

NC STATE

Cardiac Genetics Part I Genetics of Myocardial Disease

Conti Symposium 2025

Joshua Stern, DVM, PhD, DACVIM (Cardiology)
Associate Dean for Research & Graduate Studies

Stern Lab

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Disclosures

- NC State Operates a Cardiac Genetic Testing Service
- Scientific Advisory Board Member – TriviumVet
- Consultant & Collaborator Myokardia Inc. / Bristol Myers Squibb
- Relevant Sponsored Research Projects
 - Cytokinetics, Inc.
 - TriviumVet
 - Edgewise Therapeutics

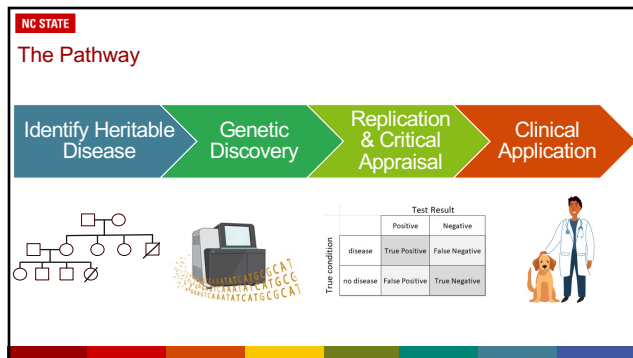
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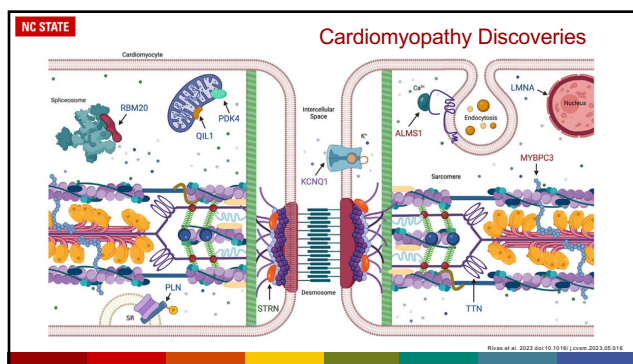
Outline

- Genetic discovery & clinical utilization – the process
- Feline hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Rare / other conditions

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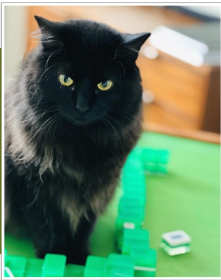
Reported Variants / Available Tests

Disease	Gene Name	Protein/DNA Change	Mutation Type	Species	Breed	MOI	Proposed Pathogenesis
DCM (4)	RYR2 (DCM3)	deletion	splice variant	Dog	Doberman + some others	Recessive	Role in Action Potential and Present in Intercalated Disc
DCM (3)	PRKAA2	splice variation	-	Dog	Doberman + some others	Dominant	Myocardial energy homeostasis
DCM	<i>PKP4</i>	16-bp 5' intron 10 deletion	Splice site deletion	Dog	Doberman	Autosomal dominant	Reduced metabolic flexibility, increased reliance on glycolytic energy production
	<i>TTN</i>	G8898R	Misense	Dog	Doberman	Autosomal dominant	Myofiber disarray, z-disk streaming, decreased protein springing
	<i>RBM20</i>	22-bp exon 11 deletion	Misense	Dog	Standard Schnauzer	Autosomal recessive	Altered intracellular calcium handling, altered cardiac transcript splicing
	<i>PLN</i>	R9H	Misense	Dog	Weiß Springer Spaniel	Autosomal dominant	Decreased myocardial calcium uptake
	<i>QIL1</i>	G109S	Misense	Dog	Rhodesian Ridgeback	Autosomal dominant	Hypertrophic mitochondria, irregular cristae formation, mitochondrial destabilization
	<i>LMNA</i>	D576T	Frameshift	Dog	Nova Scotia Duck Tolling Retriever	Autosomal recessive	Soft myocardial nuclear structures, altered chromatin organization, ventricular arrhythmogenesis
ARVC	<i>STRN</i>	8-bp 3' UTR deletion	3' UTR deletion	Dog	Boxer	Autosomal dominant	Myocardial infiltration of adipocytes and fibrosis, ventricular arrhythmogenesis
	<i>ARVC2^g</i>	-	Misense	Dog	Boxer	Autosomal dominant	-
LQTS	<i>KCNQ1</i>	T377K	Misense	Dog	English Springer Spaniel	Autosomal dominant	Prolonged QT interval, ventricular arrhythmogenesis

