

A Gene Therapy Approach for the Treatment of TNNI3 Cardiomyopathy

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Outline

- Background: Thin Filament Hypertrophic Cardiomyopathy
- TNNI3 Cardiomyopathy in Humans
- Mouse Model of TNNI3
- Swine Model of TNNI3
- AAV Gene Therapy



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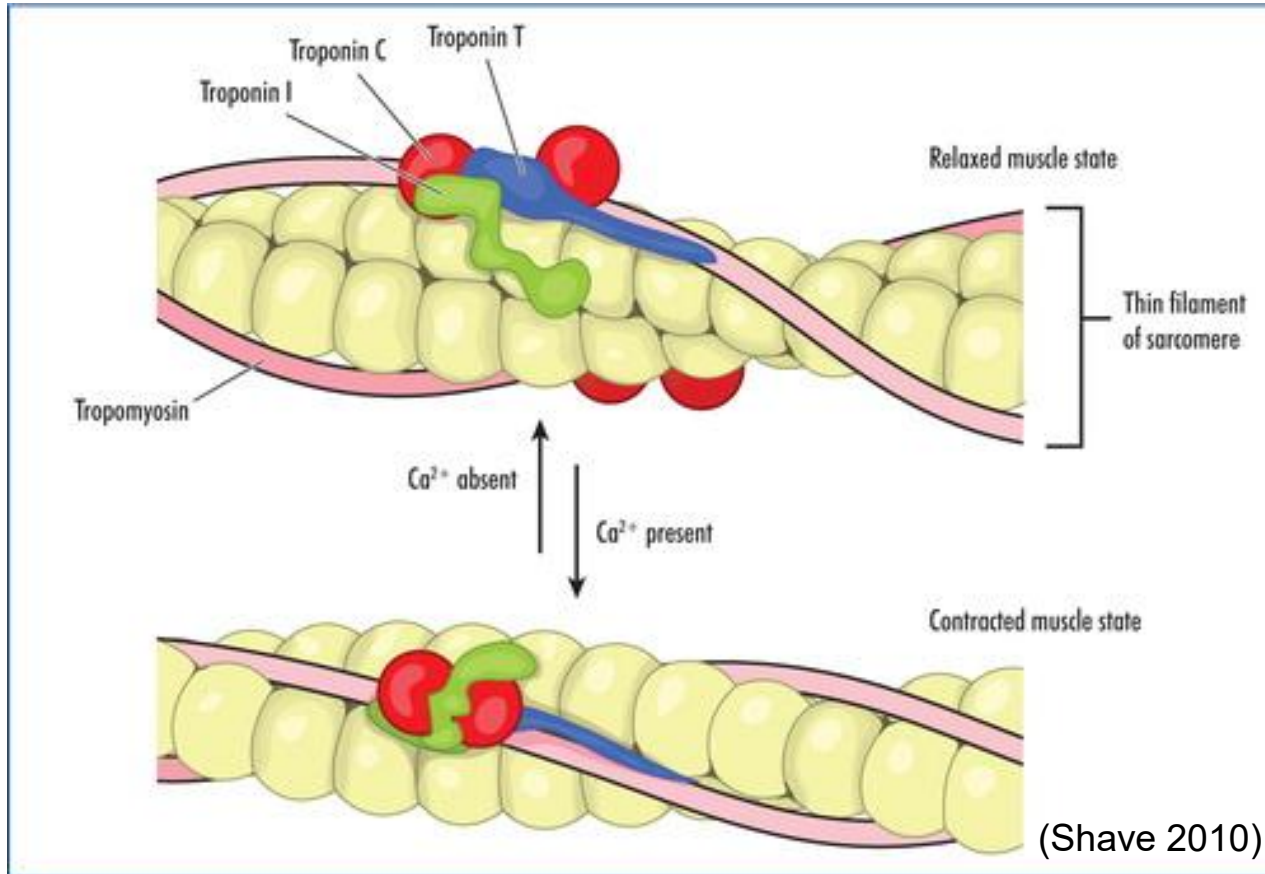


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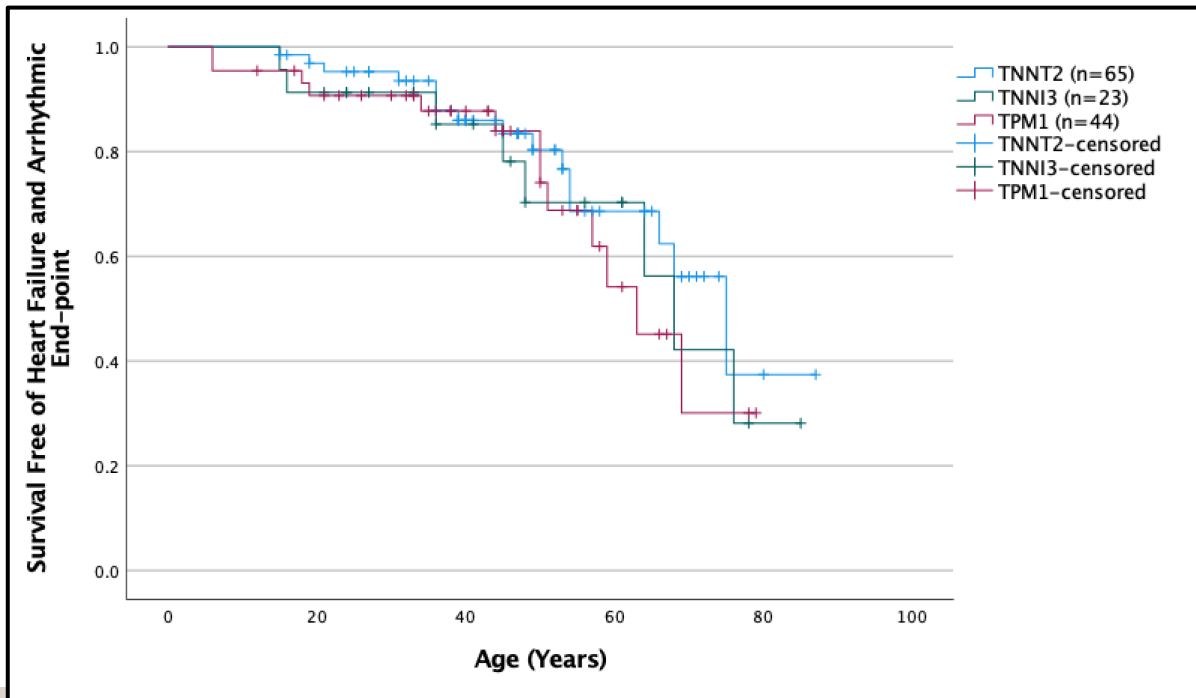
Background: Thin Filament Hypertrophic Cardiomyopathy (HCM)



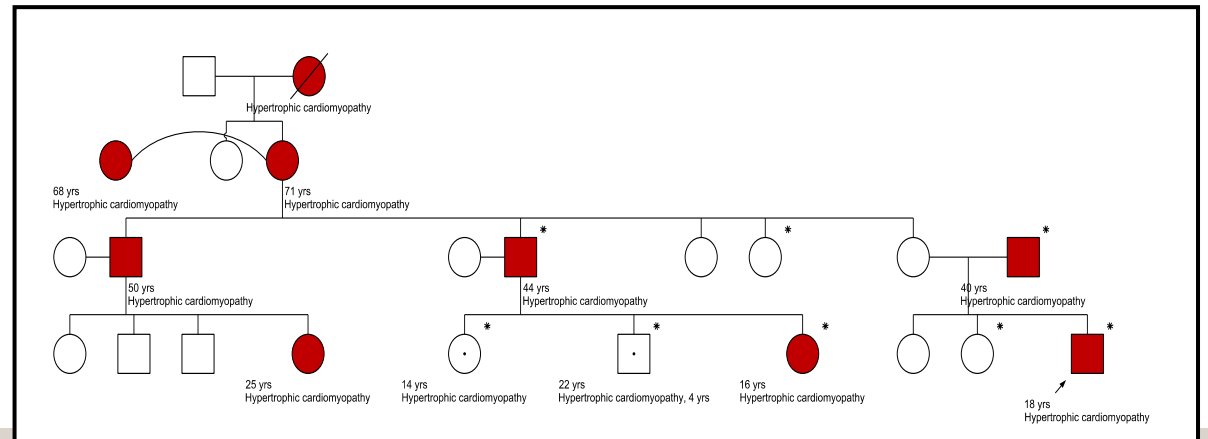
- Thin-filament mutations: ~20% of HCM cases
- High Mortality
- Cardiac Hypertrophy
- Impaired Relaxation

