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

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

<table>
<thead>
<tr>
<th>Breed</th>
<th>% of cases (N=361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doberman</td>
<td>7.32%</td>
</tr>
<tr>
<td>Great Dane</td>
<td>7.30%</td>
</tr>
<tr>
<td>Mastiff</td>
<td>6.52%</td>
</tr>
<tr>
<td>Irish Wolfhound</td>
<td>6.08%</td>
</tr>
<tr>
<td>Saluki</td>
<td>5.88%</td>
</tr>
<tr>
<td>Mix</td>
<td>0.16%</td>
</tr>
</tbody>
</table>

Breed | % of cases (N=369) |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Doberman</td>
<td>15.9%</td>
</tr>
<tr>
<td>Boxer</td>
<td>14.4%</td>
</tr>
<tr>
<td>Great Dane</td>
<td>10.3%</td>
</tr>
<tr>
<td>Cocker Spaniel</td>
<td>8.1%</td>
</tr>
<tr>
<td>German Shepherd</td>
<td>6.5%</td>
</tr>
<tr>
<td>Mix</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

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

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

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 (Weiss et al 2019)

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  - UPenn - unpublished

- **Boxer**: ARVC
  - Striatin mutation (Meurs et al 2002)

- **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.

DCM in dogs...
- Likely polygenic
- Likely more genetic variants yet to be discovered

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

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

Outreach to Vets and Consumers for Case Enrollment

Capability of DTC Genetic testing

Expertise in Nutrition

Gene Interactions

Expertise in Genetic Analysis
We are utilizing GWAS to better understand Dilated Cardiomyopathy (DCM) in Dogs

**Large Scale Research Project**
Hill’s/Embark

**Target # of Dogs:** 1,000 confirmed with DCM

**DNA Analysis of Affected Dogs**

**Control Group**
1,000 Dogs without DCM from Embark Database

**Dogs with DCM**
1,000 Dogs with DCM

**DNA compared between groups**

**Data analysis**

**Call to action**
Survey to collect diagnoses and pet information
Collect DNA samples and define control population

**Sample collection**
Confirm known DCM genetic factors
Methodically assess other potential factors
Identify potential novel genetic variants in DCM

**Gran variants can influence metabolic pathways**

**Gene variants**
SNPs
FUNCTIONAL PROTEIN
METABOLIC PATHWAYS

**Dog 1**
ATA TGA TCA ACA CTT

**Dog 2**
ATA TGA TCA ACA GCTT

**Data analysis has the potential to identify novel risk factors for DCM**

**SEX**

**Pure vs. Mixed Breed**

**Reproductive Status**

**AGE**

United States:
- SouthEast 19.8%
- NorthEast 20.7%
- MidWest 14.7%
- West 23.3%
Canada: 21.6%

We have recruited 540 dogs (150 confirmed with DCM to date) with the following demographic information

- SouthEast 19.8%
- NorthEast 20.7%
- MidWest 14.7%
- West 23.3%
- Canada: 21.6%

Data analysis has the potential to identify novel risk factors for DCM
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. Broekman  Matthew J. Huertelman  Christopher B. Kingsley  Ashley L. Sniard  Ryan Richott  Jean A. Hall

First published: 01 April 2013 https://doi.org/10.1093/fatsaj/27.1_supplement.345.3

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Many nutrients are involved in heart function

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

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

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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 Woo  Jennifer A Smith  Hesk Vennewij  Lulu Zhang  Kathleen A Ryan  Wei Zhao  Erin B Ware  Ron T Gansevoort  Marguerite R Irvin  Jung Eun Lee ... Show more


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

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Gene activity/expression is influenced by many factors

- Health Influencers
- Environment
- Microbiome
- Lifestyle/Nutrition

- Genes

- Health Influencers

- Environment

- Microbiome

- Lifestyle/Nutrition
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

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

**Hill’s Research**

**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.

**So, what could this study lead to?**

- **Gene variants identified**
- **Metabolic pathways involved**
- **Nutrient relationships**
  - Vitamins
  - Minerals
  - Amino Acids
  - Fatty Acids

- **DNA-based health condition tests**
- **New diagnostic tests for early detection**
- **Ways to aid in management**
- **Strategies for health**

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