



Highly Efficient Base Correction of Adult Dystrophic Mice Using iABE-NG

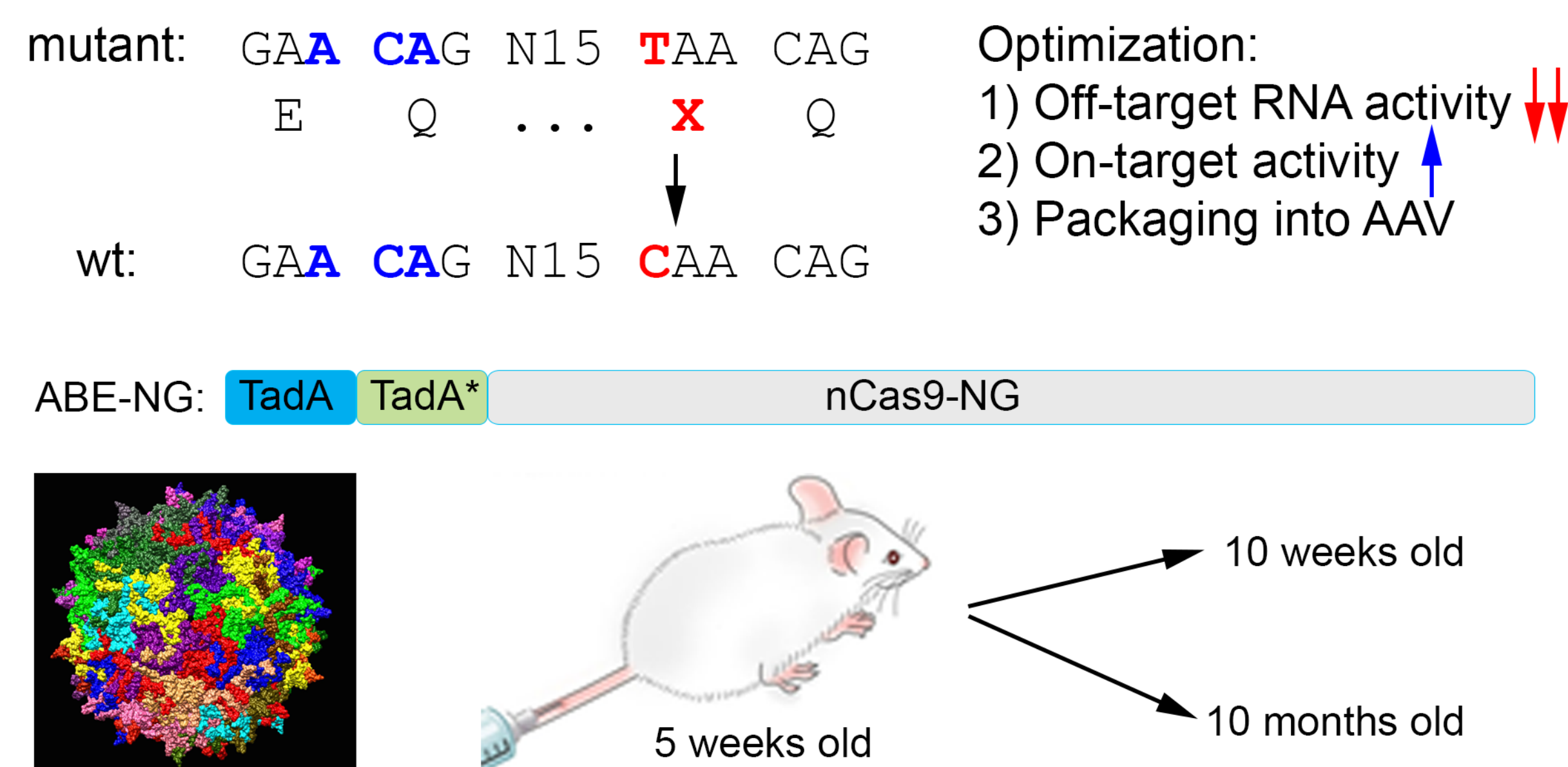
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Background & Innovation

