RISK ALLELE FREQUENCY & GENOMIC HEALTH IN 1700 DOBERMANS

PRELIMINARY FINDINGS FROM THE DOBERMAN DIVERSITY PROJECT

Samantha Amey-Gonzalez[1,3], Sophie K. Liu[2], Robin Loreth[2], Andrea Slavney[3], Aaron J. Sams[3], and Erin T. Chu[3,4]

1 Current Address:One IDEXX Drive Westbrook, Maine 04092 ; 2 The Doberman Diversity Project; 3 Embark Veterinary, Inc, 186 Lincoln St Fl 6, Boston, MA 02111 * Presenting author, chue@embarkvet.com

INTRODUCTION

- The Doberman Pinscher (Doberman or Dobermann) is a popular working dog breed worldwide, valued for its intelligence and drive
- Developed in Germany, historically thought to trace back to a single male lineage
- Several bottlenecks (WW1, WW2) and popular sire effect have resulted in breed predispositions for disease and concern for long-term breed survival
- The Doberman Diversity Project (DDP), in partnership with Embark Vet, Inc, is committed to genetically-informed breed preservation

DOBERMAN DISEASE PREDISPOSITIONS

Acquired Hypothyroidism
- Estimated 10% of adult Dobermans affected compared to 1-2% general dog population (Beier *et al*, 2015)
- Annual thyroid panel recommended

Courtesy of Robin Loreth

Chronic Active Hepatitis
- Widely thought to be underdiagnosed
- Roughly 20% of a random population diagnosed with subclinical liver disease (Mandigers *et al* 2004)

Dilated Cardiomyopathy
- >50% of adult Dobermans
- Two mutations: DCM1, DCM2
- Both dominant with incomplete penetrance (40% and 50% respectively)
- DCM1 + DCM2 are 60% predictive
- Annual Holter monitoring and echocardiograms recommended

Craniocervical Spondylomyelopathy
(Wobbler Syndrome)
- Affects up to 5% of Dobermans (anecdotal)
- Variable age of onset makes selective breeding difficult

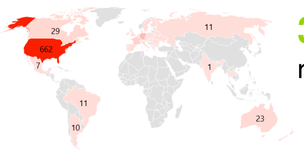
METHODS

- gDNA was collected using Genotek PG-100 saliva swabs and extracted using standard methods
- Dogs were genotyped on the custom Embark SNP chip, based on the Illumina CanineHD 173K Beadchip array
- Clinical and demographic data were collected via the DDP website, email, and external survey platforms
- Ancestry and linkage analyses were performed as described (Deane-Coe *et al*, 2018)
- F_{ROH} was calculated as described (Sams *et al*, 2018)

RESULTS

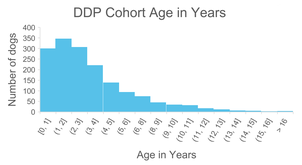
THE DDP COHORT BY THE NUMBERS

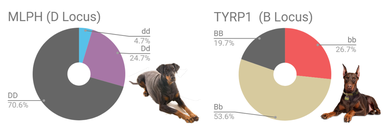
55% female
45% male
85% intact



33 countries represented

Map reflects Jan 2019 numbers

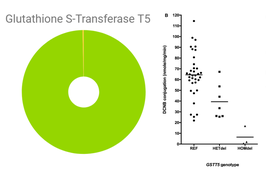




INSIGHTS INTO DISEASE ALLELE FREQUENCY WITH MULTIPLEXED GENOTYPING

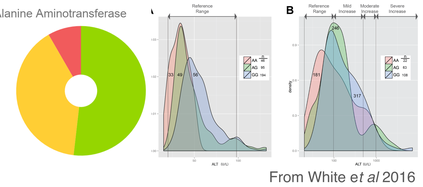
Health Risk	Citation	MAF
DCM1	Meurs *et al* 2012	0.193
DCM2	Meurs *et al* 2019	0.289
DvDOB	Webb *et al* 2019	$4.00e10^{-2}$
Type I vWD	Brooks *et al* 2000	0.271
DM	Awano *et al* 2009	$8.67e10^{-4}$
MDR1	Mealey *et al* 2000	$2.60e10^{-3}$
HUU	Bannasch *et al* 2008	$2.89e10^{-4}$

