AAV9. LAMP-2B Reverses Metabolic and Physiologic Multiorgan Dysfunction in a Murine Model of Danon Disease

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Disclosure Information

- Ana Maria Manso is a consultant for Rocket Pharmaceuticals.
- Pavan Battiprolu and Annahita Keravala are employees of Rocket Pharmaceuticals
- Eric Adler is a shareholder of Rocket Pharmaceuticals.

Danon Disease: Clinical Manifestations

- Lethal X-linked disorder caused by mutations in the Lysosomal Associated Membrane Protein 2 (*LAMP-2*) gene, a lysosomal protein critical for autophagy.
- Cardiomyopathy, skeletal myopathy, and intellectual disability.
- Other less prevalent symptoms include **retinal disease, hepatic disease,** and **pulmonary disease.**
- Patients develop severe hypertrophic cardiomyopathy that progresses to heart failure
- Most patients die in their 20-30s without heart transplantation
- Affected males have the most severe phenotype, some heterozygous females will also show evidence of disease.

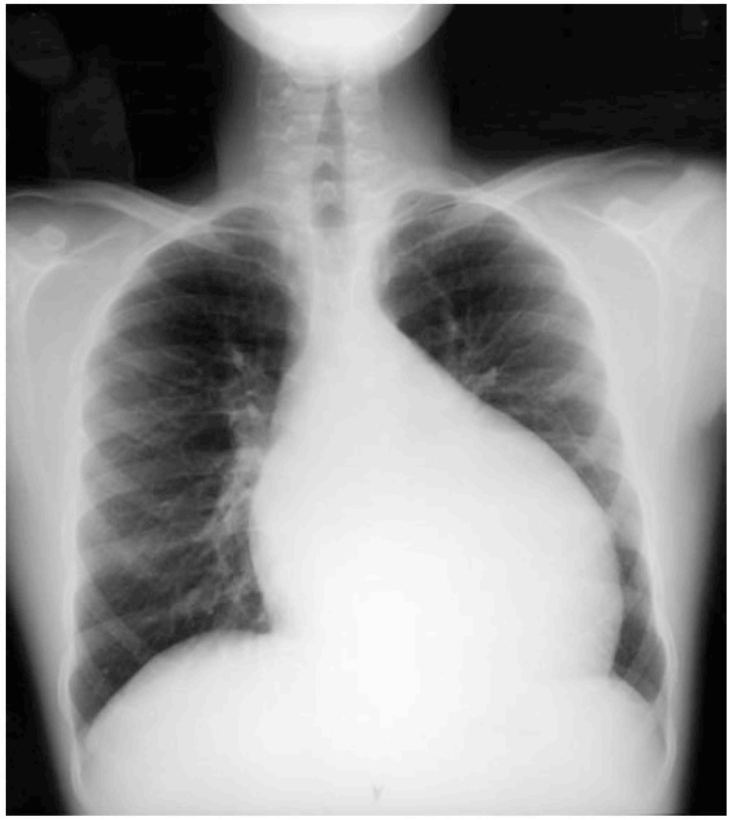
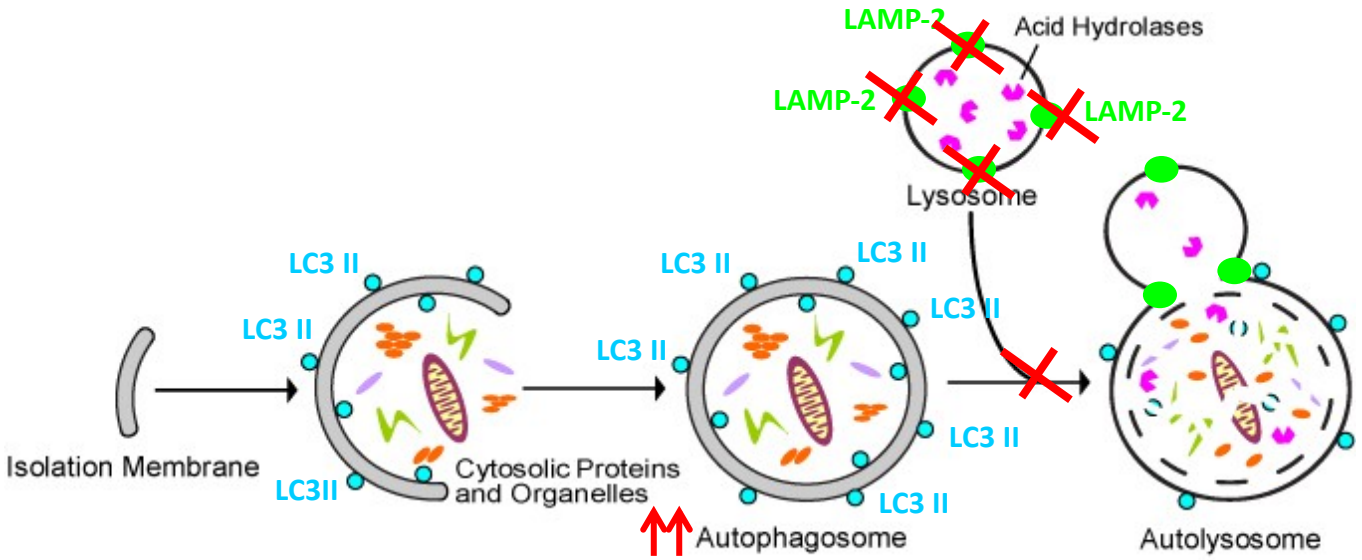