TNNI3 Cardiomyopathies are a Distinct and Lethal Form of HCM

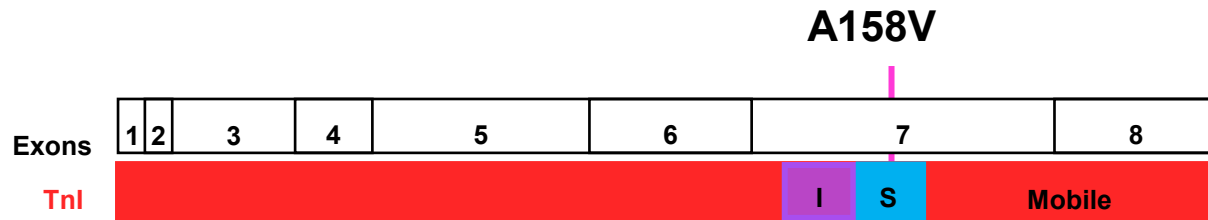
- TNNI3 mutations: 3-5% of HCM cases
- Characterized by increased mortality, hypertrophy, and diastolic dysfunction
- No current targeted therapies



Family with TNNI3-cardiomyopathy (A157V variant)



Mouse model of TNNI3 A158V shows impaired cardiac relaxation but no fibrosis and normal lifespan



CRISPR/Cas9

**Homozygous TNNI3
A158V knock-in**



100% 1-year survival

No hypertrophy

No systolic dysfunction

No fibrosis

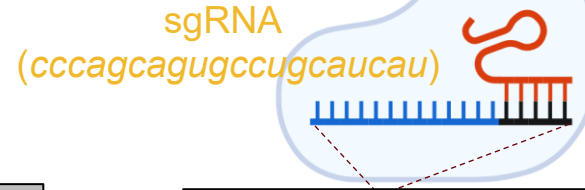


Objectives

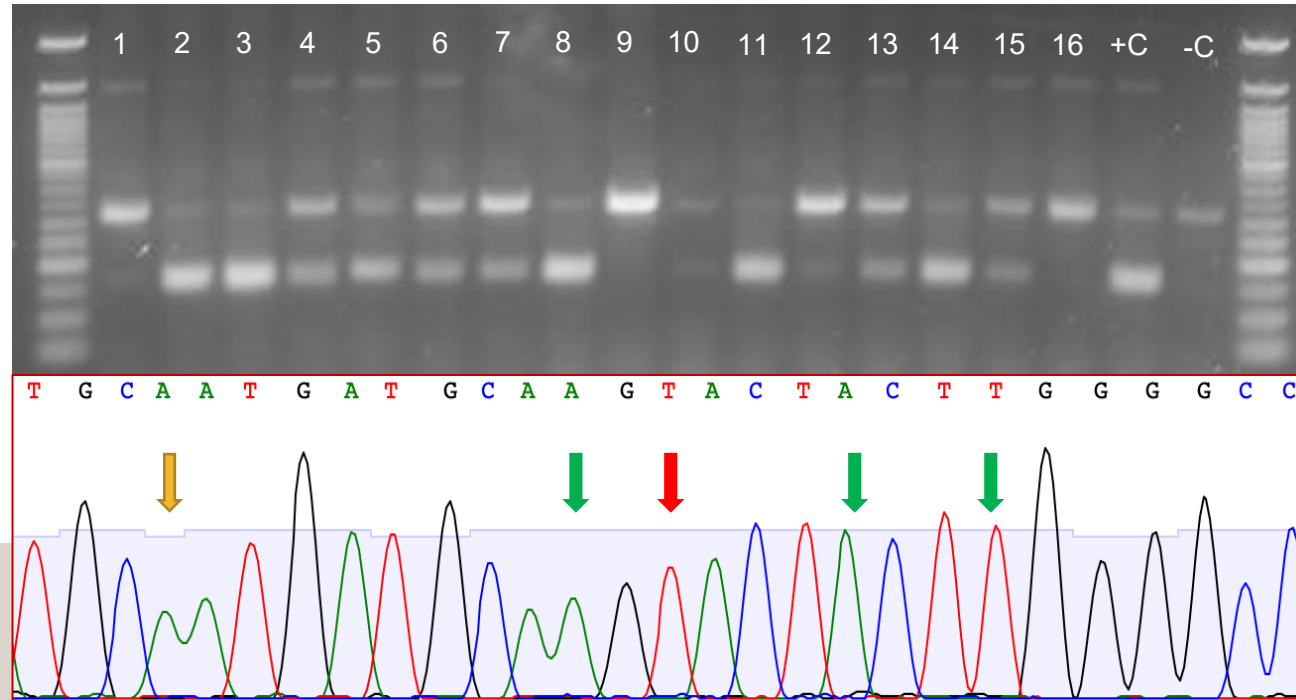
- Establish and characterize a large animal model of TNNI3 hypertrophic cardiomyopathy which recapitulates the human disease
- Test a novel TNNI3 Gene Therapy



