





**September 29, 2020**

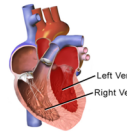
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Hill's Pet Nutrition and Embark Veterinary

**Investigation of potential genetic interactions behind dilated cardiomyopathy (DCM) in dogs via a genome-wide association study (GWAS)**



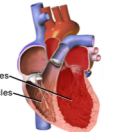
**Veterinarians have observed an increase in the number of dilated cardiomyopathy (DCM) in dogs**

**Normal Heart**





Chambers relax and fill, then contract and pump.

**Heart with Dilated Cardiomyopathy**



Muscle fibers have stretched. Heart chambers enlarge.





**Certain dog breeds have been observed to be predisposed to dilated cardiomyopathy (DCM)**

Breed	% of cases (N=361)	Breed	% of cases (N=369)
<b>Doberman</b>	7.32%	<b>Doberman</b>	15.9%
<b>Great Dane</b>	7.30%	<b>Boxer</b>	14.4%
<b>Mastiff</b>	6.52%	<b>Great Dane</b>	10.3%
<b>Irish Wolfhound</b>	6.08%	<b>Cocker Spaniel</b>	8.1%
<b>Saluki</b>	5.88%	<b>German Shepherd</b>	6.5%
<b>Mix</b>	0.16%	<b>Mix</b>	0.2%


Bellumori et al, 2013      Martin et al, 2009

DCM cases are more likely to be purebred, though many mixed breed dogs also develop the condition




**Some breeds can be genetically predisposed to heart disease depending upon several identified genetic factors**


**Doberman Pinscher**  
*DCM1*: PDK4 mutation (Meurs et al 2012)  
*DCM2*: TTN mutation (Meurs et al 2019)  
 Autoimmune component (Wess et al 2019)




**Portuguese Water Dog**  
**Juvenile DCM**  
 UPenn - unpublished



**Boxer**  
**ARVC**  
 Striatin mutation (Meurs et al 2012)



**Cocker Spaniel**  
**Taurine responsive DCM**  
 The MUST Study (Kittleson et al, 1997)



**\*DCM 1 and 2:** Embark has identified both of these mutations in non-Dobermans; association with disease risk in these dogs is as of yet unknown.

## More than 50 genetic loci contributing to the development of DCM have been identified in humans

1 Genetic cardiac disorder  
 2 Gene associated with rare phenotype  
 3 Gene associated with late phenotype  
 4 Gene associated with these phenotypes


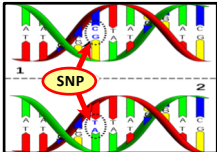
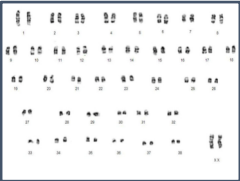
**DCM in dogs...**

- Likely polygenic
- Likely more genetic variants yet to be discovered

<http://www.medicinalgenomics.com/human-exome-sequencing>

## We explore differences in DNA called Single Nucleotide Polymorphisms (SNPs)

99.9% of dog DNA is similar....



...However, at certain nucleotides, we can find polymorphisms, or differences

## We study SNPs to understand the difference between health and disease in genome-wide association (GWAS)

We compare a patient population with a control (non-disease) population

large patient sample      large control sample

simultaneous genotyping of > 500,000 SNPs

Genes at these loci may be important in this condition!!

"Manhattan plot"