Fig. 2 Chest X-ray film taken at age 14 years showing severe cardiomegaly

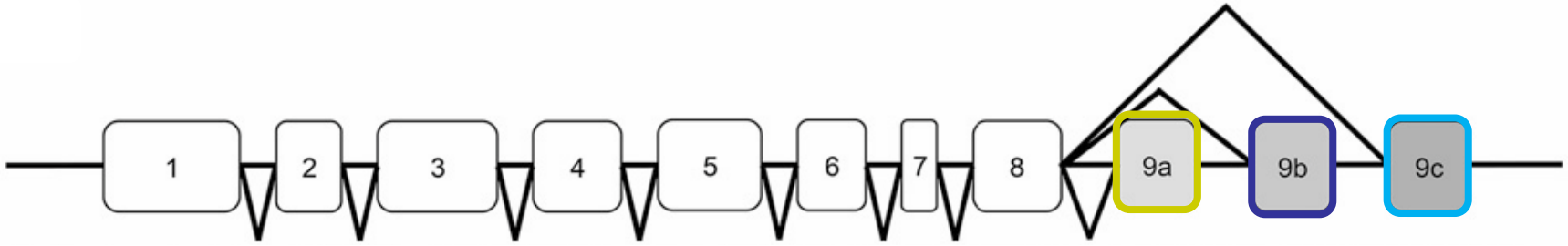
Autophagy

Danon Disease



Impaired autophagosome-lysosome fusion impairs autophagy flux in Danon disease

LAMP-2 isoforms



LAMP-2A (NP_002285.1) : AQDCSADDDNFLVPIAVGAALAGVLILVLLAYFIGLKHHHAGYEQF

LAMP-2B (NP_054701.1) : AQECSLDDDTILIPIIVGAGLSGLIIVIVIAYVIGRRKSYAGYQTL

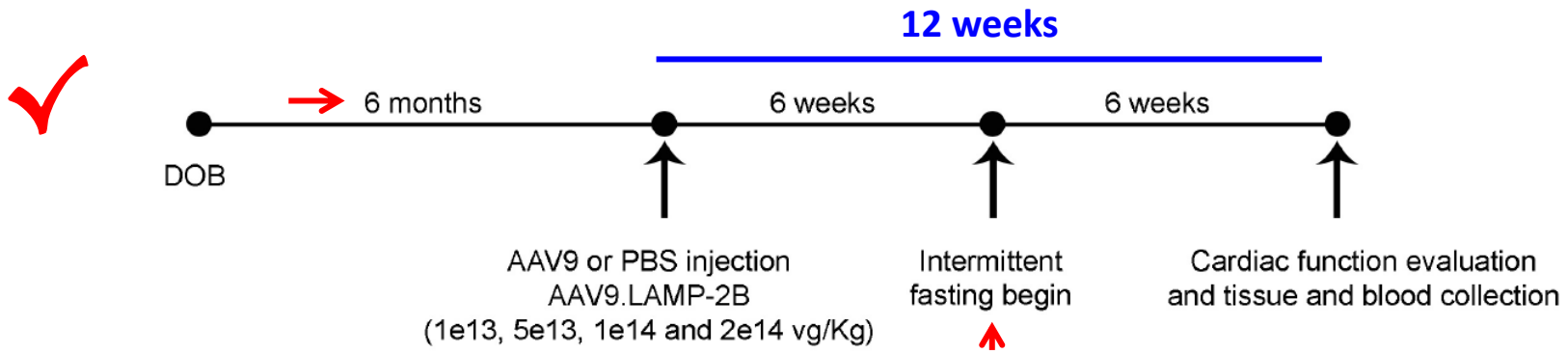
LAMP-2C (NP_001116078.1) : AEECSADSDLNFLIPVAVGVALGFLIIVVFISYMIGRRKSRTGYQSV

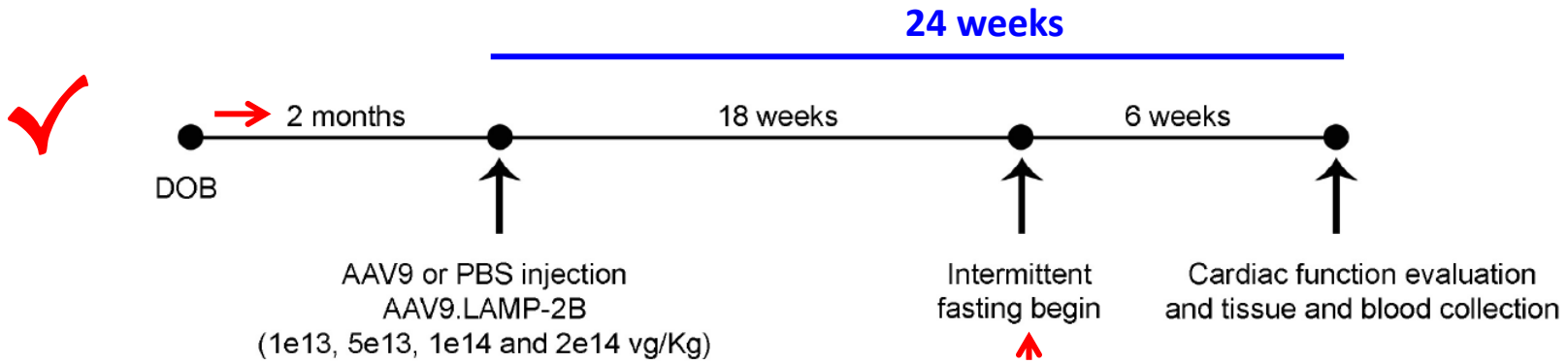
Chi et al., 2018

LAMP-2B is the predominant isoform expressed in cardiomyocytes and has been postulated to be critical in the pathogenesis of Danon disease.

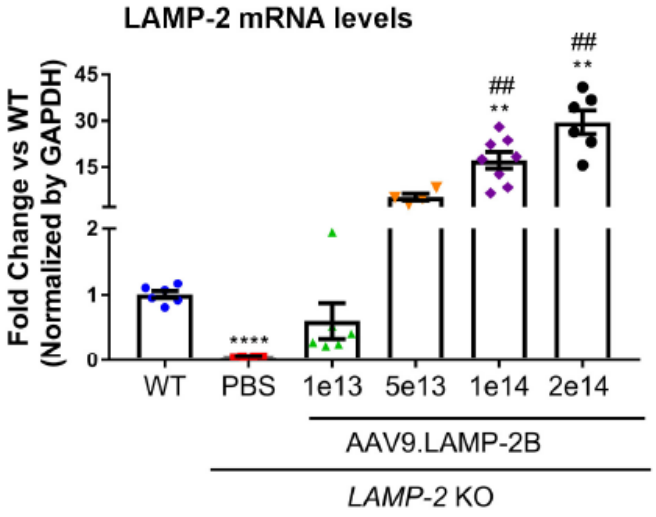
Aim: Evaluate the efficacy of gene therapy with adeno-associated viral 9 (AAV9-LAMP-2B) vector in a mouse model of Danon disease.

