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
- A novel, naturally occurring feline MLII model has been identified
- Those with MLII show 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

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

Characterization of 2D, M-Mode, Color, & Spectral Doppler Echocardiographic Parameters

Gross and Histopathologic Characterization of MLII-Affected Kittens

Whole Genome Sequencing

Results

- 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

Acknowledgements

References