Recent advances in base editing have created an exciting opportunity to precisely correct disease-causing mutations. However, the large size of base editors and their inherited off-target activities pose challenges for in vivo base editing. Moreover, the requirement of a protospacer adjacent motif (PAM) sequence within a suitable window near the mutation site further limits the targeting feasibility. In this work, we rationally improved the NG-targeting adenine base editor (iABE-NG) to overcome these challenges and demonstrated the exceptionally high efficiency to precisely edit the Duchenne muscular dystrophy (DMD) mutation in adult mice. Intramuscular and intravenous administration of AAV9-iABE-NG resulted in dystrophin restoration and functional improvement. At 10 months after AAV9-iABE-NG treatment, a near complete rescue of dystrophin was measured in dystrophic mouse hearts. The off-target activities remained low and no obvious toxicity was detected. This study highlights the promise of permanent base editing using iABE-NG for the treatment of monogenic diseases.

Overall Design



Contact Information

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Results

Figure 1. A split technology overcomes the packaging limit of AAV

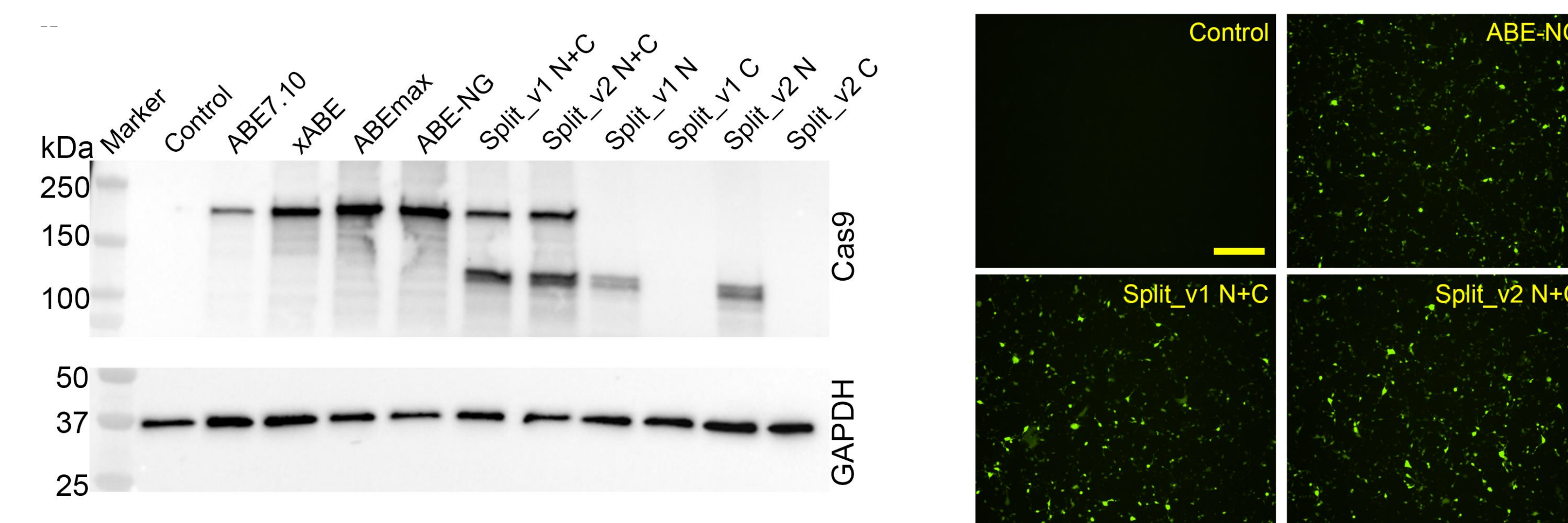


Figure 2. Elimination of off-target RNA editing activity

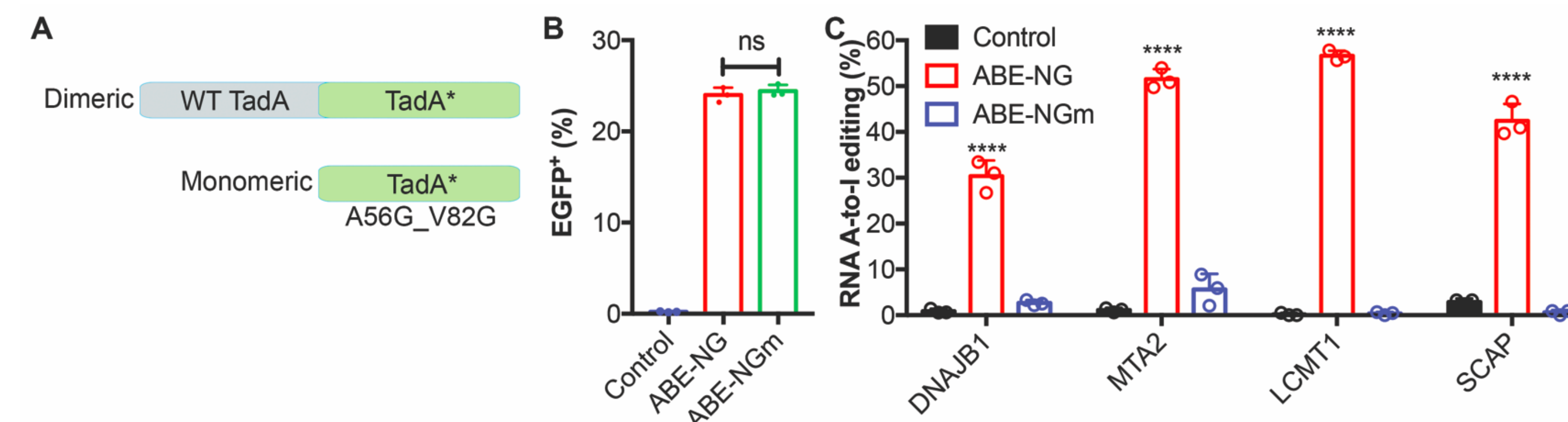


Figure 3. Rational design to improve the on-target DNA editing activity

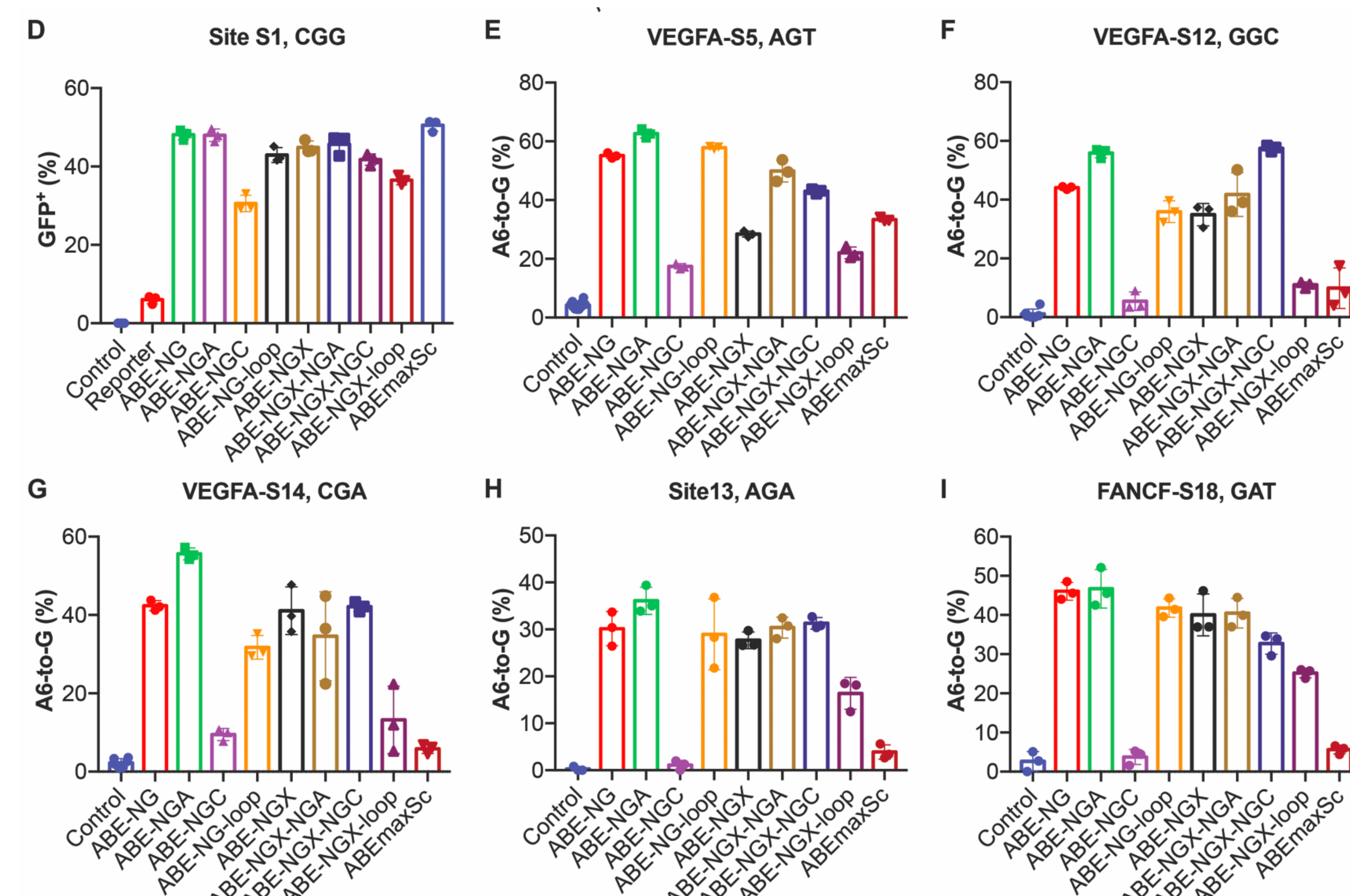
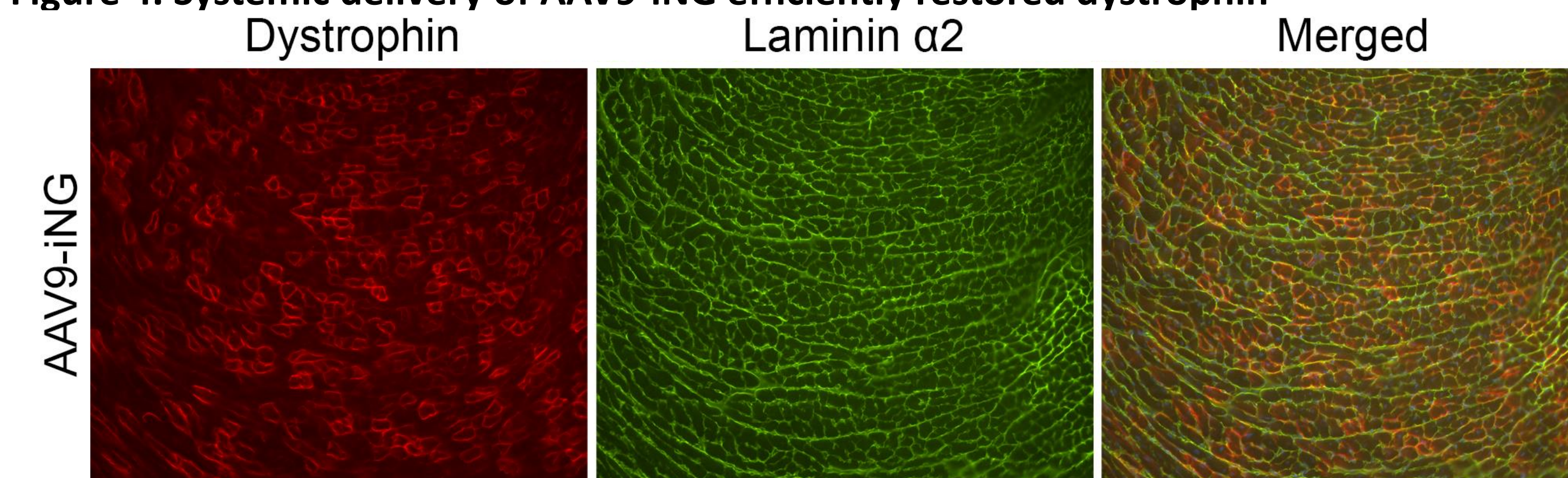


