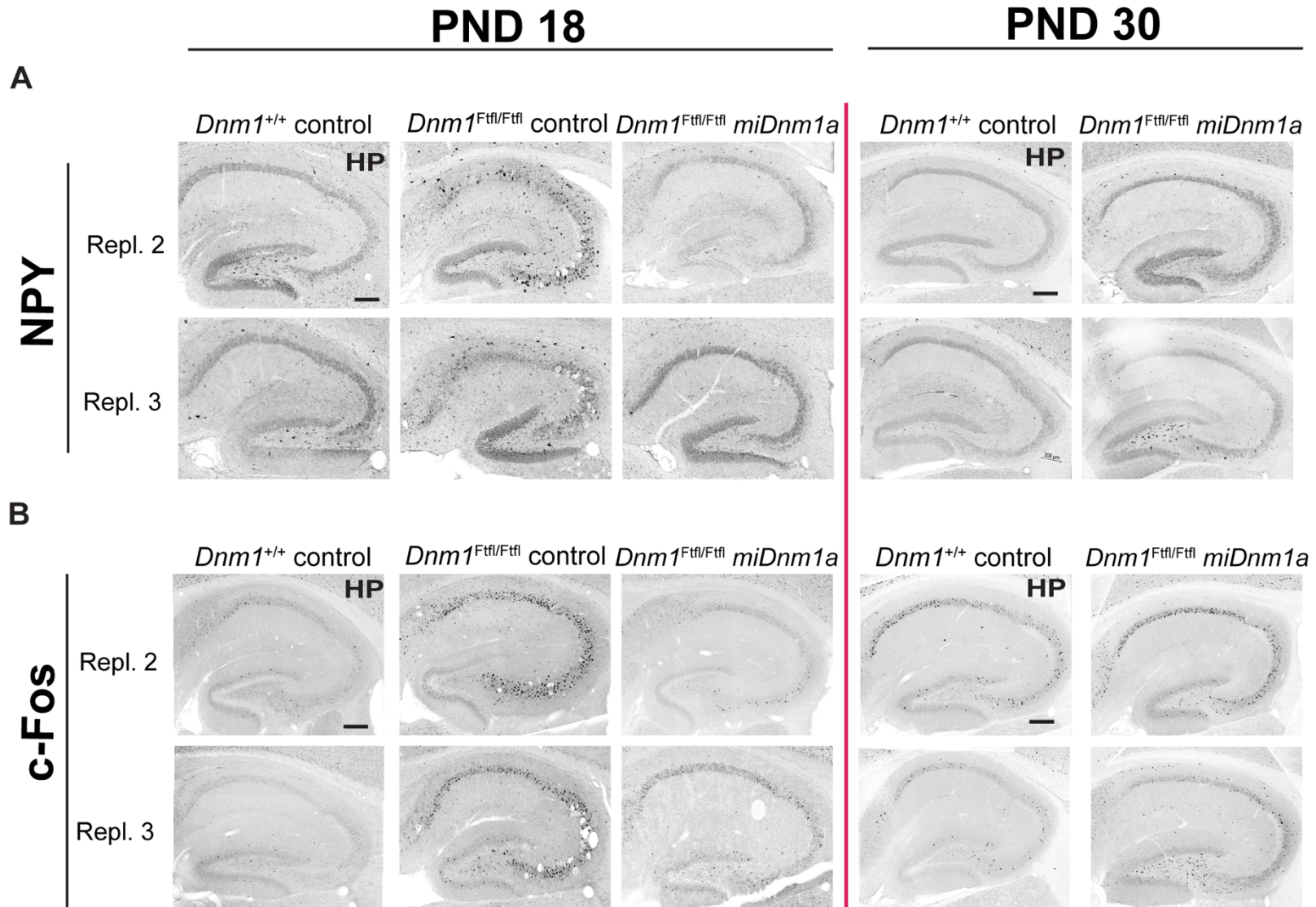
Figure S1. *miDnm1a* improves survival in a dose dependent manner (C57BL/6J strain background pilot experiment; related to Figure 2A-C). **A**) Experimental plan for pilot studies. Three *miDnm1a* doses were administered to neonates and examined for survival and growth. **B**) The survival curve for treated *Dnm1*<sup>Ftfl/Ftfl</sup> mice is significantly different from untreated *Dnm1*<sup>Ftfl/Ftfl</sup> mice only for the 1.85x10<sup>11</sup> (n=10) and 3.2x10<sup>11</sup> (n=6) doses ( $p=0.0001$ ,  $p=0.01$ , respectively, log-rank Mantel-Cox test). **C**) For these doses, treated *Dnm1*<sup>Ftfl/Ftfl</sup> mice show growth improvement compared to untreated mice ( $p=0.003$ , repeated measures ANOVA).

Figure S2. PND 18 and PND 30 cellular phenotypes images (GFAP and FJC; 2 other representative replicate sets; related to Figure 4)



**Figure S2. PND 18 and PND 30 cellular phenotypes images (GFAP and FJC; 2 other representative replicate sets; related to Figure 4).** **A)** Control-injected *Dnm1<sup>Ftfl/Ftfl</sup>* mice show increased hippocampal GFAP which is absent from treated *Dnm1<sup>Ftfl/Ftfl</sup>* mice and *Dnm1<sup>+/+</sup>* controls at PND 18. At PND 30, treated *Dnm1<sup>Ftfl/Ftfl</sup>* mice show a significant increase in GFAP compared to *Dnm1<sup>+/+</sup>* controls. Scale bar correspond to 200  $\mu\text{m}$ . **B)** Control-injected *Dnm1<sup>Ftfl/Ftfl</sup>* mice show cell death in the hippocampal CA1. This phenotype is absent from treated *Dnm1<sup>Ftfl/Ftfl</sup>* mice and *Dnm1<sup>+/+</sup>* controls at PND 18. However, by PND 30 there is some noticeable cell death in the CA1 of treated mice compared to *Dnm1<sup>+/+</sup>* controls. Scale bar correspond to 100  $\mu\text{m}$ .

Figure S3. PND 18 and PND 30 cellular phenotypes images (NPY and c-Fos; 2 other representative replicate sets; Related to Figure 5).



**Figure S3. PND 18 and PND 30 cellular phenotypes images (NPY and c-Fos; 2 other representative replicate sets; Related to Figure 5)** **A)**  $Dnm1^{Ftfl/Ftfl}$  treated mice show a decrease of NPY+ cells in the hippocampus at PND 18 and PND 30 compared to control-injected  $Dnm1^{Ftfl/Ftfl}$  mice. By PND 30 treated mice start to show increased NPY compared to  $Dnm1^{+/+}$  controls in the CA3. **B)** Treated  $Dnm1^{Ftfl/Ftfl}$  mice show decrease in c-Fos compared to control-injected  $Dnm1^{Ftfl/Ftfl}$  mice at PND 18. By PND 30 treated mice show variable increase in hippocampal c-Fos expression compared to  $Dnm1^{+/+}$  mice. Scale bars correspond to 200  $\mu$ m

## Multimedia Files

Movie S1. Ataxia in eGFP injected *Dnm1<sup>Ftfl/Ftfl</sup>* mouse (left) and absent from *miDnm1a* treated *Dnm1<sup>Ftfl/Ftfl</sup>* mouse (right) at PND 15.

Related to Figure 3D.