Porcine TNNI3 A158V

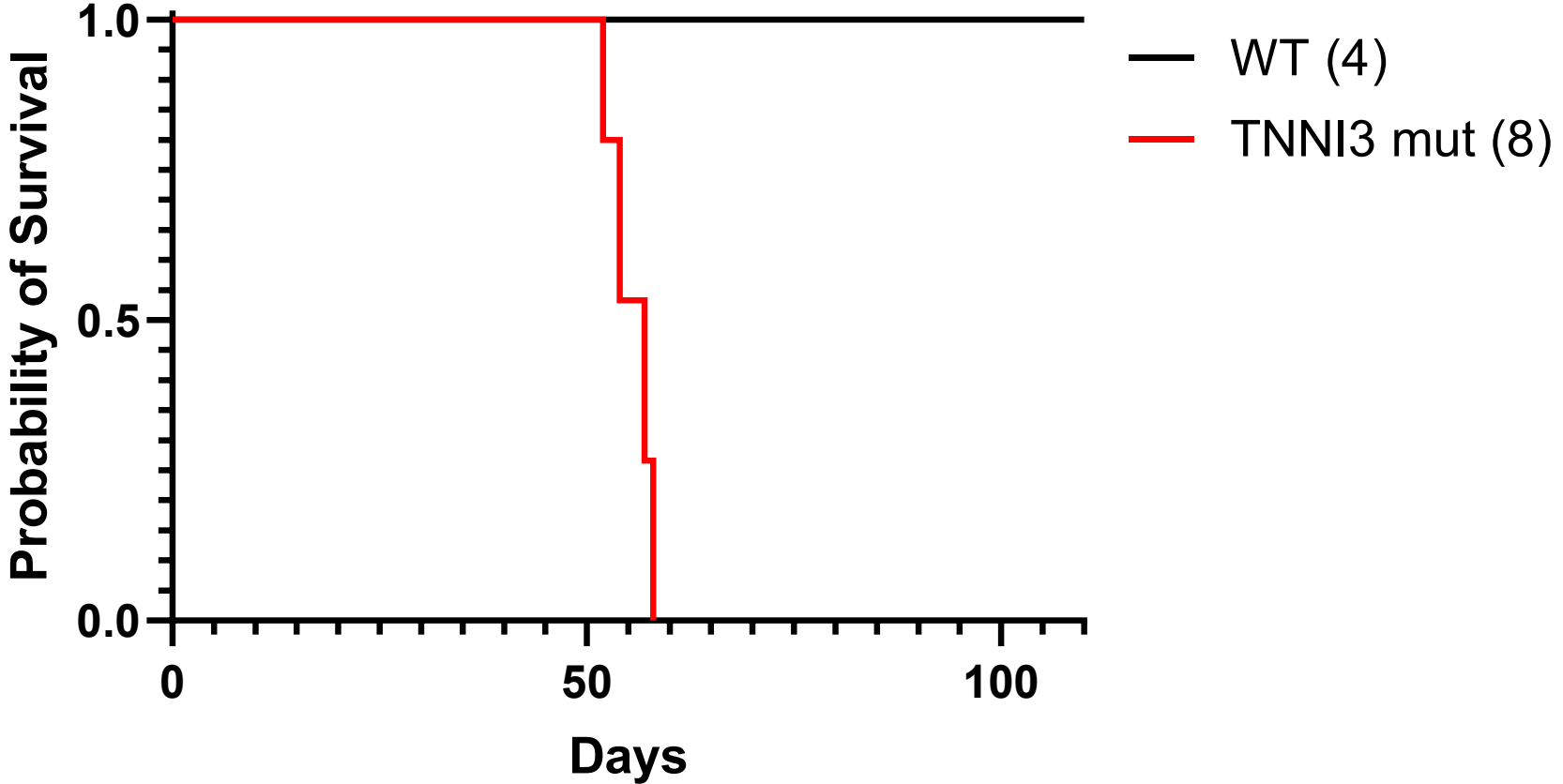


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RsaI



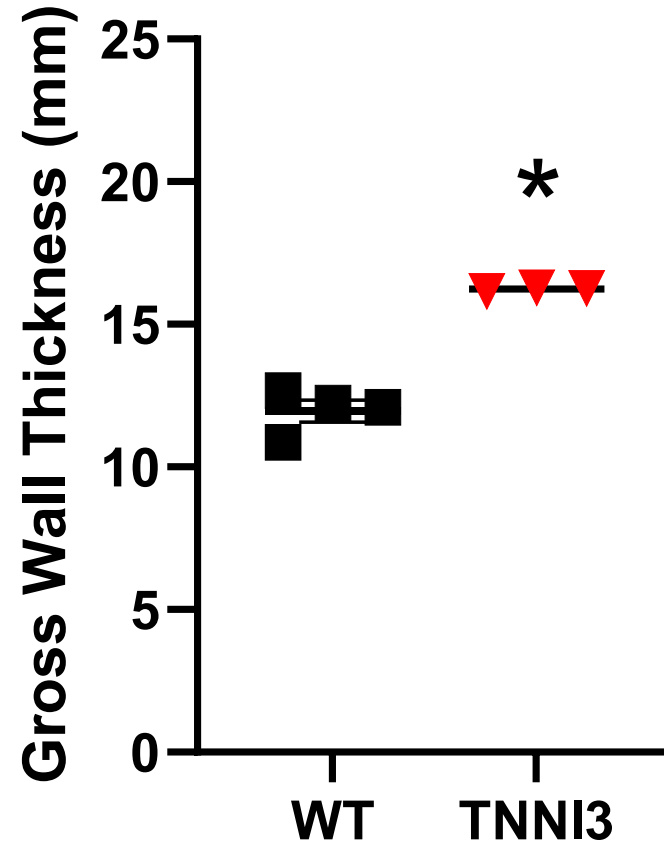
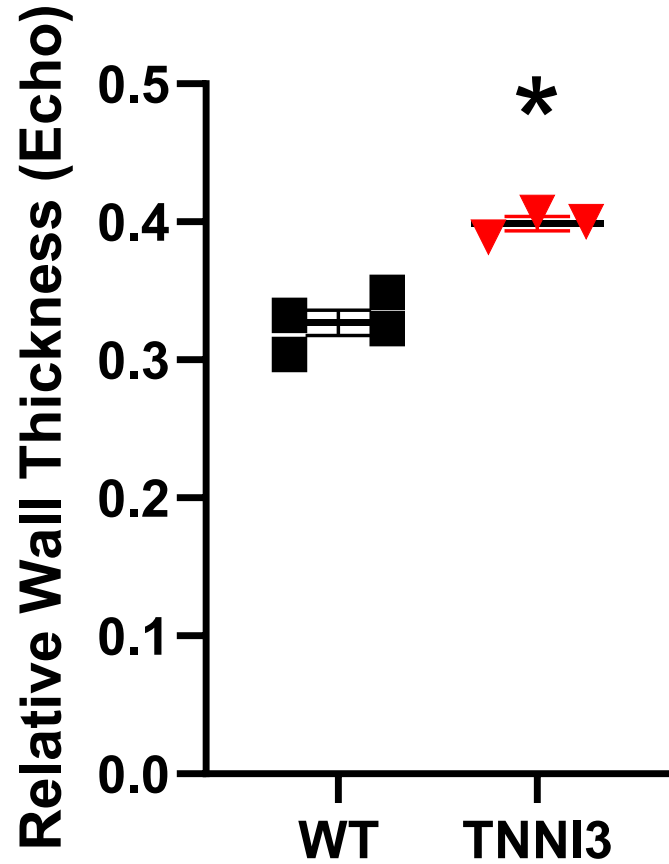
Bhanu Telugu

Survival Data



TNNI3 mutant pigs have increased mortality

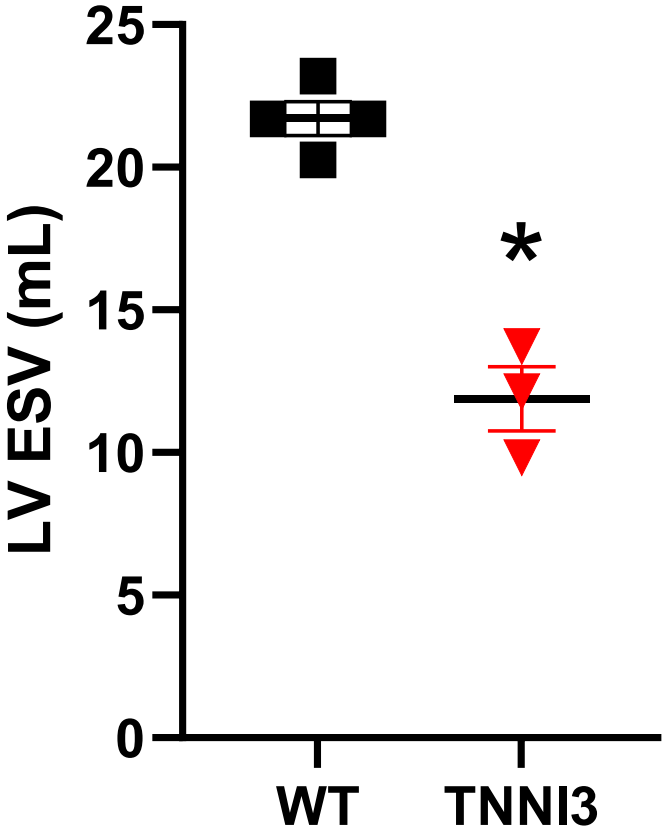
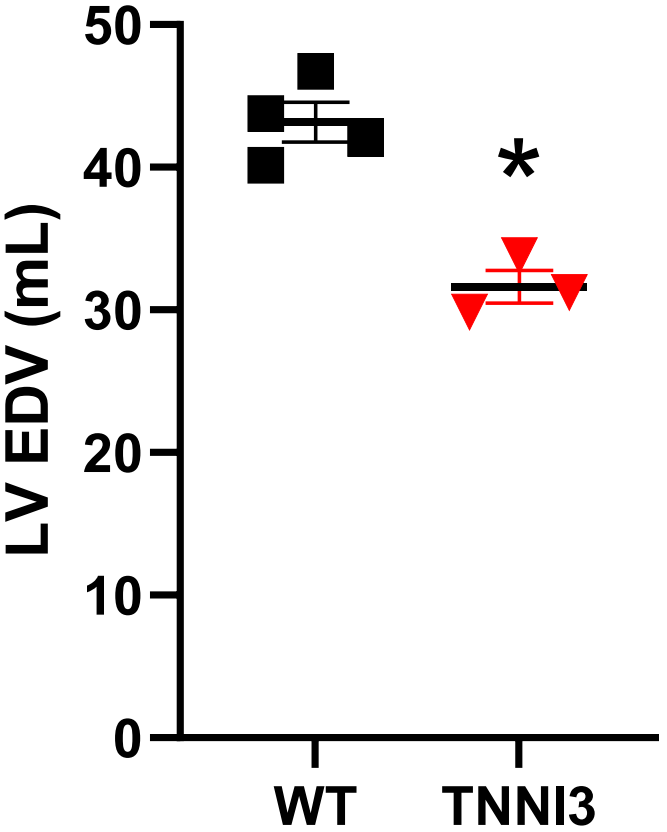
Wall Thickness