Figure 4. Systemic delivery of AAV9-iNG efficiently restored dystrophin



Results

Figure 4 (cont.). Systemic delivery of AAV9-iNG efficiently restored dystrophin

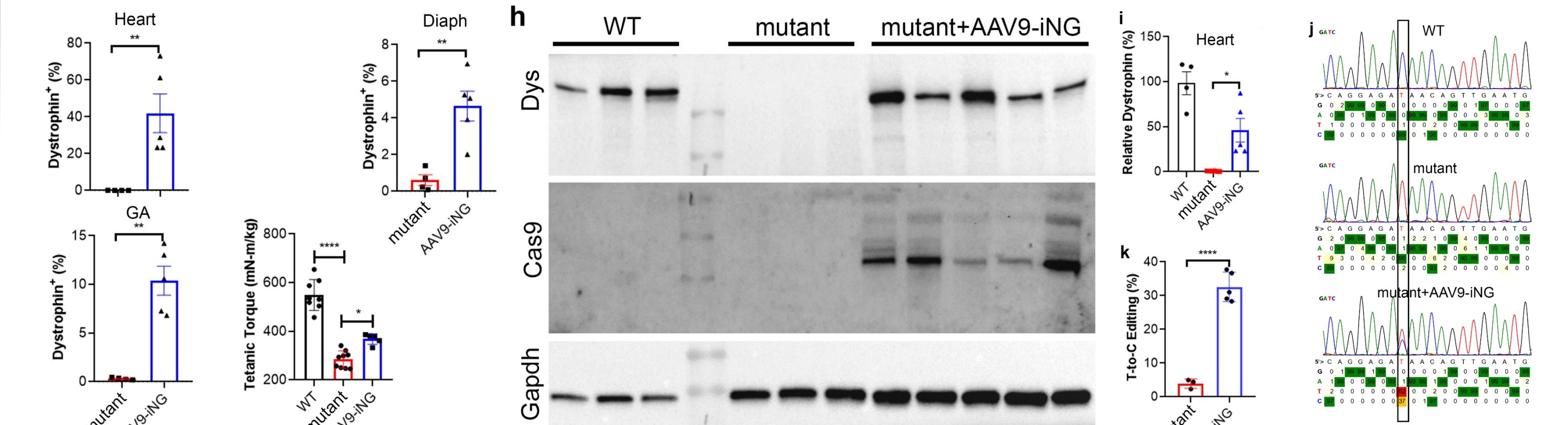
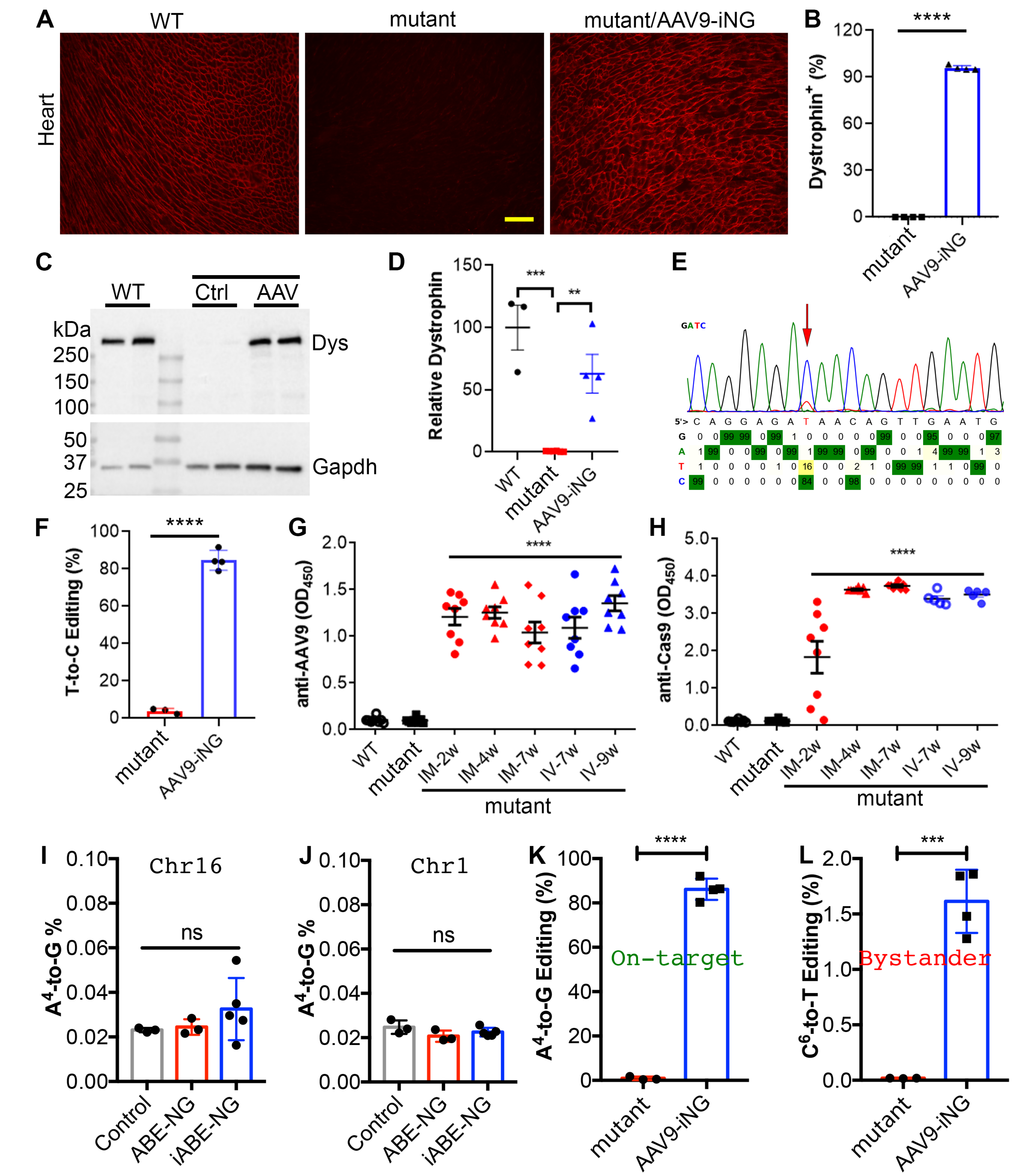


Figure 5 Long-term efficacy, host response and toxicity studies of AAV9-iNG therapy in dystrophic mice



Conclusions

Our results have shown that AAV9-mediated delivery of a rationally improved NG-targeting ABE allowed systemic restoration of dystrophin expression and functional improvement in *Dmd* mice. The study highlights the great promise of ABE-NG for permanent base correction of monogenic diseases.