Cardiovascular Manifestations of Mucolipidosis II: A Translational Feline Model

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Introduction

- MLII is an autosomal recessive lysosomal storage disorder caused by a *GNPTAB* mutation, affecting infant to juvenile children
- The mutation results in a GlcNAc-phosphotransferase defect, which prevents normal trafficking of acid hydrolases into lysosomes
- Clinical presentation includes:
  - Skeletal deformities
  - Neurologic lesions
  - Heart valve thickening
- High mortality rate (MST= ~5 years)
  - Poorly characterized cardiovascular disease leading to fulminant congestive heart failure
- A novel, naturally occurring feline MLII model has been identified
  - Autosomal recessive MOI
  - Pathogenic *GNPTAB* nonsense mutation
    - Exon 13 c.2644C>T; p.Gln882*
- Cats display cardiovascular phenotypes that recapitulate human MLII with variable presence of congenital cardiac defects
- Studies interrogating the genotype-phenotype relationship of feline MLII promise continued advancements in targeted novel drug therapies in humans
- Study aims include expanding the MLII cat colony and further characterizing the disease in cats for human translational use

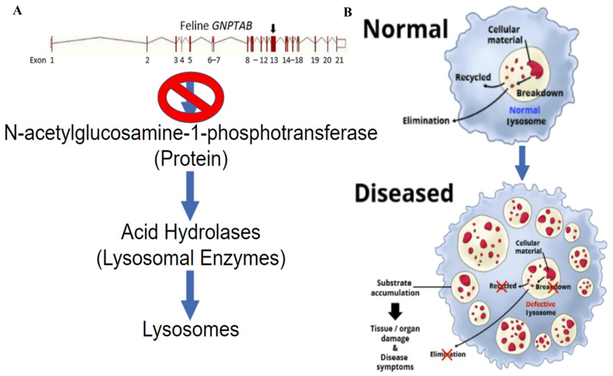
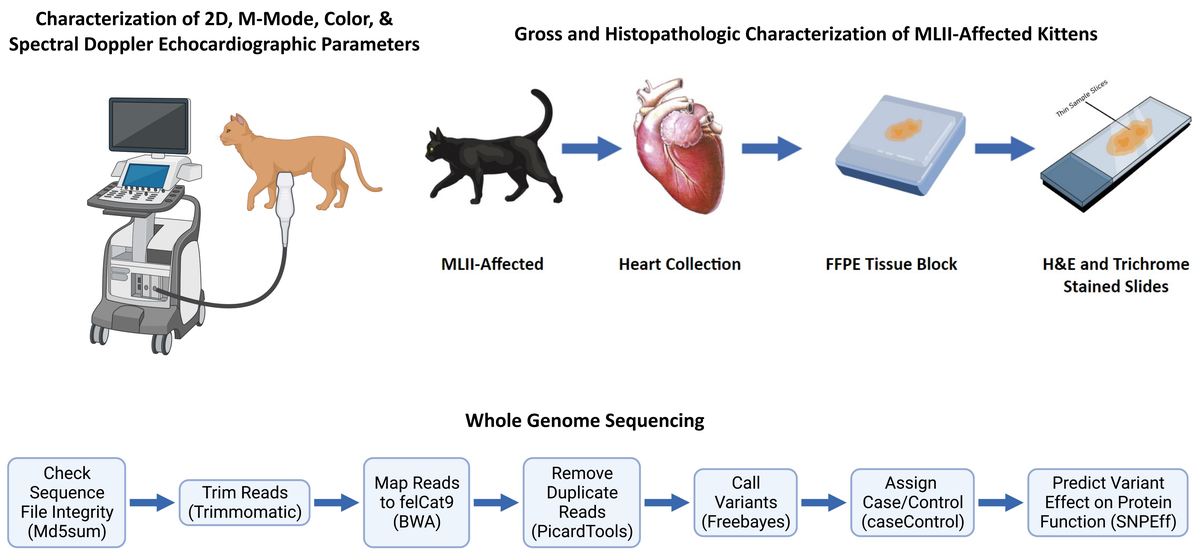


Figure 1. Pathogenic Effects of *GNPTAB* Mutation on Lysosomes. (**A**) ENSMBL illustration of *GNPTAB* gene body and downstream protein interactions. Black arrow represents positioning of previously identified *GNPTAB* MLII-associated mutation in cats. (**B**) Illustration of MLII molecular pathogenesis.

Hypothesis

Additional cardiovascular phenotypes observed in MLII-affected cats are explained by compound pathogenic mutations with implicated changes to the mitral and aortic valves, leading to volume overload and congestive heart failure. These findings will mimic those observed in children with MLII and support use of the feline MLII colony in studies aiming to alter cardiovascular outcomes.