* p<0.05 vs. WT

TNNI3 mutant pigs have hypertrophy

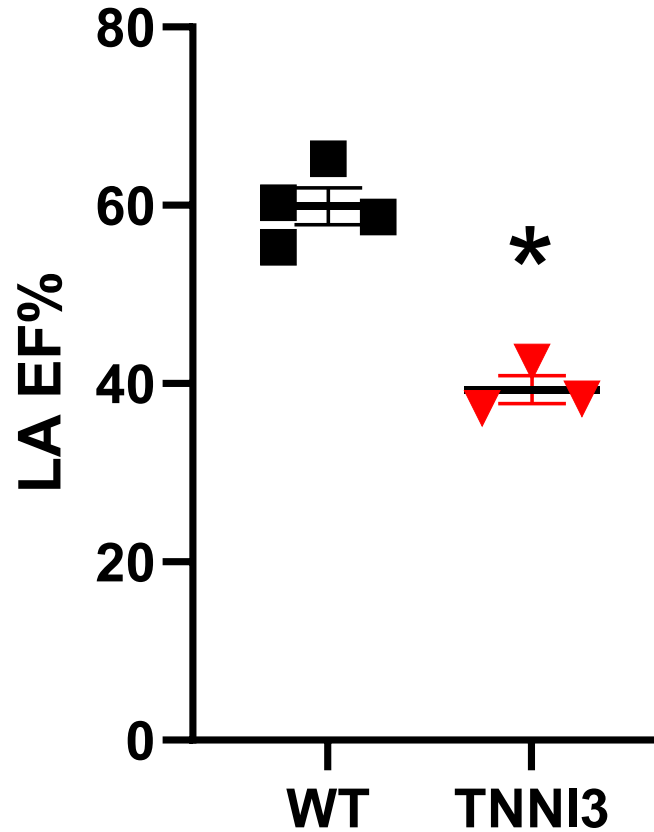
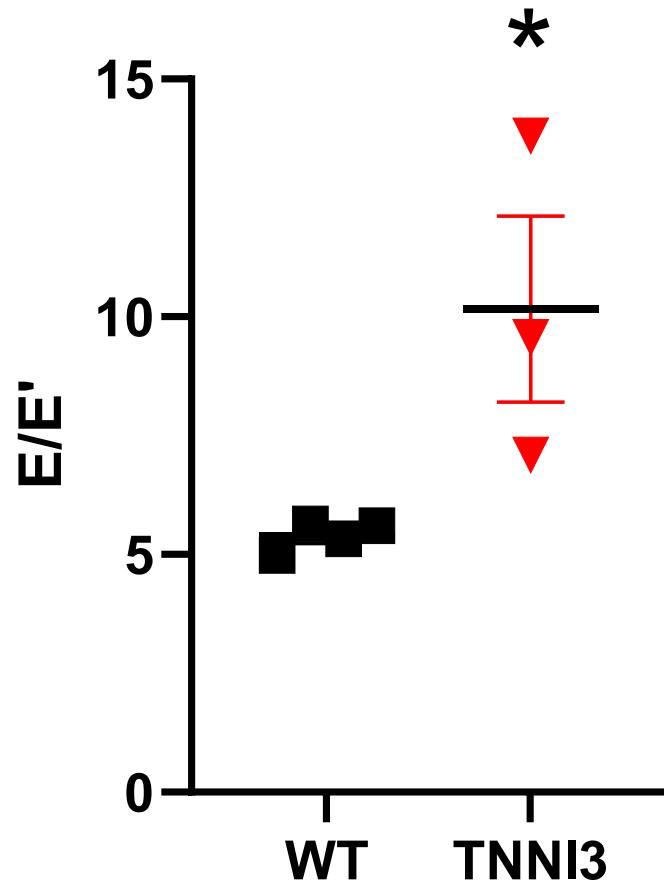
End Diastolic (EDV) and End Systolic Volume (ESV) Volumes