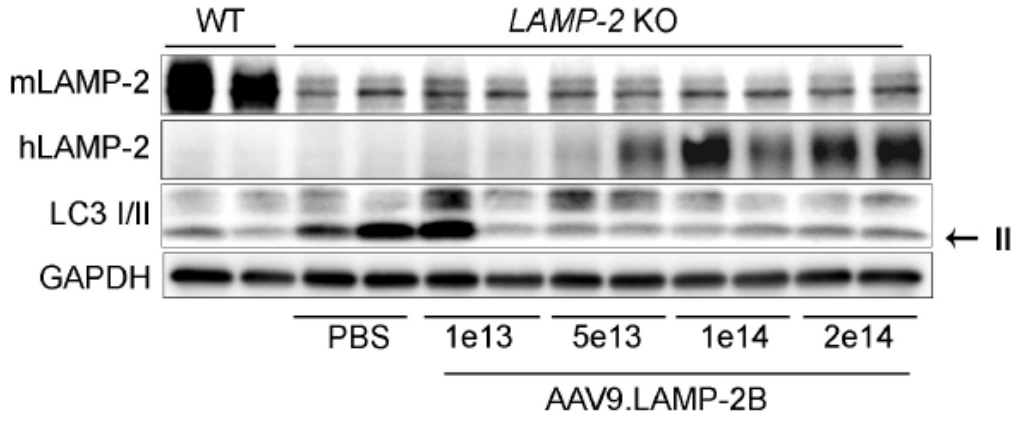
AAV9-LAMP-2B treatment in *LAMP-2* KO mice study

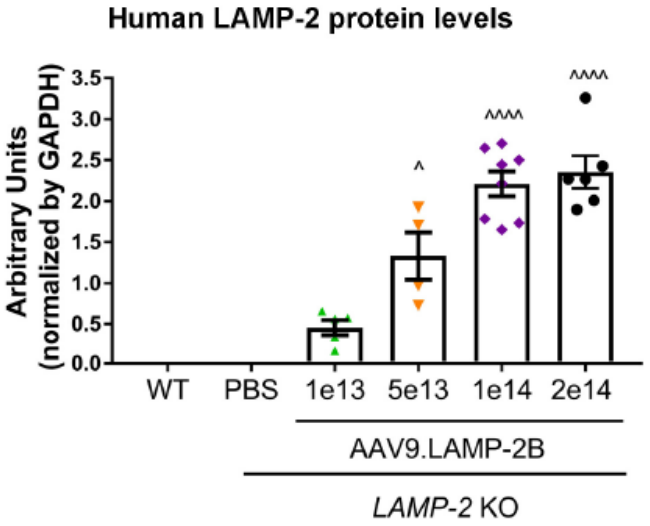


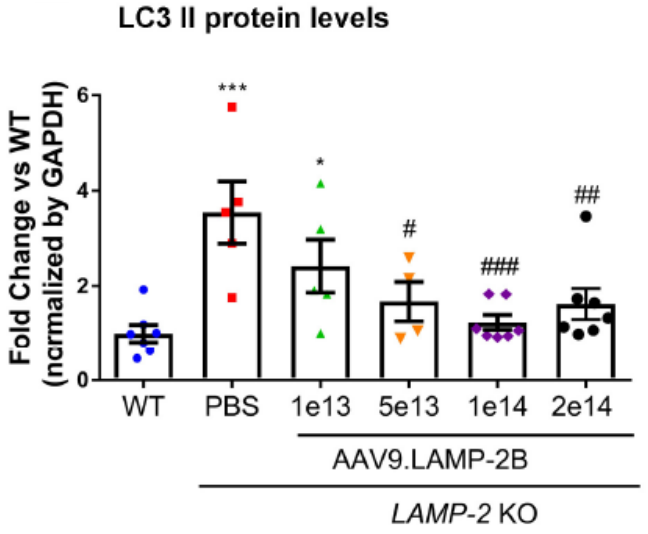


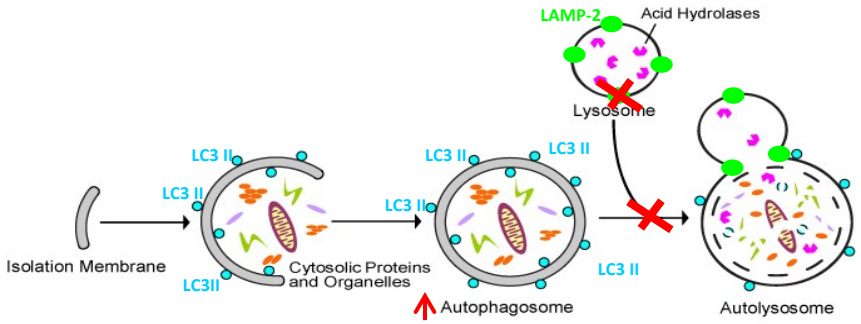
Administration of AAV9.LAMP2B showed dose-dependent expression of mRNA and human LAMP-2B protein in heart tissue from *LAMP2* KO mice together with an improvement in autophagic flux (LC3 II levels) 24 weeks post-injection