Methods



Results

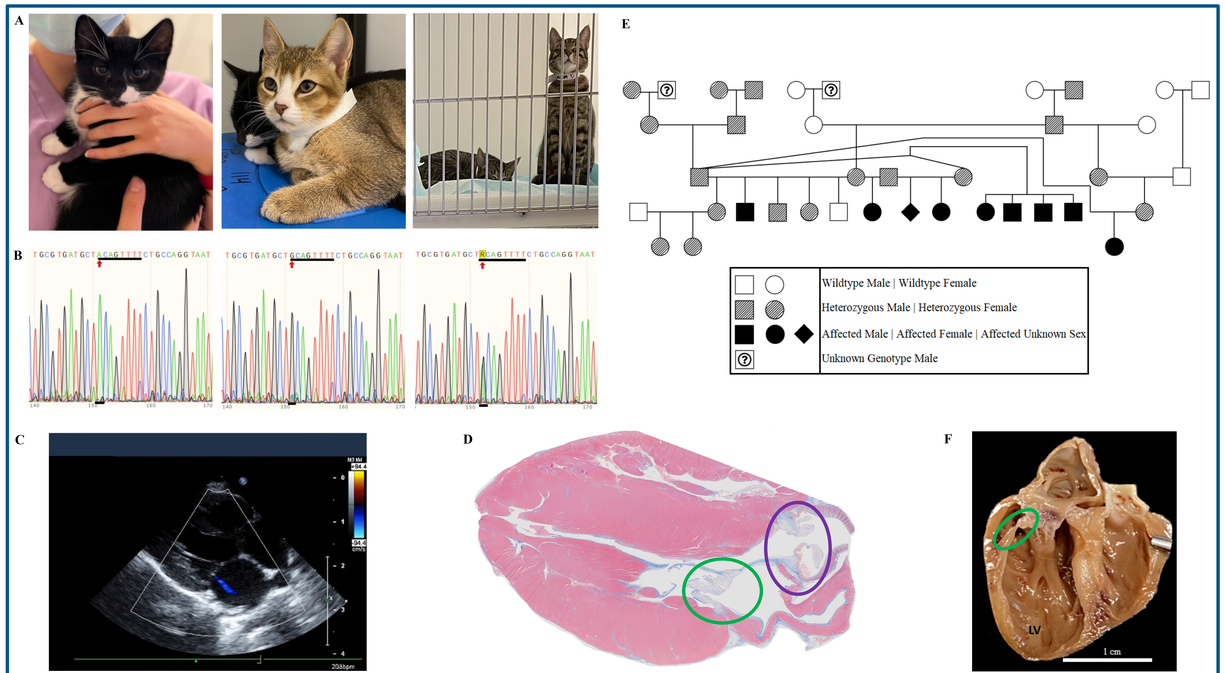


Figure 2. MLII Colony Expansion & Fine Clinical Characterization of MLII-Affected Kittens. (**A**) Addition of four new colony members; wildtype (left), heterozygous (middle & right-two). (**B**) Sanger sequencing genotyping of wildtype (left), heterozygous (middle), and homozygous (right) cats for *GNPTAB* mutation. (**C**) Right parasternal four-chamber long-axis view displaying mitral valve regurgitation (blue) in an unaffected MLII colony kitten. (**D**) Masson's Trichrome staining of a paraffin-embedded MLII-affected kitten heart depicting increased collagen deposition in the aortic (purple) and mitral valves (green). (**E**) Pedigree displaying expansion of the feline research colony. (**F**) 3-week-old formalin-fixed MLII-affected kitten heart displaying a dilated and thin-walled left ventricle (LV) with a thick mitral valve (green).

- Breeding efforts resulted in the addition of four kittens to the MLII colony
  - 3/4 kittens heterozygous for *GNPTAB* mutation
  - 1/4 kittens homozygous wildtype
- Echocardiograms for all but one unaffected cat were unremarkable
  - No volume overload
  - No valvular regurgitation
  - No chamber enlargement
- Trace mitral regurgitation was noted in one unaffected carrier
  - Disease progression is being monitored
- Increased collagen deposition in cardiac tissues was observed on Masson's Trichrome stains
  - Localization primarily to valvular structures
    - Aortic valve
    - Mitral valve
- 13 cat WGS files were successfully trimmed and mapped, and duplicate reads were removed
  - Average read depth of all covered positions: 25.3X
  - Average read depth of all positions, including zero-depth regions: 24.4X

Conclusion

- The MLII cat colony has 8 heterozygous cats; breeding pairs will be established to produce additional affected kittens
- A whole genome association study to identify disease-modifying variants is in progress to further characterize the genetics of MLII cardiovascular pathology
- Expansion and maintenance of the MLII cat colony is essential for continued WGS efforts and for further characterization of cats as an important translational model to propel future therapeutic discoveries

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References