* p < 0.05 vs. WT

TNNI3 mutant pigs have reduced EDV and ESV

Left Ventricular and Atrial Function

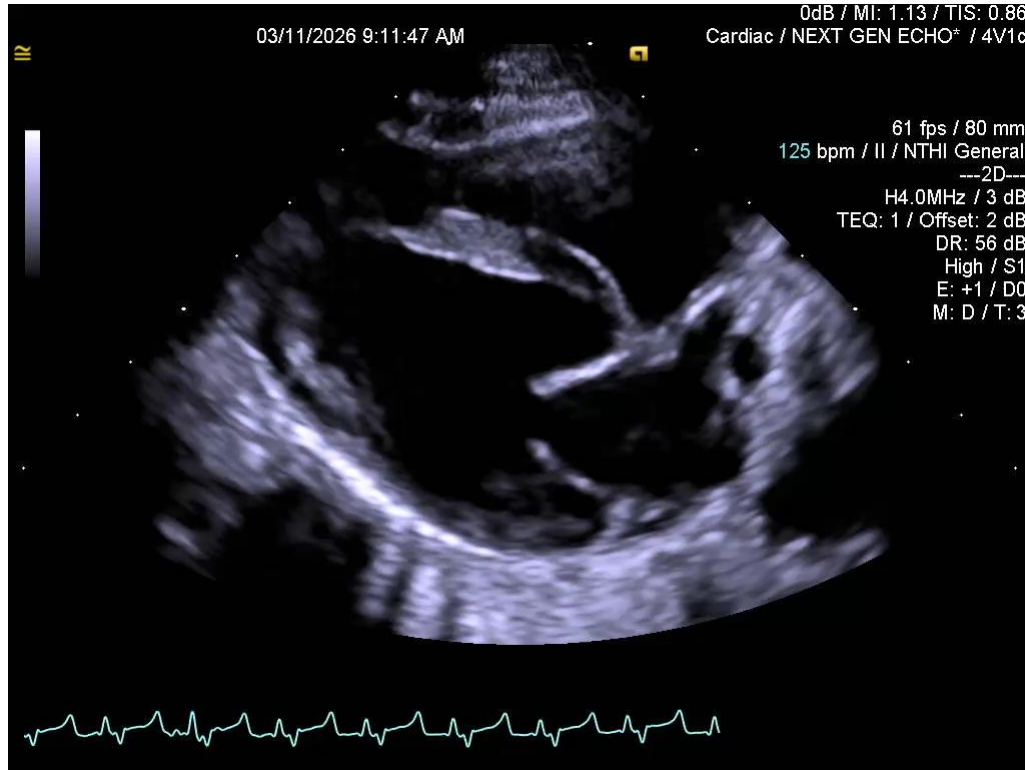


* p<0.05 vs. WT

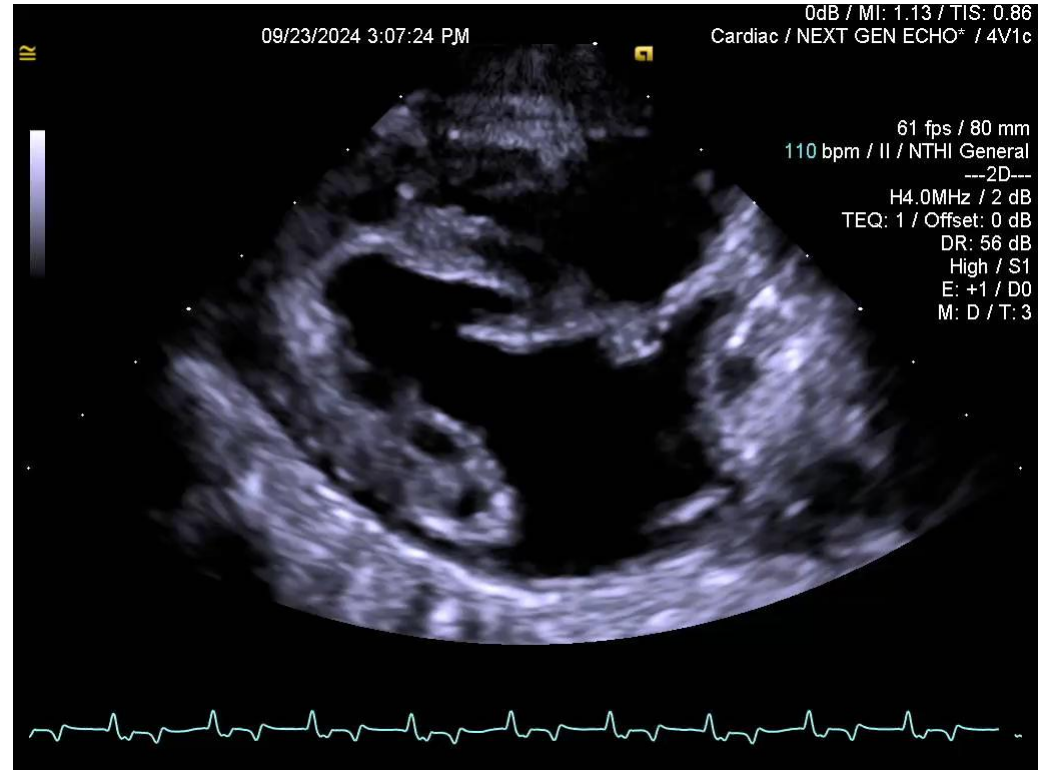
TNNI3 mutant pigs have LV and LA Dysfunction

2D Longitudinal Echocardiography

Wild-Type Control



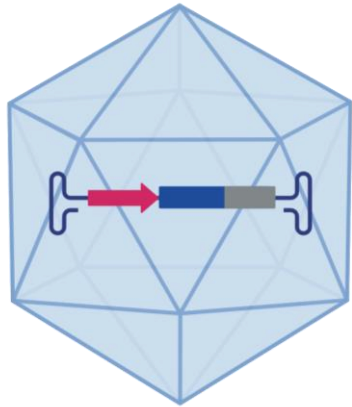
TNNI3 Mutant



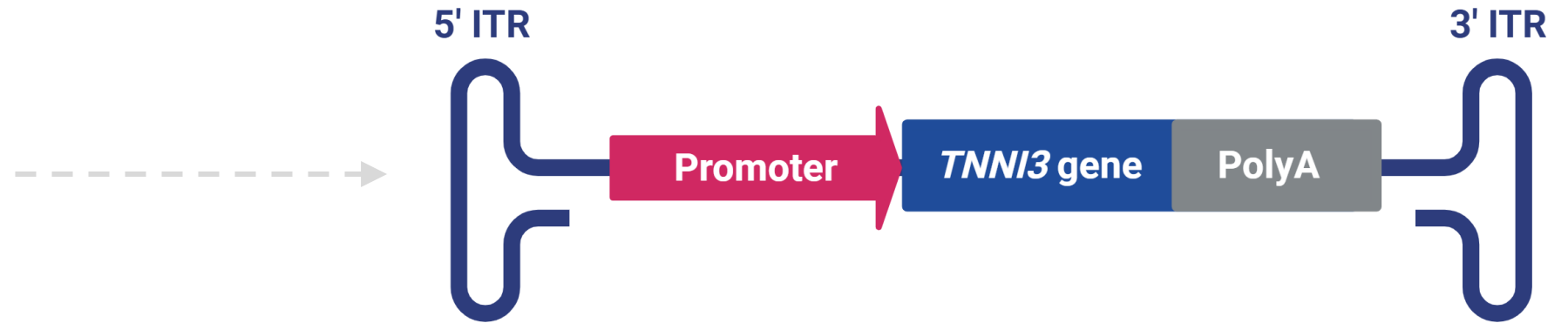
TNNI3 mutant pigs recapitulate human disease

TNNI3 Gene Therapy Construct: MyoAAV-hTNNI3

Previously described and published construct (Bushway et al., 2026)



Capsid: MyoAAV

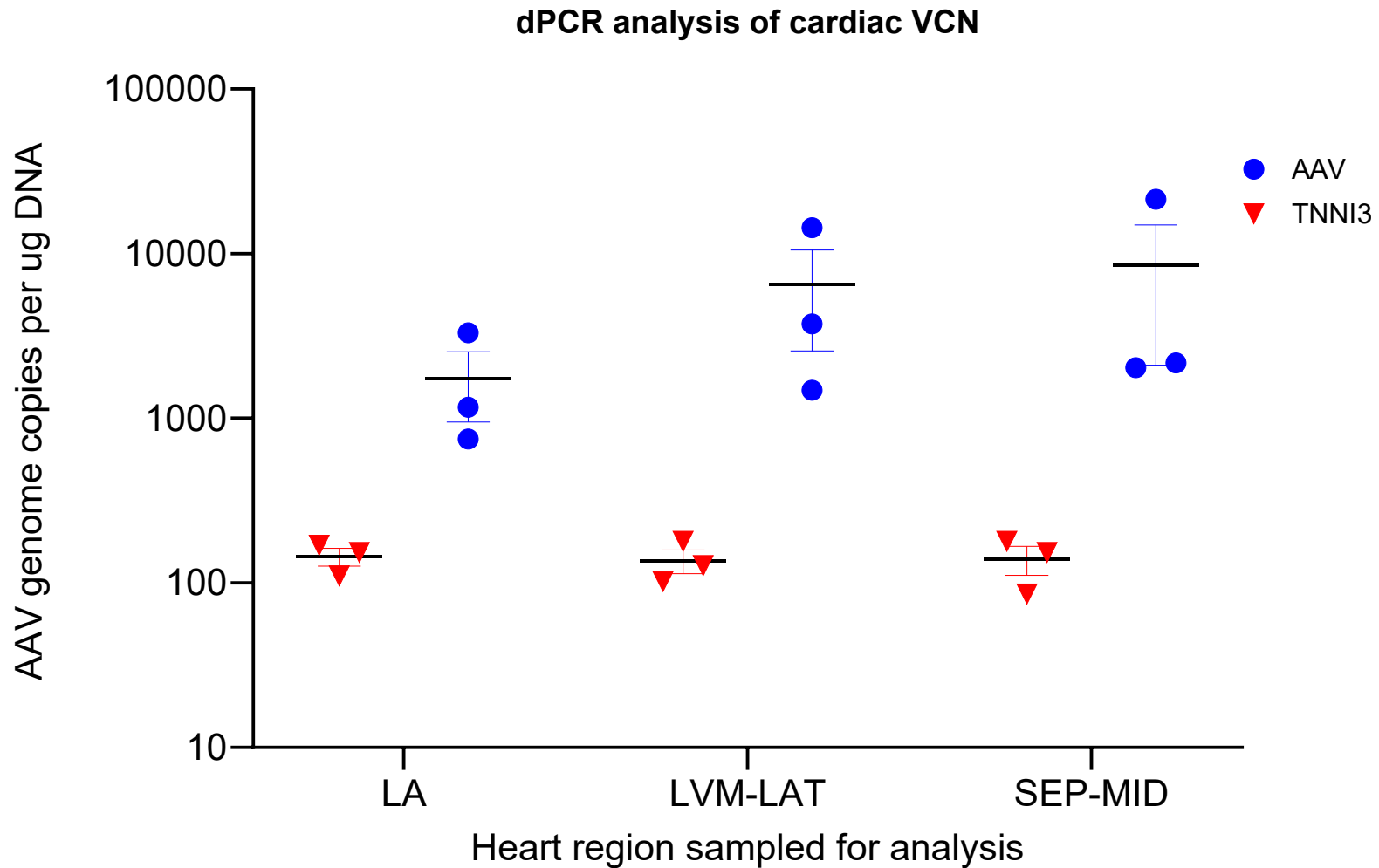


- **Transgene:** Full-length human TNNI3 cDNA
- **Regulatory elements:** MCK enhancer upstream of the human *TNNT2* promoter, augmented by MYH6-derived regulatory elements and polyadenylation signal
- **Configuration:** AAV2 ITR-flanked expression cassette