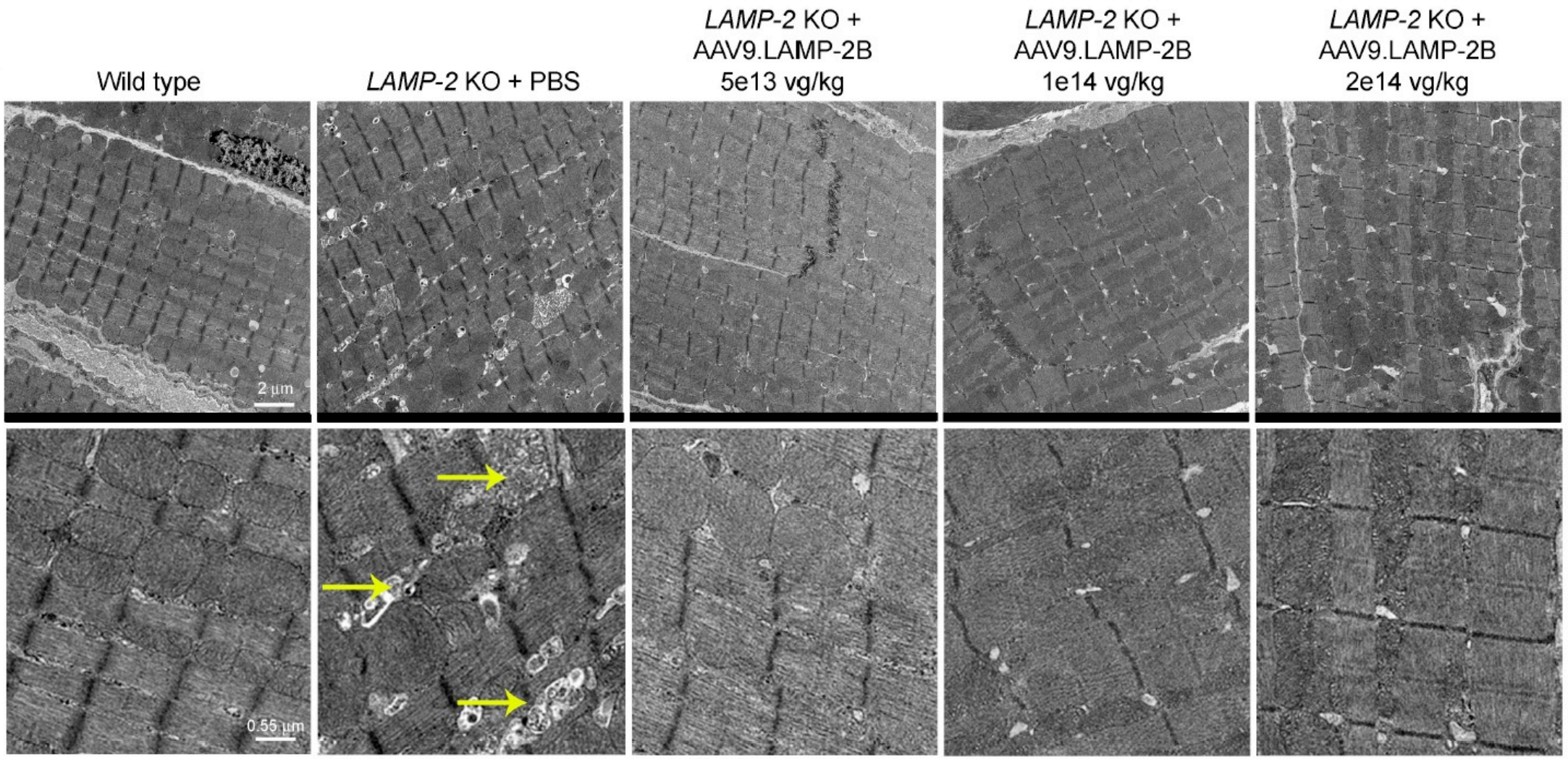


*P<0.05, **P<0.01, ***P<0.001, ****P<0.001 vs WT

#P<0.05, ##P<0.01, ###P<0.001 vs PBS

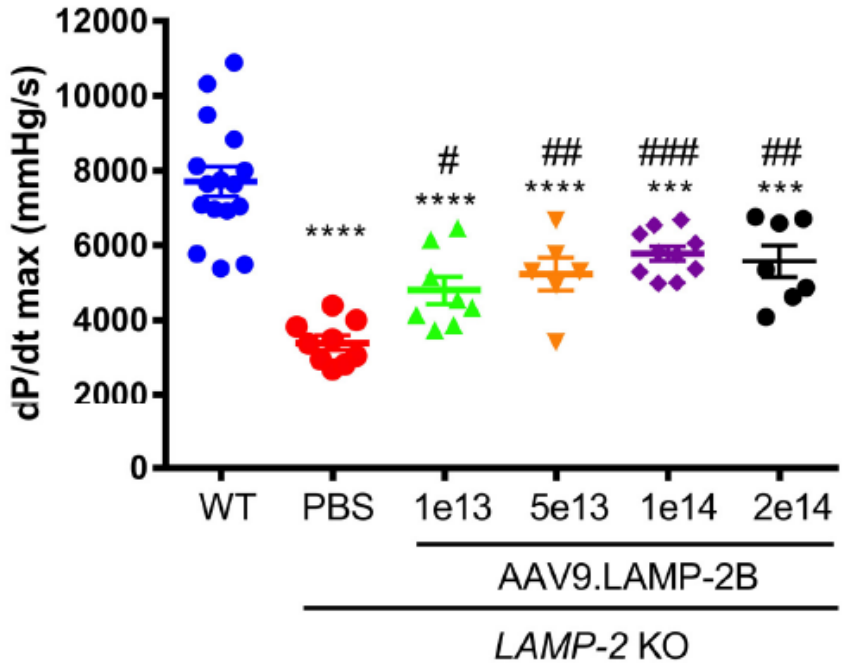
^P<0.05, ^^^^P<0.001 vs 1e13

AAV9.LAMP-2B administration was associated with an improvement in the accumulation of autophagic structures in hearts of *LAMP-2* KO mice.