## Complementary strengths comprise the Hill's-Embarc collaboration for understanding DCM

**Hill's**  
Transforming Lives™

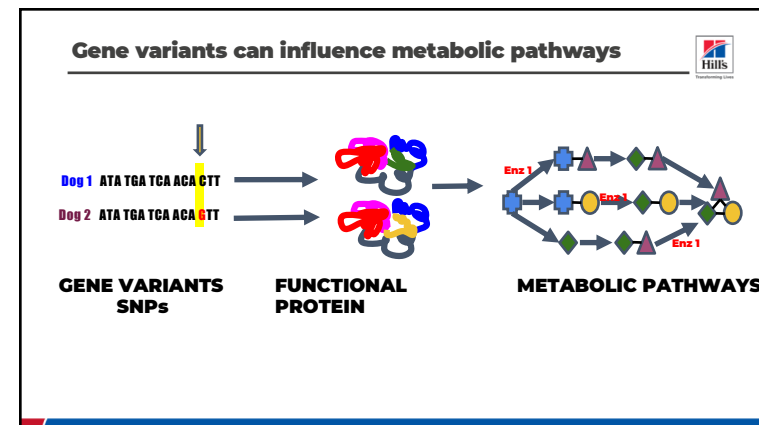
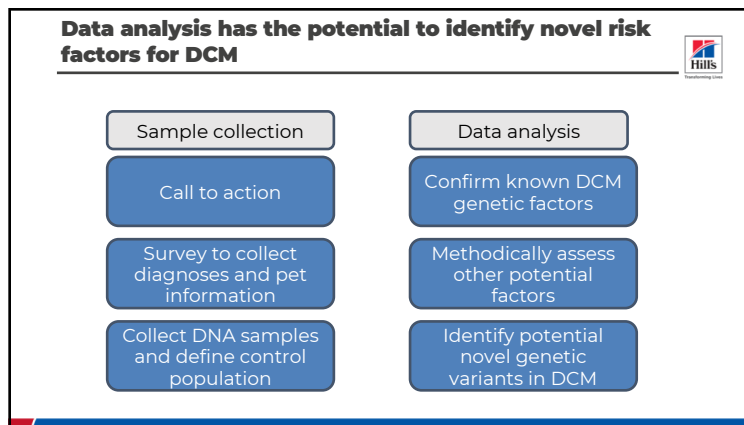
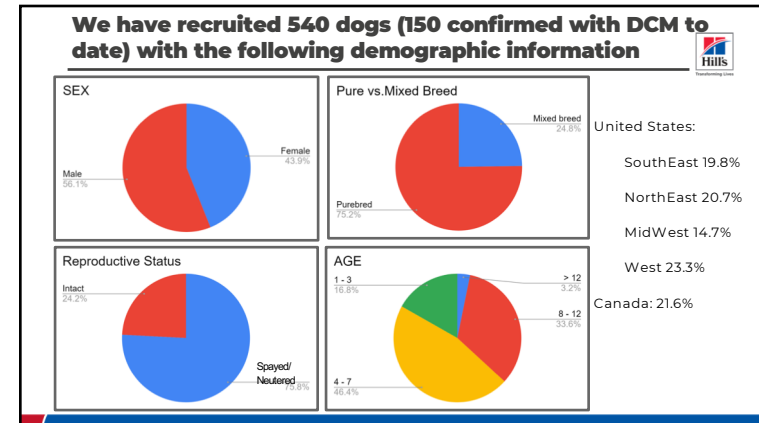
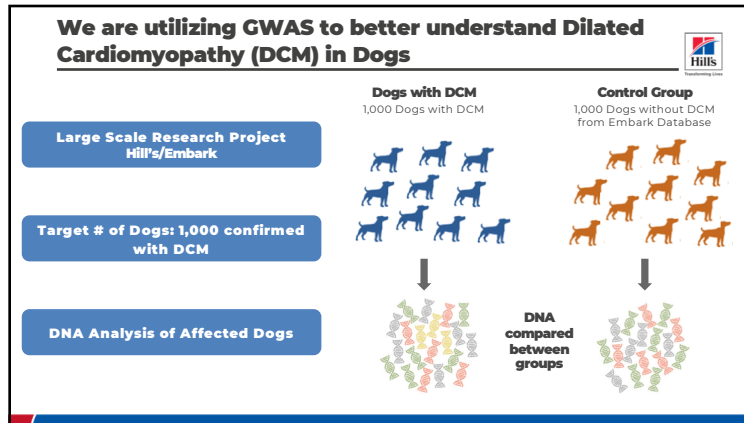
**embarc**

Outreach to Vets and Consumers for Case Enrollment

Expertise in Nutrition Gene Interactions

Capability of DTC Genetic testing

Expertise in Genetic Analysis



## Gene variants are linked to health, disease and nutrition



### Hill's Research:

## Lean body mass and loci containing genes involved in insulin and glucose regulation are associated with calorie intake in dogs