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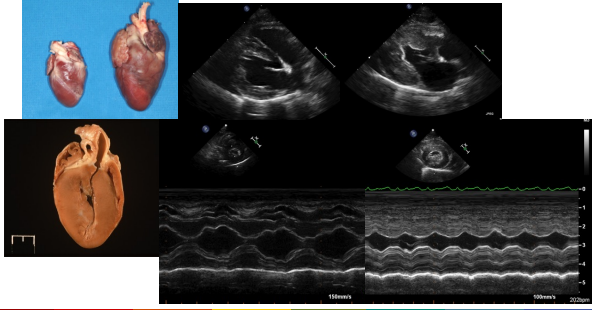
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Hypertrophic Cardiomyopathy



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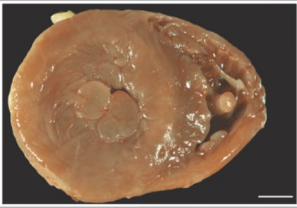


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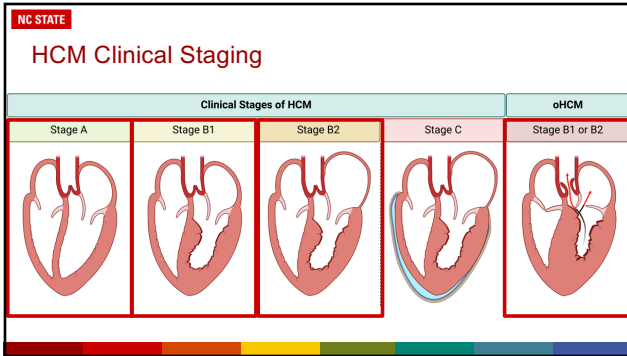
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HCM – Common & Without Effective Therapy

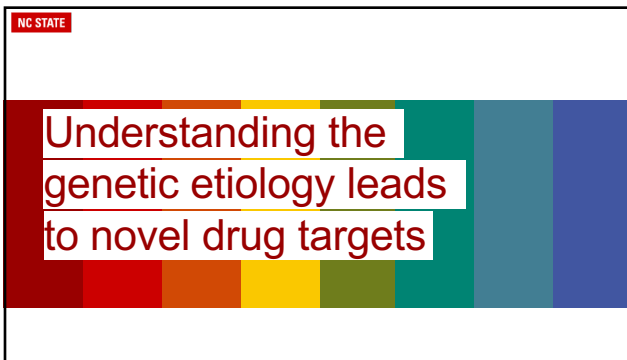
- ~1 in 7 cats with age-related penetrance
- Impact of great disparity in disease expression
- Impact of genetic heterogeneity
- Lack of ideal translational model organisms
- Adverse outcome frequency dictates large study sizes