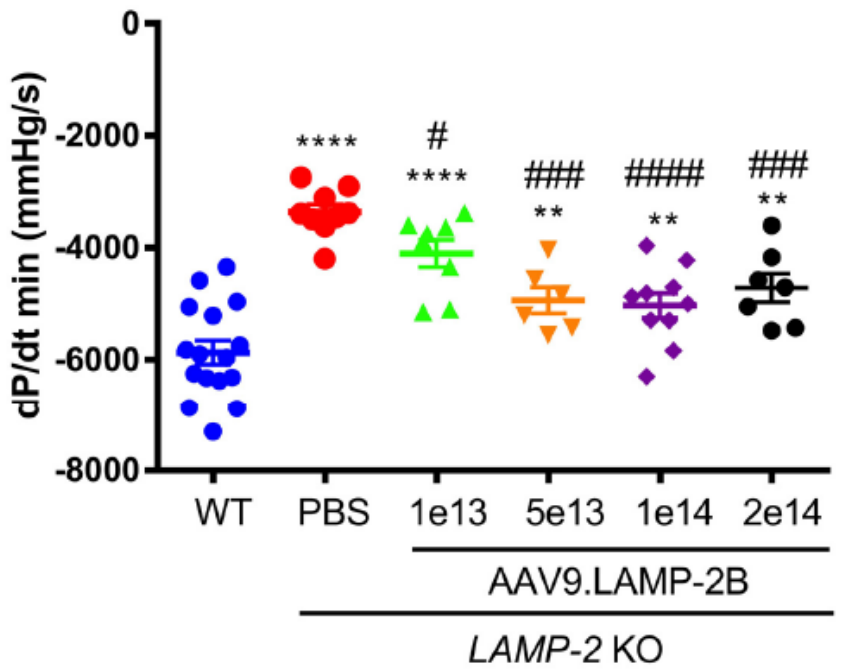


Cardiac contractility and relaxation were also improved in a dose-dependent manner in the AAV9.LAMP2B treated *LAMP2* KO mice compared to PBS controls 24 weeks post-injection

Cardiac Contractility



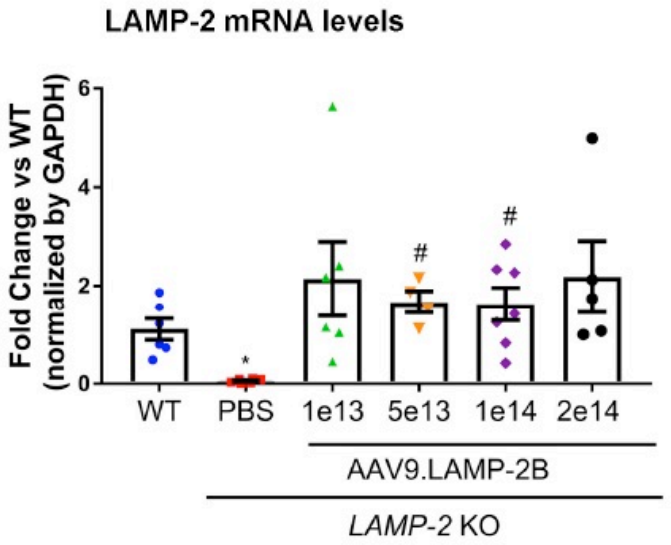
Cardiac Relaxation

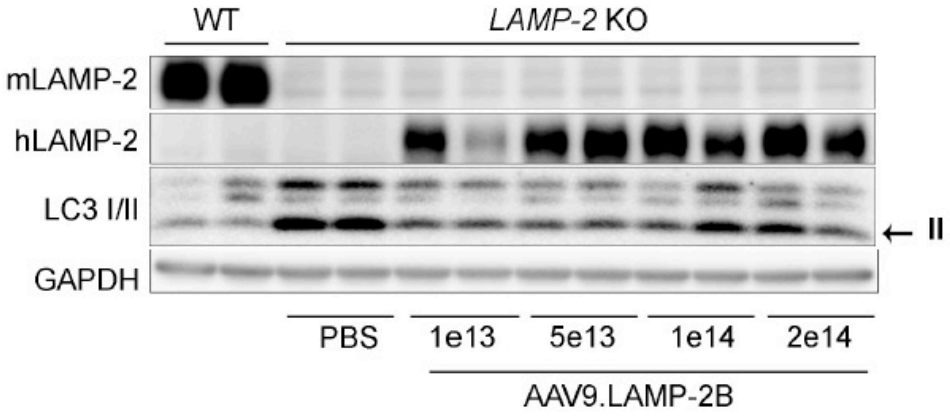


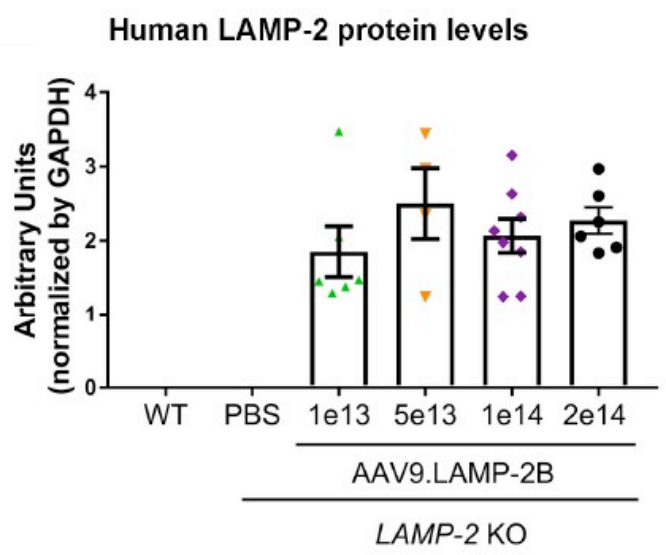
$^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.001$ vs WT

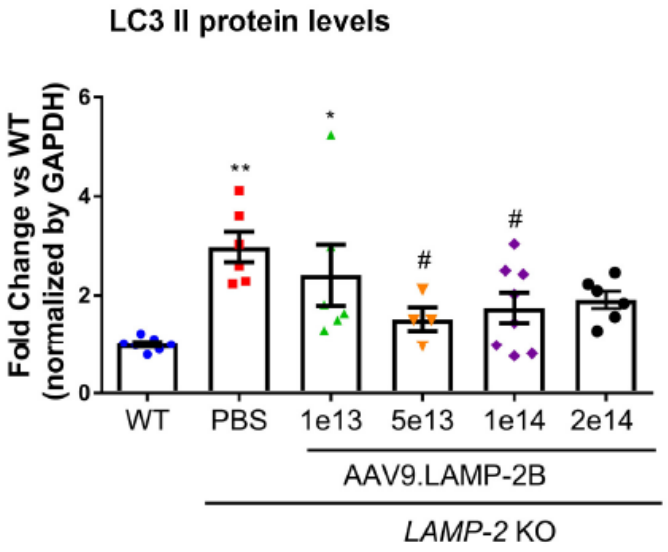
$^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$ vs PBS