Dennis Edward Jewell Jeffrey A. Brockman Matthew J. Huentelman Christopher B. Kingsley  
Ashley L. Siniard Ryan Richholt Jean A. Hall

First published: 01 April 2013 [https://doi.org/10.1096/fasebj.27.1\\_supplement.345.3](https://doi.org/10.1096/fasebj.27.1_supplement.345.3)

## Many nutrients are involved in heart function



Vitamins	Minerals	Amino Acids	Fatty Acids
Thiamine Riboflavin Niacin Pyridoxine Folate Cobalamin Vitamin C Vitamin D Vitamin E Choline Carnitine Glutathione CoQ10	Calcium Cadmium Cobalt Copper Iron Lead Magnesium Manganese Potassium Selenium Sodium Zinc	Arginine Cysteine Methionine Taurine Tryptophan	Long chain fatty acids Short chain fatty acids

- Roles in hundreds of metabolic pathways
- Impact heart structure and function

## In people, GWAS identified potential links to nutrition



## Genome-Wide Association Meta-Analysis of Individuals of European Ancestry Identifies Suggestive Loci for Sodium Intake, Potassium Intake, and Their Ratio Measured from 24-Hour or Half-Day Urine Samples

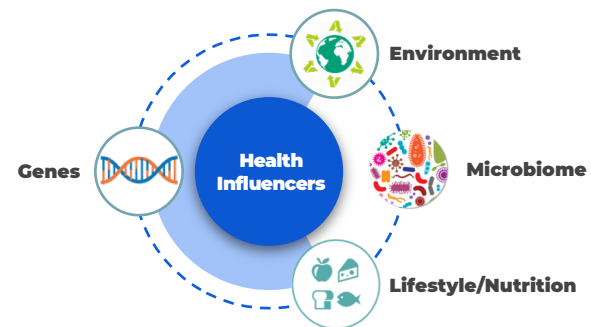
Minjung Kho ✉, Jennifer A Smith, Niek Verweij, Lulu Shang, Kathleen A Ryan, Wei Zhao, Erin B Ware, Ron T Gansevoort, Marguerite R Irvin, Jung Eun Lee ... Show more

The Journal of Nutrition, nxaa241, <https://doi.org/10.1093/jn/nxaa241>

Published: 25 August 2020 Article history ▼

**Multiple SNPs found associated with Sodium and Potassium intake that show promise for better management of blood pressure and cardiovascular diseases**

## Gene activity/expression is influenced by many factors



## Considering gene expression with GWAS results will lead to deeper understanding

**Hill's Research:**

**Identification of *gene changes* in geriatric dogs fed a test or control *food***

Nolan Z. Frantz, Ryan M. Yamka, Kim G. Friesen, Xiangming Gao, Samer Al-Murrani

First published: 01 April 2007 <https://doi.org/10.1096/fasebj.21.6.A744-c>

**Identification of *genes altered* with growth phase *nutrition* in growing puppies**

Nolan Z. Frantz, Steve C. Zicker, Kim G. Friesen, Ryan M. Yamka, Xiangming Gao, Samer Al-Murrani

First published: 01 April 2007 <https://doi.org/10.1096/fasebj.21.5.A4-b>

**FOOD**

**AGE**

**GENDER**

**MEDICATIONS**

**SUPPLEMENTS**


**ACTIVITY**

**SPAY/NEUTER**

**DISEASE**

## So, what could this study lead to?

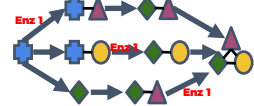
**Gene variants identified**



**DNA-based health condition tests**

**Early monitoring**

**Metabolic pathways involved**




**New diagnostic tests for early detection**

**Nutrient relationships**

- Vitamins
- Minerals
- Amino Acids
- Fatty Acids

**Ways to aid in management**

**Strategies for health**



**embark**

**OUR MISSION**

To help enrich and lengthen the special relationships between people and their pets.

Combat disease in all pets through the power of genomics.

