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PROGRESSION OF CARDIAC DYSFUNCTION AND MORTALITY IN A Bcl2-ASSOCIATED ATHANOGENE-3 HAPLOINSUFFICIENCY MOUSE MODEL OF DILATED CARDIOMYOPATHY

Valerie D. Myers,[1] Gavin P. Landesberg,[2] Arti V. Shinde,[1] Justin M. Percival,[1] Arthur M. Feldman,[3] Matt Killeen[1]

[1]Renovacor, Boston, MA; [2]The Center for Neurovirology and Gene Editing, Temple University Lewis Katz School of Medicine, Philadelphia, PA; [3]Department of Medicine, Division of Cardiology, Temple University Lewis Katz School of Medicine, Philadelphia, PA

Introduction

- Bcl2-associated athanogene-3 (BAG3) is a multifunctional protein expressed predominantly in the heart, skeletal muscle, and central nervous system. Truncating variants of BAG3 have been shown to result in haploinsufficiency and are associated with the development of dilated cardiomyopathy (DCM) clinically.[1] To better understand the role of decreased BAG3 in the development of DCM and assess the potential of a model in which to study therapeutics targeting BAG3-associated DCM, we determined the impact of BAG3 haploinsufficiency on the timing and extent of cardiac dysfunction and mortality in a genetic mouse model haploinsufficient for cardiac BAG3 (cBAG3+/-).

Methods

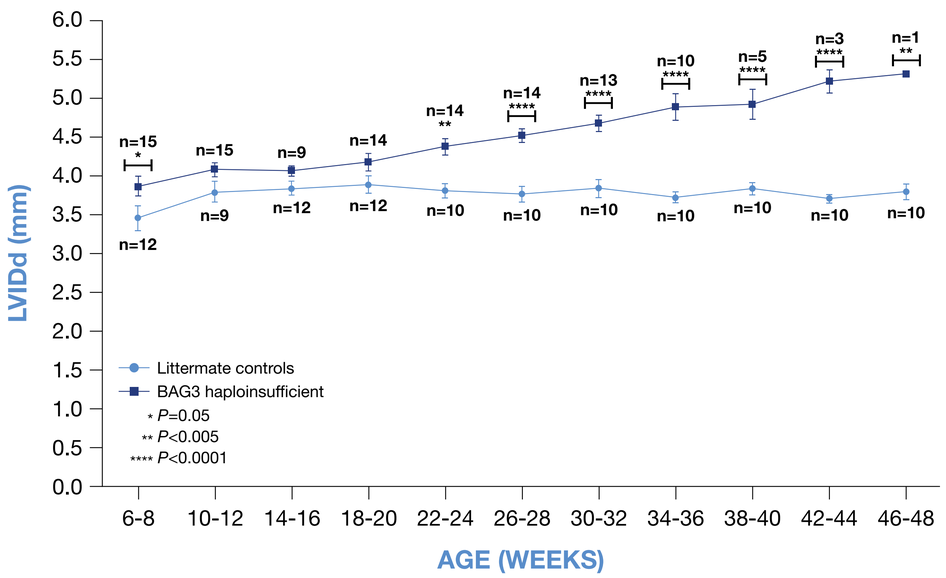
- cBAG3+/- mice were generated by crossing mice with one BAG3 allele flanked by loxP recombination sites (BAG3fl/+) with α-MHC-Cre mice. Littermate controls were either BAG3fl/+ or BAG3fl/fl without α-MHC-Cre.
- Left ventricular (LV) remodeling and function were determined by M (motion) mode transthoracic echocardiography performed monthly up to 48 weeks of age in cBAG3+/- mice and littermate controls.
- Survival was determined by Kaplan-Meier analysis until 80% mortality was achieved in the cBAG3+/- cohort.

Results

CARDIAC DIMENSIONS

- At age 22 to 24 weeks, cBAG3+/- mice showed significant enlargement of the LV and systolic dysfunction that worsened with time. Relative to littermate controls, 22- to 24-week-old cBAG3+/- mice exhibited a significant 15% increase in LV internal diameter end diastole (LVIDd) from 3.81 to 4.39 mm (Figure 1). By age 46 to 48 weeks, LVIDd in cBAG3+/- mice had increased 40% above controls regardless of loss of cBAG3+/- mice to increased mortality over time. At this time point, 93% of cBAG3+/- mice had died.

Figure 1. Significantly increased LVIDd in cBAG3+/- mice



SYSTOLIC CARDIAC FUNCTION

- LV dilatation in 22- to 24- and 46- to 48-week-old cBAG3+/- mice was accompanied by significant 23% and 81% decreases in ejection fraction (EF; Figure 2), respectively. Similarly, fractional shortening (FS) was decreased by 40% in 22- to 24-week-old cBAG3+/- mice and by 119% in 46- to 48-week-old cBAG3+/- mice relative to littermate controls (Figure 3).

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For more information, please contact Valerie D. Myers at vmyers@renovacor.com

Key Findings

- We provide genetic and physiological evidence that cardiac BAG3 haploinsufficiency is sufficient to cause DCM and premature mortality in mice.
- This cBAG3+/- mouse model exhibits progressive LV chamber dilation and systolic dysfunction.
- Genetically induced cardiac BAG3 haploinsufficiency in mice leads to increased mortality.