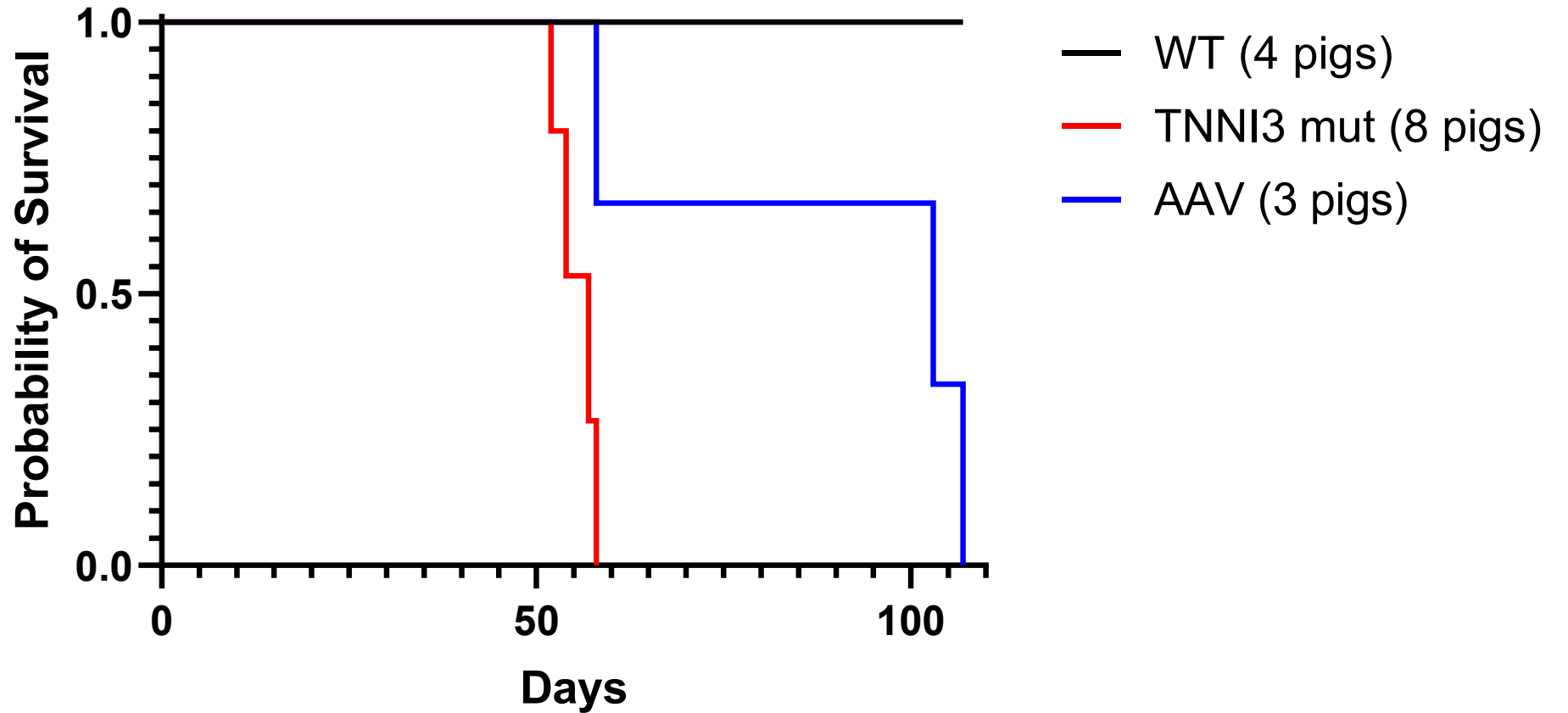
This gene therapy construct is designed to enable cardiac-targeted TNNI3 expression and support functional rescue in the porcine model