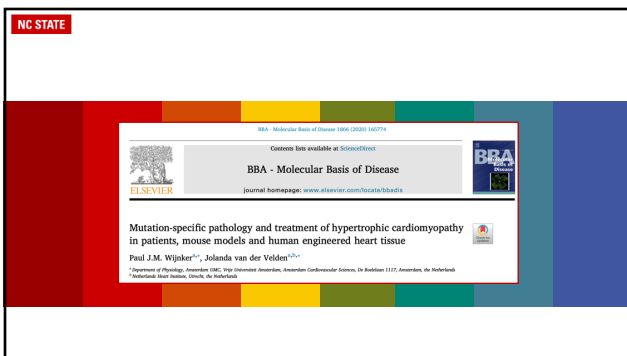
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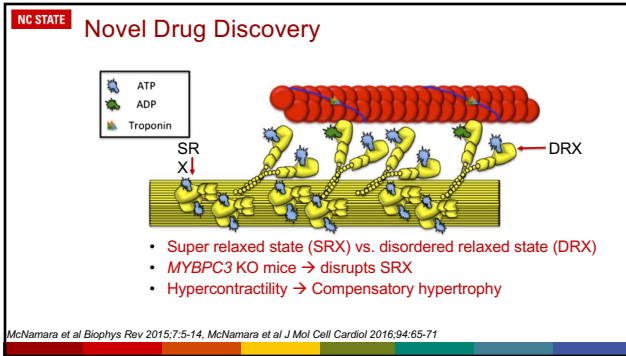
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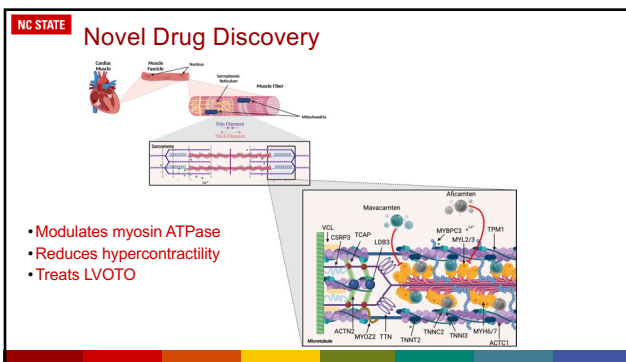
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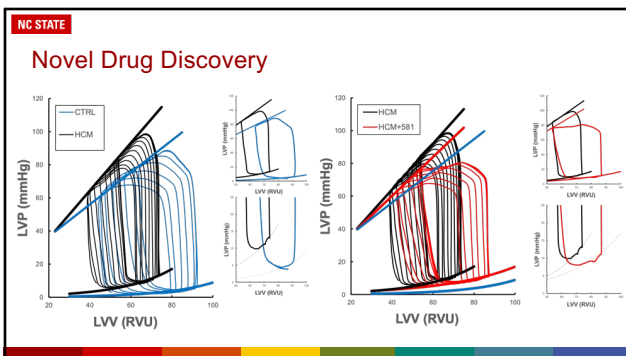
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NC STATE Novel Drug Discovery

PLOS ONE

RESEARCH ARTICLE

A Small Molecule Inhibitor of Sarcomere Contractility Acutely Relieves Left Ventricular Outflow Tract Obstruction in Feline Hypertrophic Cardiomyopathy

Joshua A. Stern¹, Svetlana Markova¹, Yu Li^{1,2}, Jan B. Klein^{1,3}, Peter J. Passan⁴, Marc J. Chavakis⁵, Eric M. Cooper^{1,6}, Samantha P. Harris^{1,7}

EDG-7500 (EDG-002), A FIRST-IN-CLASS TARGETED SARCOMERE REGULATOR THAT PRESERVES INTRINSIC MYOSIN-MOTOR FUNCTION, NORMALIZES SYSTOLIC FUNCTION AND ELIMINATES LVOT OBSTRUCTION IN CATS WITH HYPERTROPHIC CARDIOMYOPATHY

Kaplan, A.C., Cullinan, D.F., Dunbar, M., Johnston, M.P., Tong, J., Hwang, J.H., Schaefer, S.J., Poon, V.H., Jerng, C., Guller, A., Harris, S.P., Stern, J.A., and Roy, C.C., Hwang, A.Y., Eisenberg, M.R.

SHORT COMMUNICATION

Pharmacokinetics of a single dose of Aficamten (CK-274) on cardiac contractility in a A31P MYBPC3 hypertrophic cardiomyopathy cat model

Ashley N. Sharpe¹ | Maureen S. Oldach¹ | Joanna L. Kaplan¹ | Victor Rivas² | Samantha L. Kovacs³ | Darren T. Hwee⁴ | Bradley P. Morgan⁵ | Fady I. Malik⁶ | Samantha P. Harris⁷ | Joshua A. Stern¹

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CAMZYOS
[mavacamten]

STUDY RESULTS | **NEW OFFERS**

CAMZYOS IMPROVED SYMPTOMS AND THE ABILITY TO BE ACTIVE

ScienceAdvances

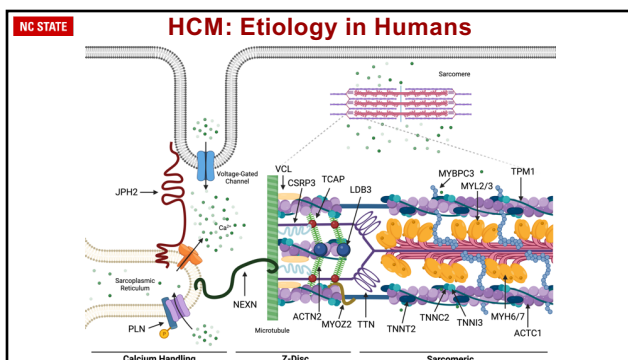
Mavacamten, a precision medicine for hypertrophic cardiomyopathy: From a motor protein to patients