Administration of AAV9.LAMP-2B showed dose-dependent expression of mRNA and human LAMP-2B protein in liver tissue from *LAMP-2* KO mice together with an improvement in autophagic flux (LC3 II levels)



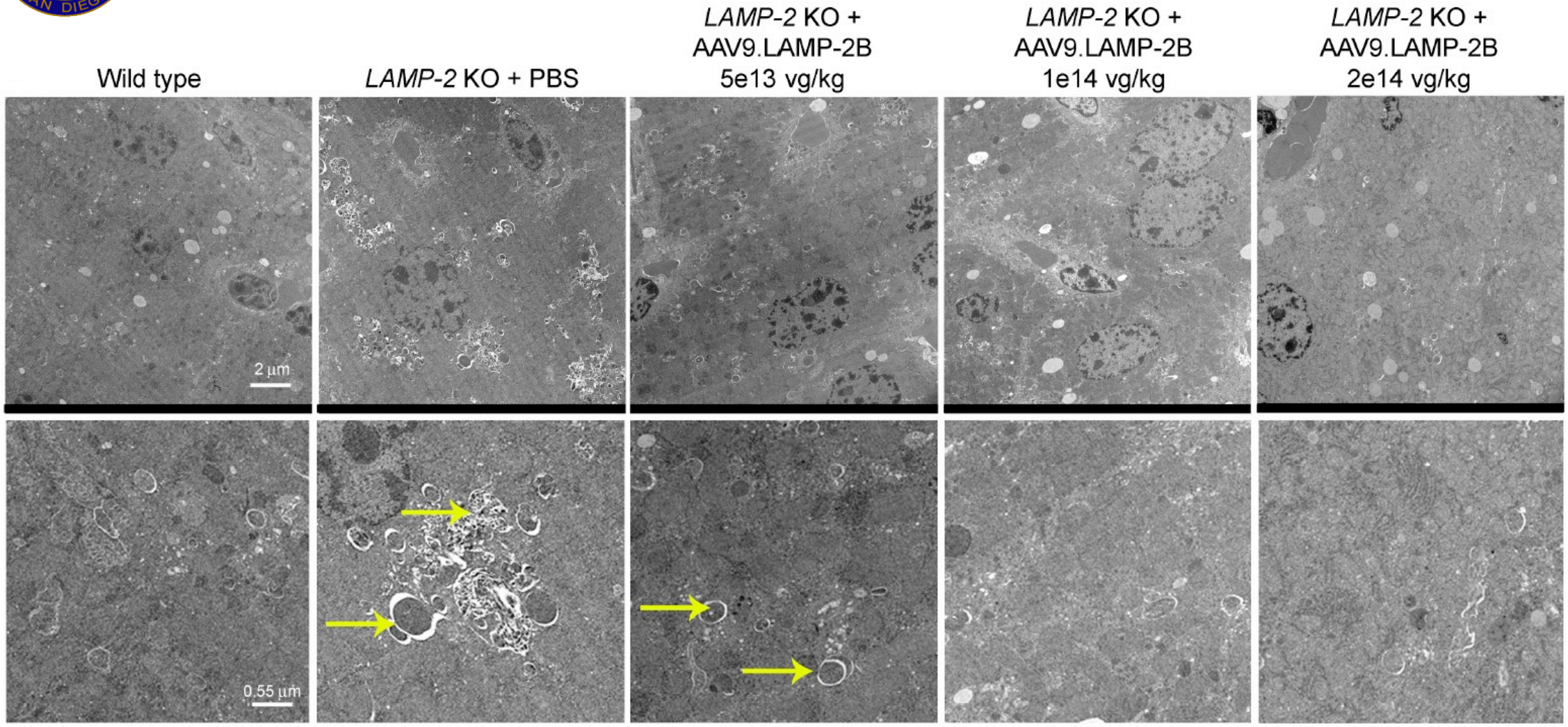






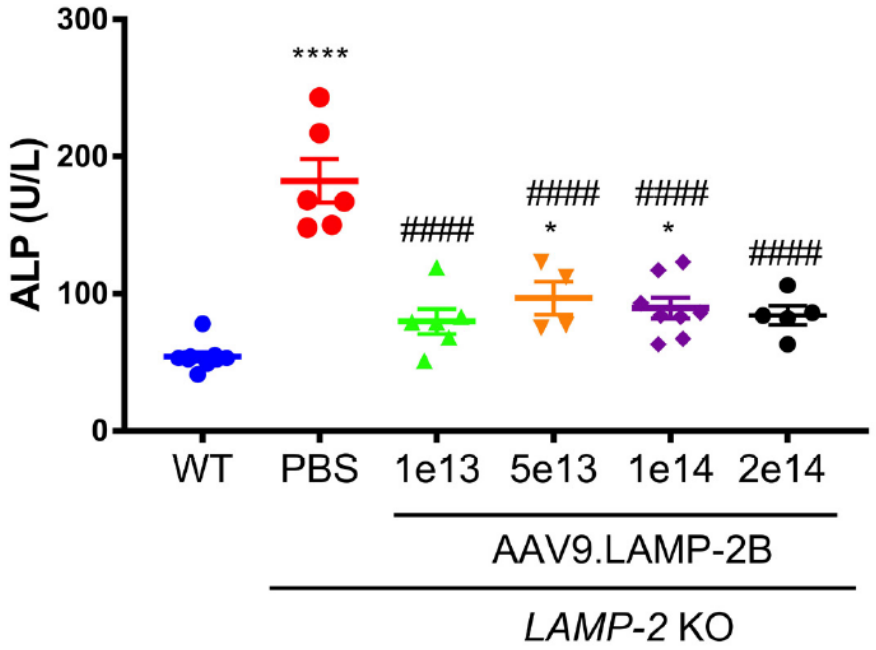
#*P*<0.05 vs PBS ******P*<0.01, vs WT

AAV9.LAMP2B administration was associated with an improvement in the accumulation of autophagic structures in livers of *LAMP-2* KO mice.