Conclusions

- A genetic mouse model of cardiac BAG3 haploinsufficiency demonstrated progressive LV dilatation and systolic dysfunction accompanied by a substantial increase in mortality.
- The progressive DCM and shortened life span of cBAG3+/- mice parallel findings observed clinically in patients with BAG3-associated DCM in which BAG3 protein is also decreased by ~50%.[2]
- Further in-depth evaluation of this genetic mouse model will play an important role in supporting preclinical development of a potential adeno-associated virus serotype 9 (AAV9)–based precision therapy approach for BAG3 DCM.
- Based on these natural history data, we are leveraging this model in ongoing evaluations of an AAV9-BAG3 gene transfer therapeutic approach for the potential treatment of BAG3-associated DCM.

Results (cont)

Figure 2. Significantly decreased EF in cBAG3+/- mice

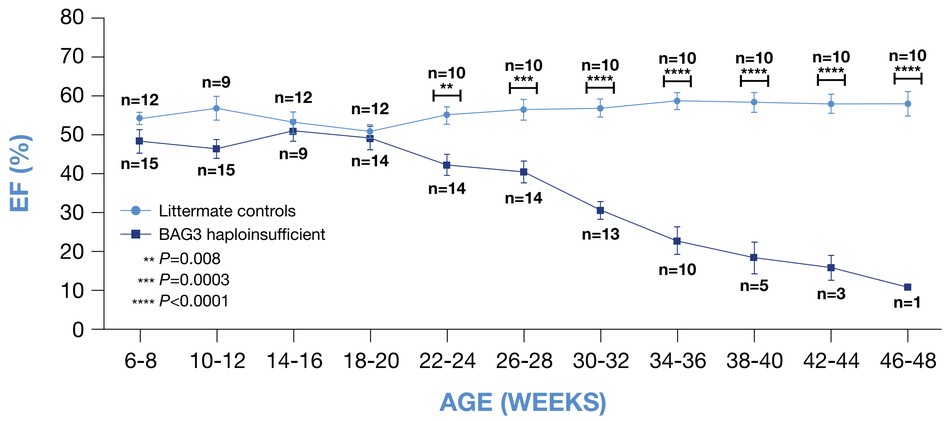
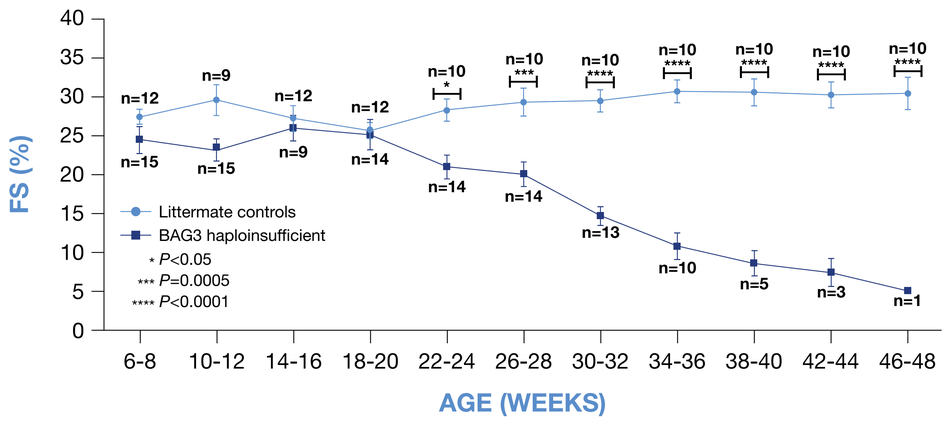


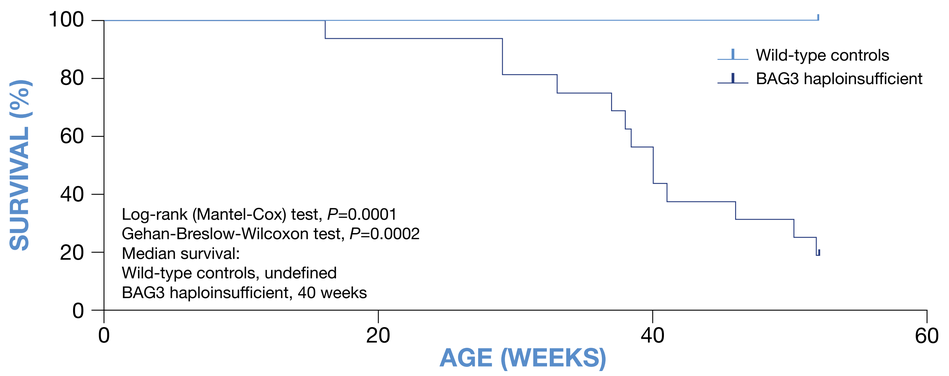
Figure 3. Significantly decreased FS in cBAG3+/- mice



LIFE SPAN

- Cardiac haploinsufficiency of BAG3 led to a significant and progressive increase in mortality. cBAG3+/- mice exhibited a significantly shortened life span, with a median survival of 40 weeks (Figure 4).

Figure 4. Significantly shortened life span in cBAG3+/- mice



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2. Feldman AM, et al. *J Cell Physiol*. 2014;229:1697-1702.

DISCLOSURES

Drs Myers, Shinde, Percival, and Killeen are employees of Renovacor, Inc and have either equity or options in the company. Mr Landesberg is a consultant with Renovacor, Inc. Dr Feldman is the founder of Renovacor, Inc, has equity in the company, and has pending US patents that have been optioned by Temple University to Renovacor, Inc.

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