All MAF calculated using n > 1700 except DvDob (n = 886)



Ongoing research; no correlation of GST to TCC, cyclophosphamide toxicity, or LSA risk

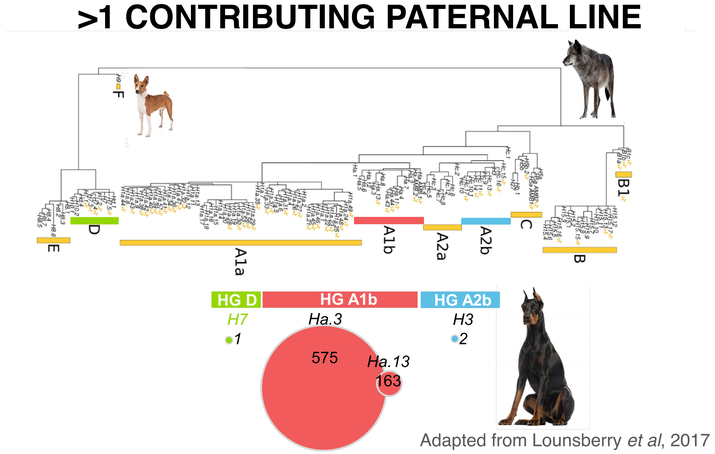
From Craft *et al* 2017



From White *et al* 2016

Legend WT WT/Mut Mut/Mut

CHRY HAPLOTYPE ANALYSIS SUGGEST >1 CONTRIBUTING PATERNAL LINE

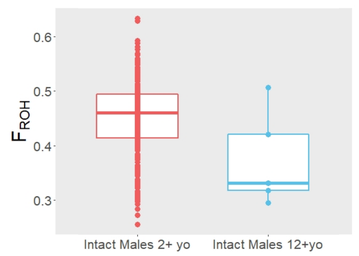


Adapted from Lounsberry *et al*, 2017

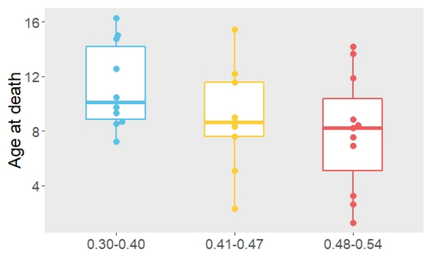
DOBERMAN DIVERSITY PROJECT™ embark

LOWER F_{ROH} FAVORS LONGER LIFESPANS

F_{ROH} OF LIVING INTACT MALES BY CURRENT AGE



AGE OF REPORTED MORTALITIES BY F_{ROH}



INFORMATIVE RISK ANALYSIS OF DCM1 & DCM2 REQUIRES AGING COHORT

		FULL DDP COHORT (n=1734)			DIAGNOSED DCM CASES (n=28)		
		DCM1			DCM1		
		NN	NM	MM	NN	NM	MM
DCM2	0	36.50%	17.30%	1.32%	39.29%	17.86%	3.57%
	1	20.70%	9.99%	1.44%	7.14%	14.29%	3.57%
	2	7.60%	4.13%	0.87%	3.57%	10.71%	0.00%

FUTURE DIRECTIONS

- The DDP cohort represents one of the largest Doberman dataset in the world
- High-quality high-density genotyping reveals low frequency of uncommon disease risk variants, presents opportunity for genetically informed long-term breed management
- Ultimately, we intend to identify genomic regions associated with longevity or mortality
- As the (currently youth-skewed) DDP cohort ages, analyses for *de novo* discovery and risk allele penetrance will gain greater power

COLLABORATE WITH US!

Learn more at dobermandiversityproject.org and embarkvet.com/research