Green et al. 2023 doi:10.1126/science.adv3456

Group	Fractional Shortening (%)
Untreated	~15
Untreated + Mavacamten	~35
Untreated + Placebo	~15
Untreated + Placebo + Mavacamten	~35

Group	Fractional Shortening (%)
Untreated	~15
Untreated + Mavacamten	~35
WT	~35

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A substitution mutation in the myosin binding protein C gene in ragdoll hypertrophic cardiomyopathy
R820W PATHOGENIC VUS
 Kathryn M. Meurs^{1*}, Michelle M. Norgard², Martina M. Ederer³, Kristina P. Hendrix⁴, Mark D. Kittleson⁵

A cardiac myosin binding protein C mutation in the Maine Coon cat with familial hypertrophic cardiomyopathy
A31P PATHOGENIC VUS
 Kathryn M. Meurs^{1*}, Ximena Sanchez², Ryan M. David³, Neil E. Bowles⁴, Jeffrey A. Towbin⁵, Peter J. Reiser⁶, Judith A. Kittleson⁷, Marcia J. Muraw⁸, Keith Dryburgh⁹, Kristin A. Macdonald¹⁰ and Mark D. Kittleson^{1*}

A deleterious mutation in the ALMS1 gene in a naturally occurring model of hypertrophic cardiomyopathy in the Sphynx cat
VUS
 Andrea M. Kessler¹, Michael S. Gorman², David G. Peterson³, Joseph C. Pridmore⁴, David L. Manning⁵, Ashley East⁶, Bruce W. Knorr⁷, Gary B. Anderson⁸, Steven C. Colbran⁹ and Sandra Yu^{1*}

A novel homozygous intronic variant in TNNT2 associates with feline cardiomyopathy
VUS
 James M. McManus^{1*}, Roger Schubert², Robert C. Becker³ and Gabriel Rodriguez⁴

Association of A31P and A74T Polymorphisms in the Myosin Binding Protein C3 Gene and Hypertrophic Cardiomyopathy in Maine Coon and Other Breed Cats
A74T - VUS
 G. Meis, C. Schonek, K. Weber, H. Kuchenhof, K. Hartmann
 First published: 07 May 2016 | <https://doi.org/10.1111/j.1469-7580.2016.01814.x> | CiteSpace 4.7

A feline orthologue of the human MYH7 c5647G>A (p.(Glu1883Y)) variant causes hypertrophic cardiomyopathy in a Domestic Shorthair cat
RARE - LIKELY PATHOGENIC VUS
 Tom Schipper¹, Marie Van Pelt², Lucien Bessot³, Franck Sirey⁴, Rémy Tranchesi⁵, Ben J. Benschop⁶ and J. Posthuma^{1*}

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What about all the other cats?

- Large-scale across-breed WGAS / targeted sequencing studies underway
- Search for common variants of interest
- Search for rare variants in families
- Identify modifying variants tied to outcomes
- What should the control group look like?

99 LIVES
 College of Veterinary Medicine

D22FE-027, Unraveling the genetics of feline hypertrophic cardiomyopathy: a novel multiomics approach
 n=150 cases; 25 controls
 Papadakis, Skovas, Stern et al.

Identification of novel genetic variants associated with feline cardiomyopathy using targeted next-generation sequencing
 n=73
 Ruffin, Nicco, Marini, Phares et al. | <https://doi.org/10.1093/qjz/000>

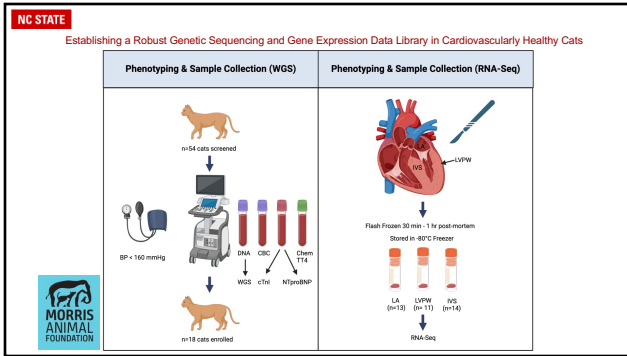
Novel variants of interest were identified in sarcomeric and non-sarcomeric genes
 Variants were shared between a HCM and RCM cohort suggesting pleiotropic effects are possible