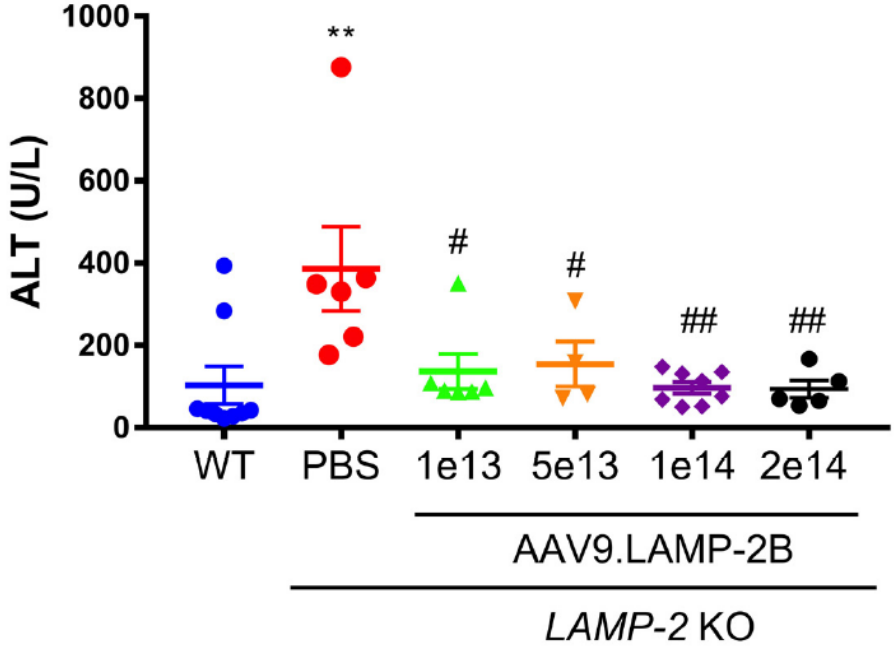


AAV9.LAMP-2B administration was associated with an improvement in the serum levels of ALP and ALT in *LAMP-2* KO mice.