AAV Gene Therapy Delivery and Expression

6×10^{13} vg/kg BW Delivered IV at 1 Week of Age

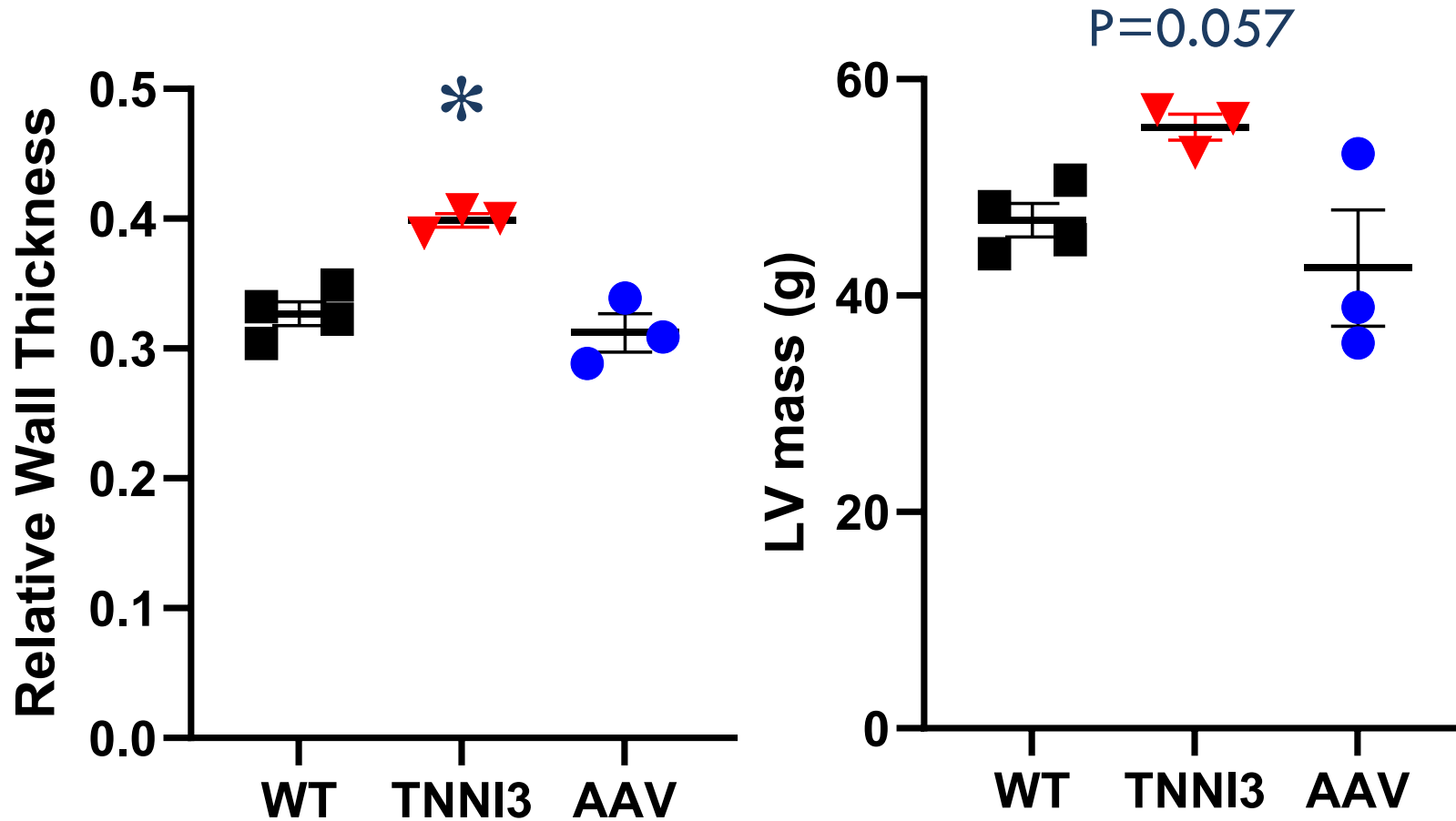


Survival Data



AAV Gene Therapy Improved Survival

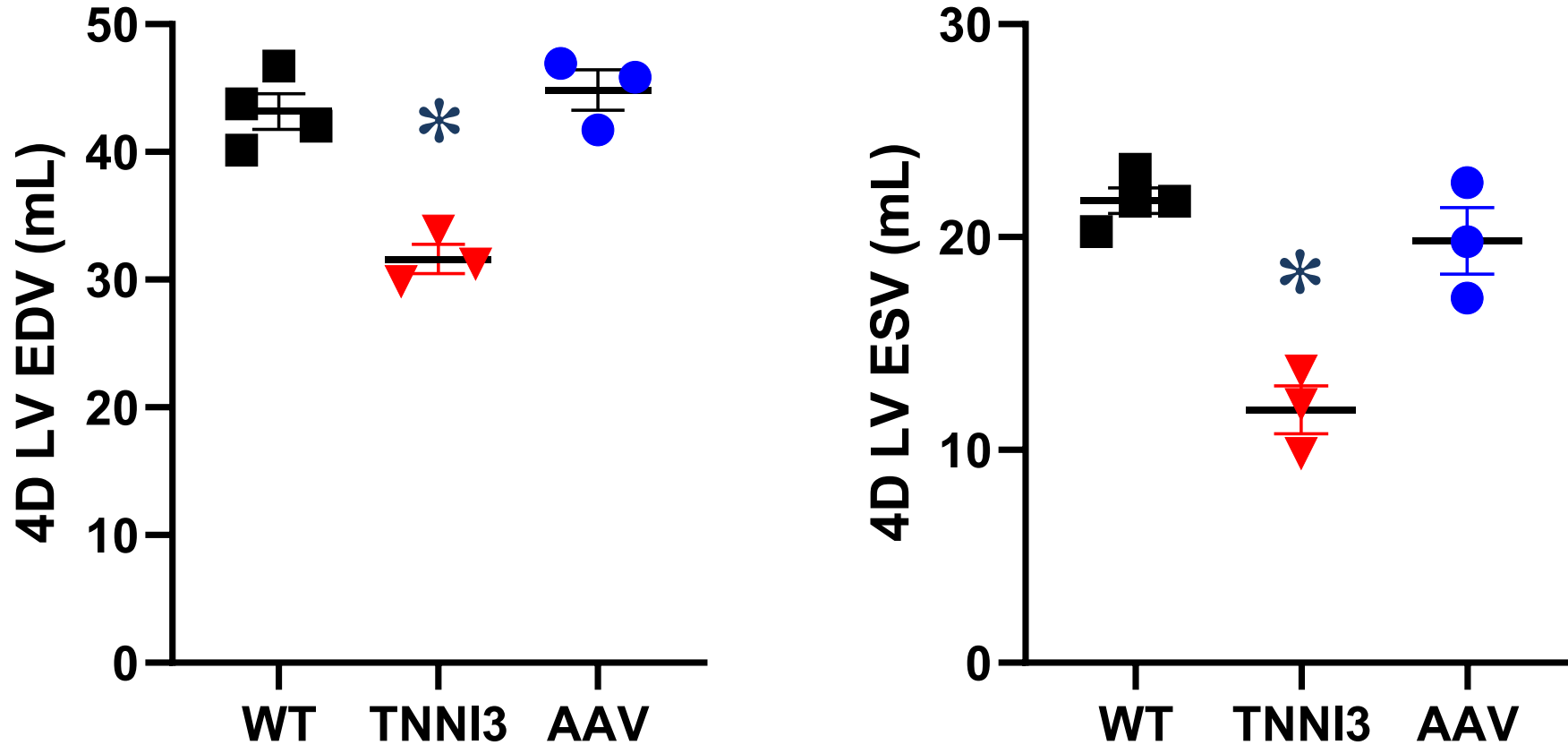
Left Ventricular Wall Thickness and Mass



* $p < 0.05$ vs. WT

AAV Gene Therapy Reduced Hypertrophy

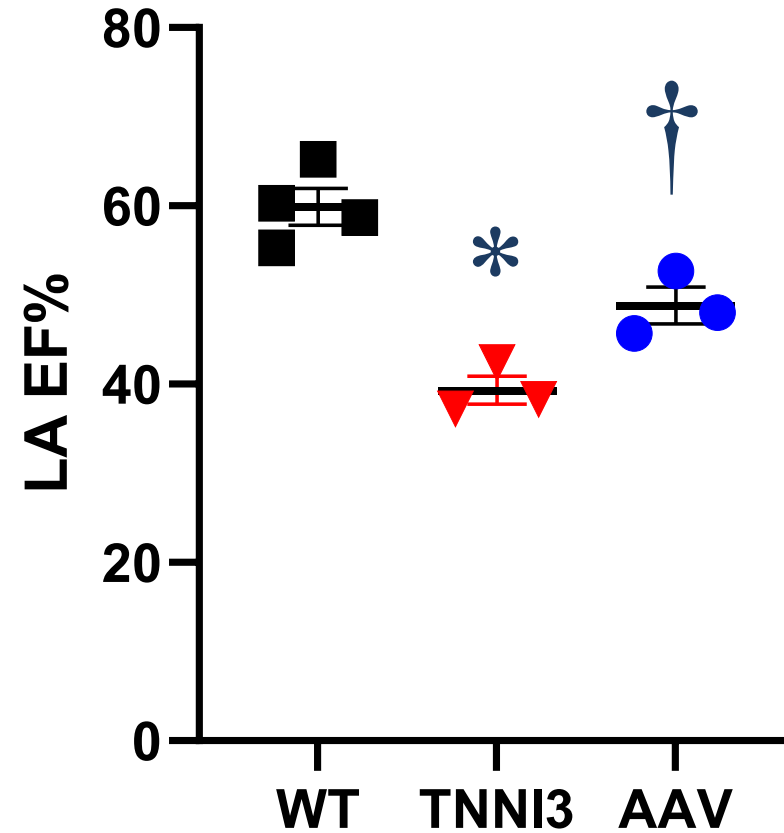
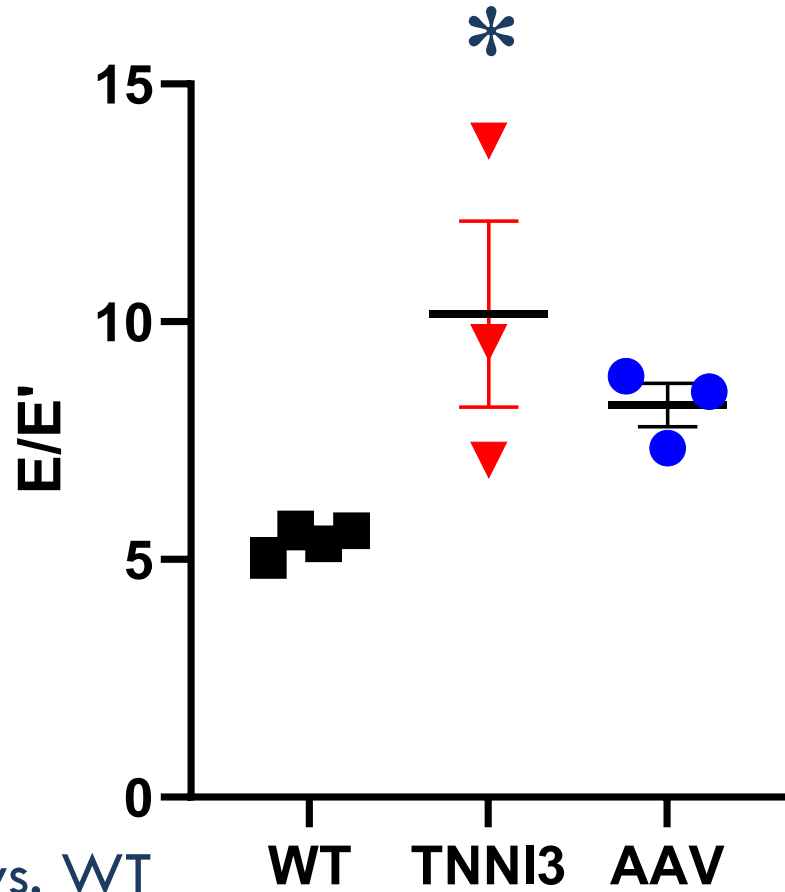
End Diastolic (EDV) and End Systolic (ESV) Volumes