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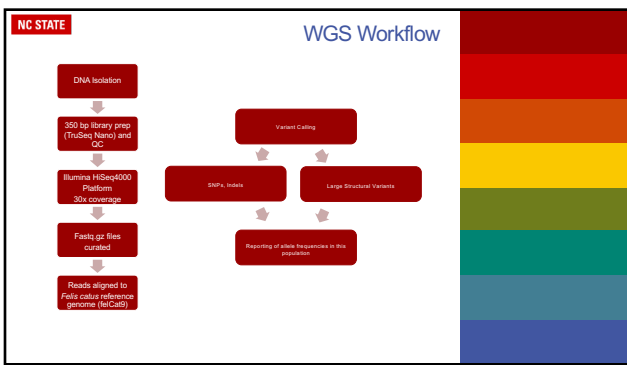
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Why Do So Many Reported Associations Become VUS?

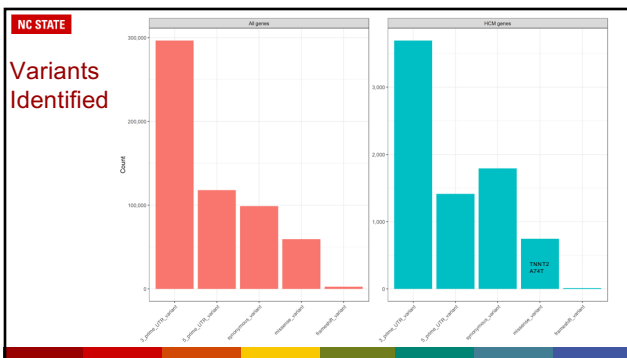
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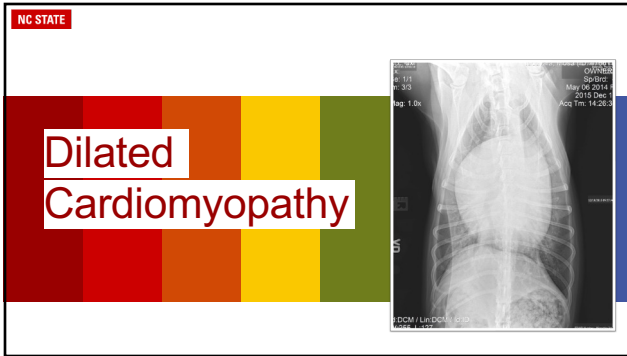
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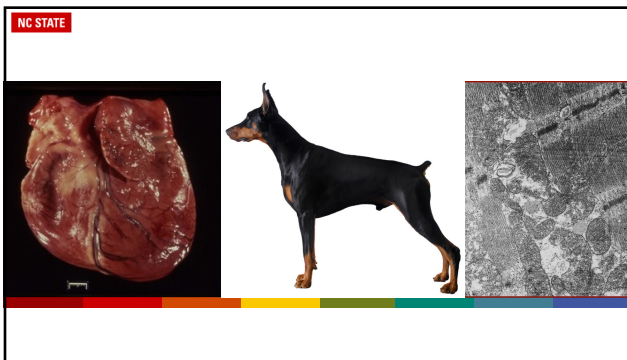
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Reported Variants / Available Tests

Disease	Gene Name	Protein/DNA Change	Mutation Type	Species	Breed	MOI	Proposed Pathogenesis
DCM (4)	RNF207 (DCM3)	deletion	splice variant	Dog	Doberman + some others	Recessive	Role in Action Potential and Present in Intercalated Disc
DCM (3)	PRKAA2	splice variation - candidate variants yet to be determined		Dog	Doberman + some others	Dominant	Myocardial energy homeostasis
DCM	<i>POK4</i>	16-bp 5' intron 10 deletion	Splice site deletion	Dog	Doberman	Autosomal dominant	Reduced metabolic flexibility, increased reliance on glycolytic energy production
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LQTS	<i>KCNQ1</i>	T377K	Misense	Dog	English Springer Spaniel	Autosomal dominant	Prolonged QT interval, ventricular arrhythmogenesis