Alkaline phosphatase



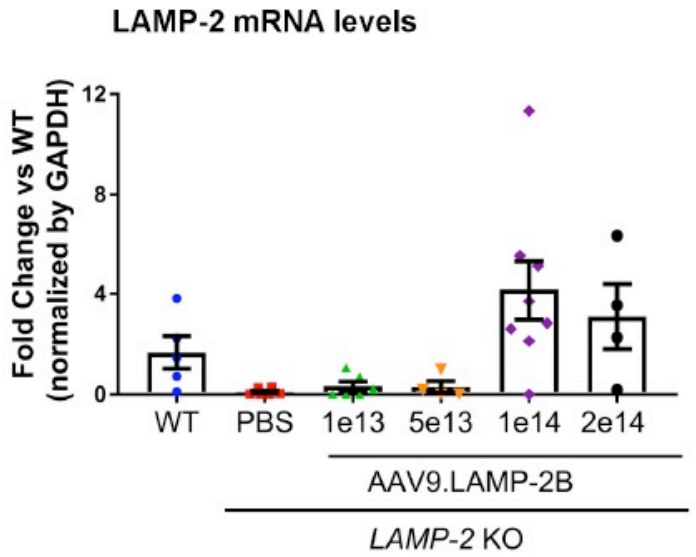
Alanine aminotransferase

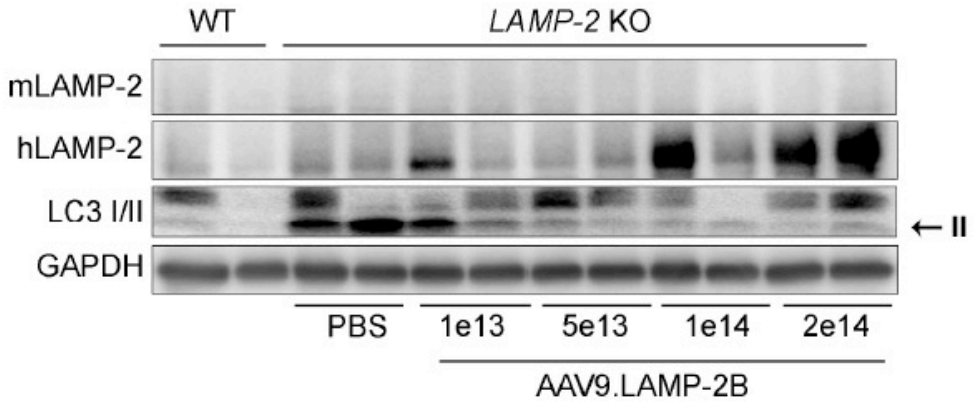


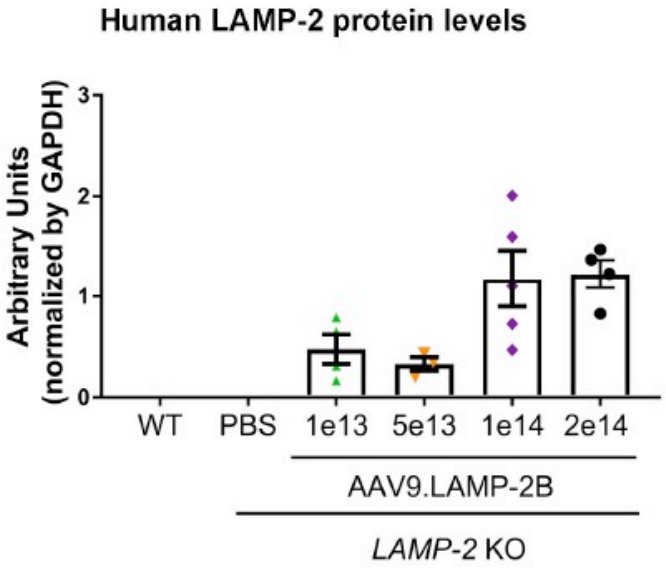
$^{**}P<0.01$, $^{****}P<0.001$ vs WT

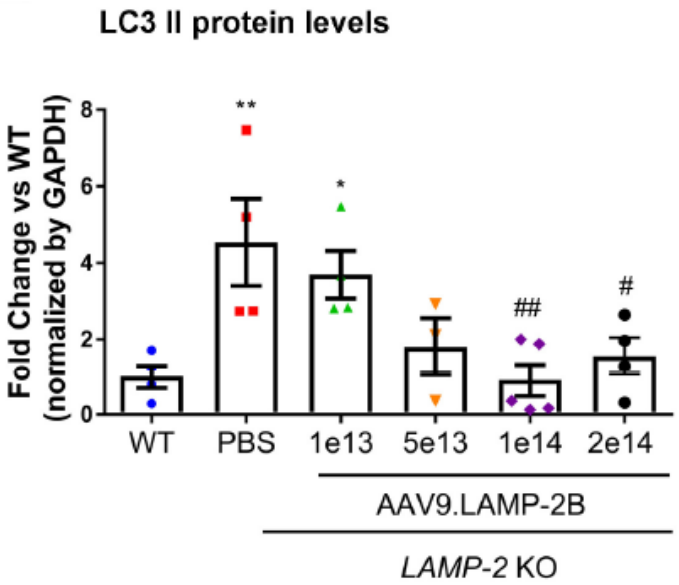
$^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#\#}P<0.0001$ vs PBS

Administration of AAV9.LAMP-2B showed dose-dependent expression of human LAMP-2B protein in skeletal muscle tissue from *LAMP-2* KO mice together with an improvement in autophagic flux (LC3 II levels)





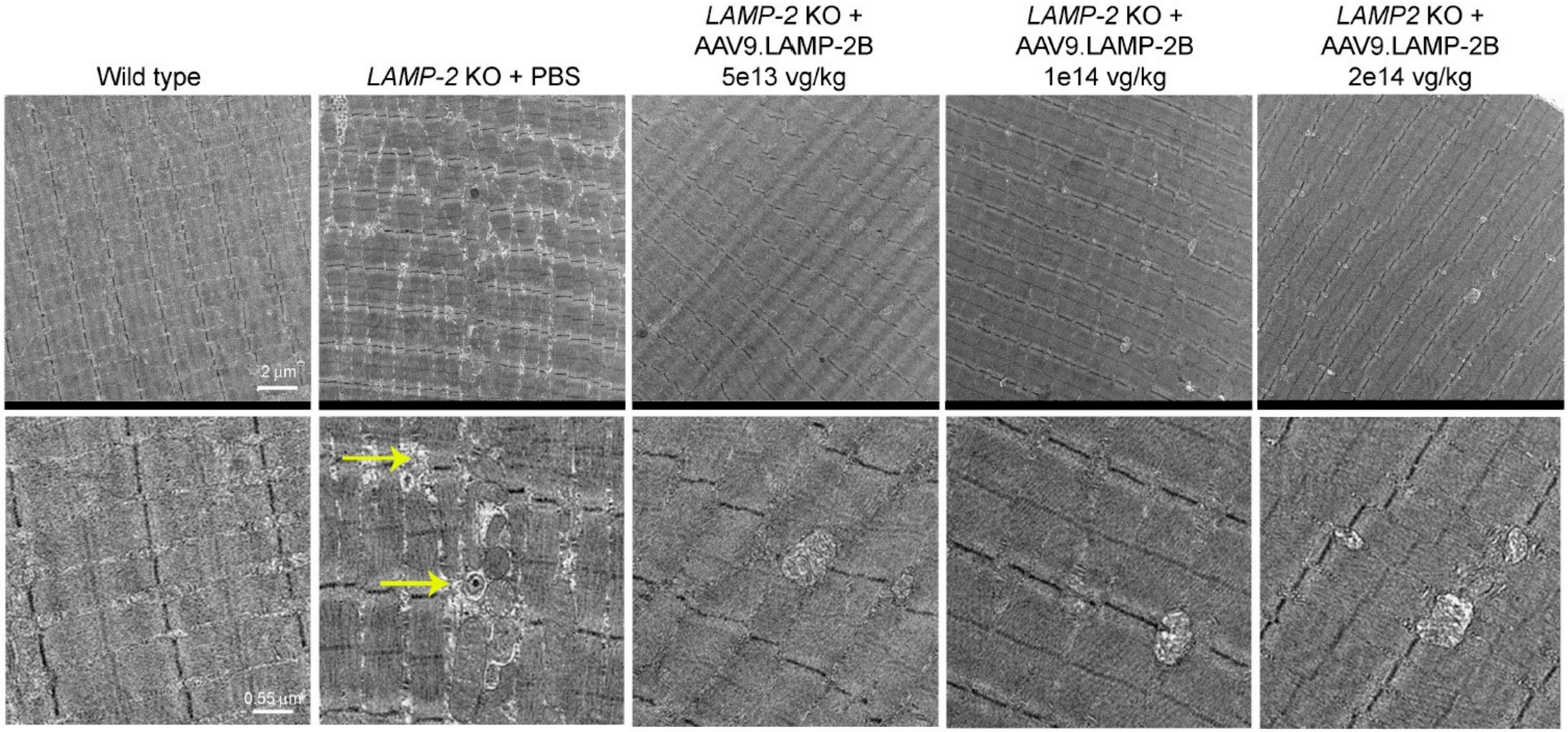




*P<0.05 ,**P<0.01 vs WT

#P<0.05, ##P<0.01 vs PBS

AAV9.LAMP-2B administration was associated with an improvement in the accumulation of autophagic structures in skeletal muscle of *LAMP-2* KO mice.



Summary

- Administration of AAV9.LAMP-2B showed dose-dependent expression of human LAMP-2B transcript and protein in heart, liver and skeletal muscle.
- AAV9.LAMP-2B administration was associated with an improvement in autophagic flux (LC3 II levels) as well as in the accumulation of autophagic structures in all three tissue.
- Cardiac function as well as hepatic damage were also improved in the AAV9.LAMP-2B treated *LAMP-2* KO mice compared to PBS controls
- Conclusion: These data indicate that AAV9.LAMP-2B gene transfer improves the metabolic and physiologic multiorgan dysfunction in the mouse model of Danon disease and demonstrate persistent treatment effects up to 6-months post injection, indicating the durability of the therapy.

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