* $p < 0.05$ vs. WT

AAV Gene Therapy Improved EDV and ESV

Left Ventricular and Atrial Function



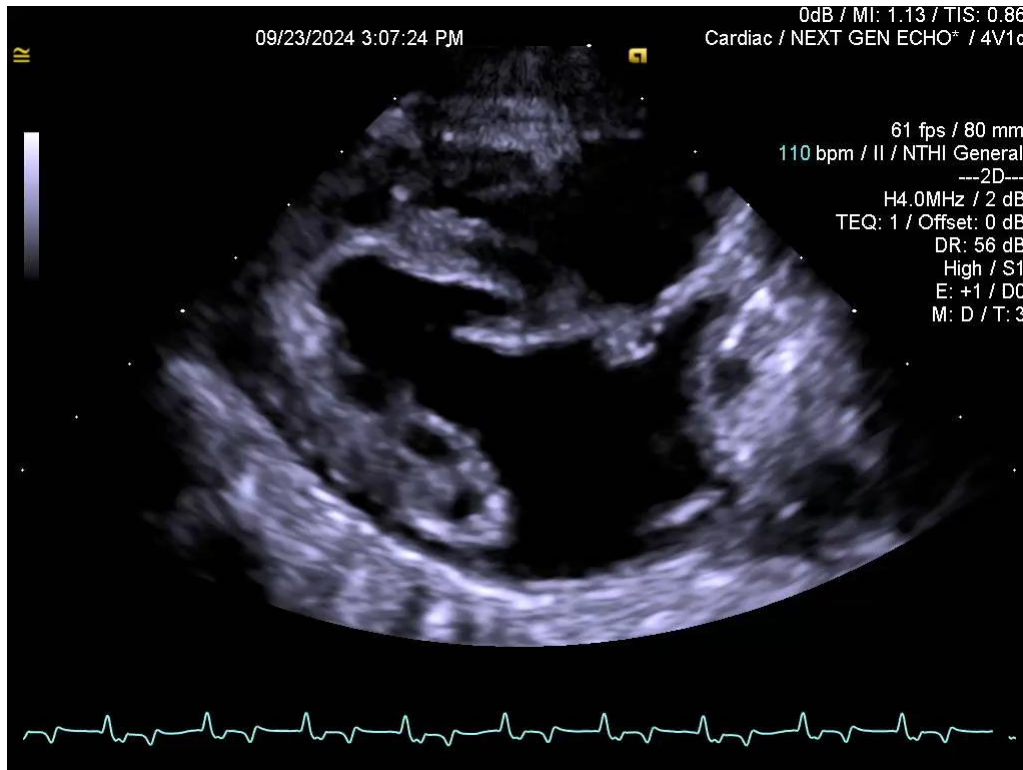
* p < 0.05 vs. WT

† p < 0.05 vs. WT and TNNI3

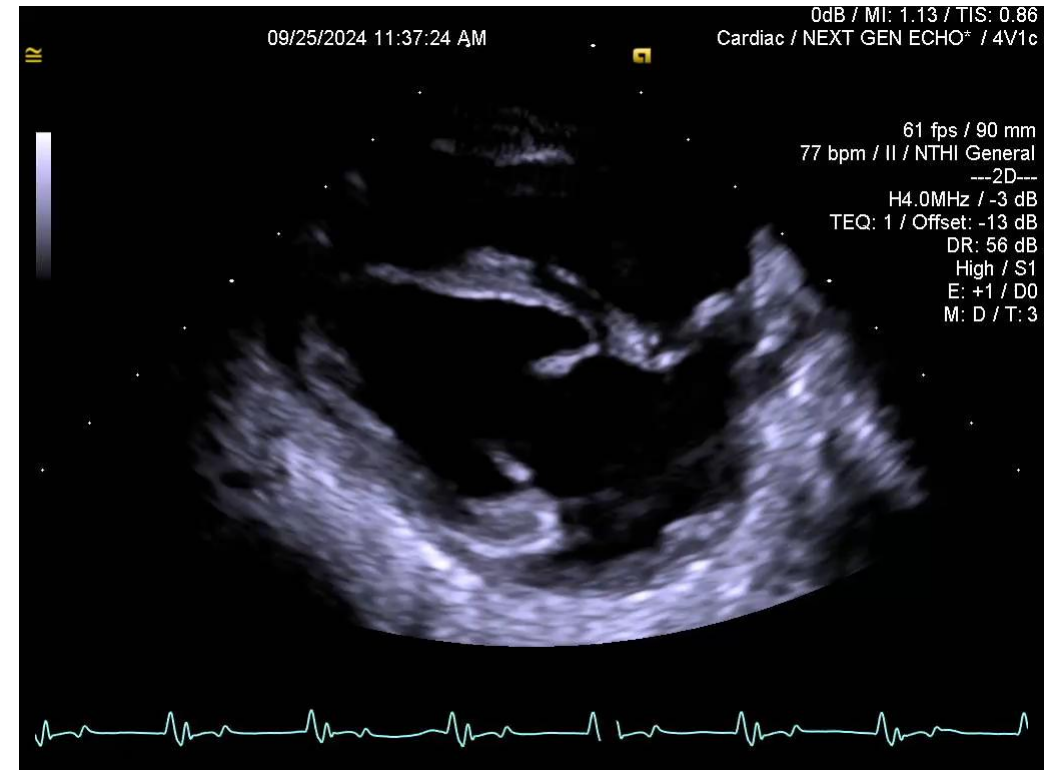
AAV Gene Therapy Improved LV and LA function

2D Longitudinal Echocardiography

TNNI3 Mutant



AAV



AAV Gene Therapy as a Treatment of TNNI3 Cardiomyopathy



Summary

- Pig Model of TNNI3 Cardiomyopathy
 - Mortality
 - Hypertrophy
 - Reduced Cardiac Function
- AAV Gene Therapy Treatment
 - Reduced Mortality
 - Reduced Hypertrophy
 - Improved Cardiac Function



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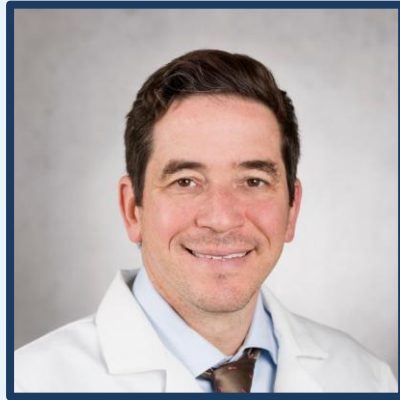
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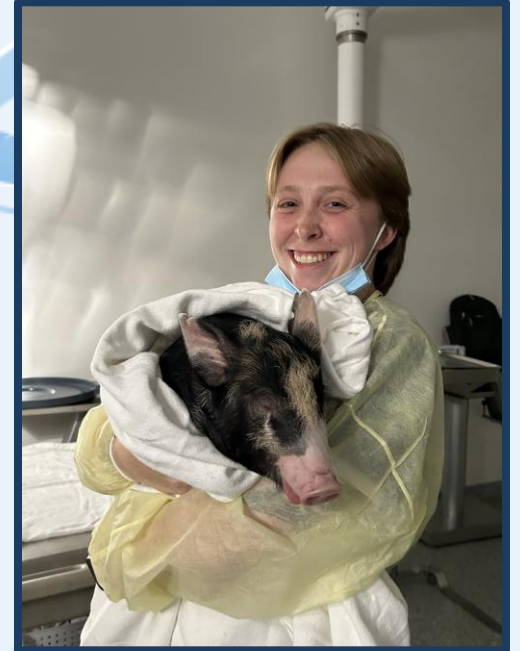
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