Nickerson et al. 2022 doi:10.1186/s13075-023-01921-3 Rowe et al. 2023 doi:10.1016/j.cvm.2023.05.010

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Opportunities – RBM20 DCM

Sci Transl Med 2022 November 23; 14(672): ead61633. doi: 10.1126/scitranslmed.2022.01633

Precise genomic editing of pathogenic mutations in RBM20 rescues dilated cardiomyopathy

Takako Makiyama^{1,2}, Yu Zhang^{1,2,3}, Miao Gu^{1,2,3}, Hai Li^{1,2,3}, Efrain Sanchez-Ortiz^{1,2,3}, James H. Mckelvey^{1,2,3}, Shui Han^{1,2,3}, Jiwang Kim¹, Kaitian Chen¹, Lin Xu¹, Rhonda Bassett-Duby^{1,2,3}, Eric N. Olson^{1,2,3}

- Precise genome editing
- Corrected phenotype
- Returned myocardial transcription to normal

A

sgRNA: 4 5 33 14 19 20 PAM
 GAGCGGCCACAGTCTCGAAGTCCAAATGAGC
 R36Q E R P Q S R S P M S
 ABEmax base editing
 GAGCGGCCACGGTCTCGAAGTCCAAATGAGC
 Corrected E R P R S R S P M S

D WT R36Q/+ R36Q/R36Q Corrected

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Population Structure/Stratification – Partially Explaining Varied Discovery Across Groups

RESEARCH
 Variation in breeding practices and geographic isolation drive subpopulation differentiation, contributing to the loss of genetic diversity within dog breed lineages

PLoS
 The impact of a fine-scale population stratification on rare variant association test results

a European countries
 USA

b Italian Greyhound K = 4
 European countries
 USA

c European countries
 USA

d Shetland Sheepdog K = 3
 European countries
 USA

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Other / Rare Myocardial Conditions


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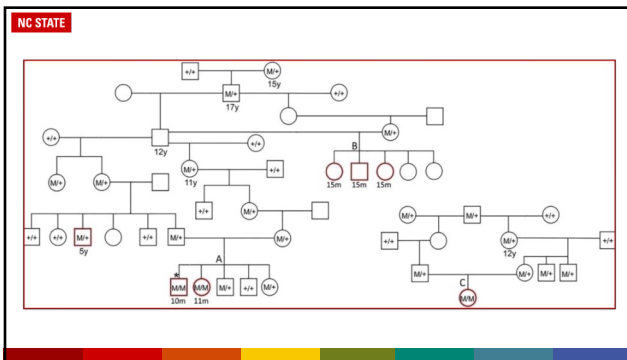
scientific reports

OPEN Naturally occurring canine laminopathy leading to a dilated and fibrosing cardiomyopathy in the Nova Scotia Duck Tolling Retriever

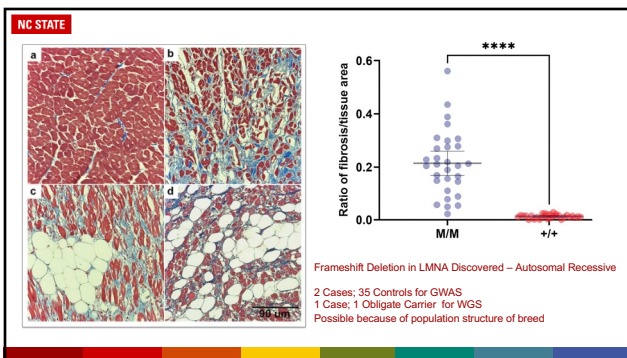
Thomas E. Schumacher^{1,2*}, Benjamin F. Shultz^{1,2}, Adam M. O'Keefe^{1,2}, Kristin L. Binkley^{1,2}, Joshua A. Stein^{1,2}, Susan E. Kessler^{1,2}, Ronald W. L. Li^{1,2}, Melissa E. Madigan^{1,2}, Matthew Chimento^{1,2}, www.ncbi.nlm.nih.gov/pmc/articles/PMC4388882/



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Questions?

NC STATE UNIVERSITY
College of Veterinary Medicine

Joshua A. Stern, DVM, PhD, DACVIM (Cardiology)
jastern@ncsu.edu

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