TWO GENETIC DISEASES IN TOY MANCHESTER TERRIERS
Genetics Review

- Cell
- Genome
- Chromosomes
- DNA
Genetics Review

- DNA
- Nucleotide
- Gene
- Proteins
Homozygous, Heterozygous, What?!
Mutations

Original sequence

Point mutation
Question?
XANTHINURIA: INTRODUCTION
Where does xanthine come from?

- Purine metabolism
  - Xanthine formation

- 2 enzymes
  - XDH
  - MOCOS

- Loss of function of enzymes
  - Increased urine levels

Diagram:

```
Purines  ↓
  MOCOS + XDH  ↓
  Xanthine  ↓
  MOCOS + XDH  ↓
  Allantoin
```
Xanthinuria

- Two subtypes of hereditary xanthinuria
  - Type I - XDH
  - Type II - MOCOS
Xanthine Urolithiasis

- Xanthine relatively insoluble
  - Uroliths (stones)

- Painful & obstructive

- Kidney disease

Minnesota Urolith Center
Recommendations

- No treatment!
- Increased water intake
- Low purine diet
  - Prescription
STUDY DESIGN

GENETIC INVESTIGATION OF CANINE XANTHINE UROLITHIASIS
Aim:

Uncover mutations underlying risk for canine xanthine urolithiasis via sequencing of XDH and MOCOS in genomic DNA from affected dogs.
Affected Dogs and Test Populations

- Six dogs affected with xanthine urolithiasis
  - 2 Cavalier King Charles Spaniels (CKCS)
  - 2 Toy Manchester Terriers (TMT)
  - 1 mixed breed dog
  - 1 English Cocker Spaniel

- DNA extracted

- Sanger sequencing
TOY MANCHESTER TERRIERS

XANTHINURIA TYPE IIα
Xanthinuria Type IIa

- No mutations in XDH
- Mutation in MOCOS (last bp)
  - Affected dogs homozygous
- Mutation predicted to affect splicing
  - Exon skipping (in frame)
Splicing?!
Splicing?
Splicing?
Exon Skipped

MOCOS

Exon 1

Exon 2

Exon 2 IS SKIPPED

Exon 3-15

MOCOS – Exon 2
Aberrant Splicing

- MOCOS Protein Prediction (Phyre2)
Xanthinuria Type IIa - Frequency

Test Population

- 241 Toy Manchester Terriers
  - 194 clear of the mutation
  - 44 carriers = ~18%
  - 6 homozygous
  - 3 with no history of stones!
Three Homozygous “Controls”

- 2 spayed females
- 1 male puppy
- Relatives of affected
What about those other breeds?

Cavalier King Charles

Mixed Breed
Questions??

I MUSTACHE YOU
A QUESTION
JUVENILE DILATED CARDIOMYOPATHY: INTRODUCTION
JDCM in Toy Manchester Terriers

- **Young age**
  - 10 weeks to 1 year

- **Appear healthy**
  - Males cryptorchid

- **Death sudden**
  - Anesthesia/surgery
  - Exercise

- **Presumed fatal arrhythmia**
Histology and Necropsy

- Mild enlargement of heart
- Degeneration and scarring of tissue
- Inflammation of tissue

- Mild
- Widespread
Genome Wide Association Study

- Numerous cardiomyopathy genes

- Compare cases to controls and look for markers that are in a higher frequency in cases.
  - 170K “markers”

- 12 Cases
- 36 Controls
- Genes associated with cardiomyopathy
- Potassium Channels
  - Regulate the electrical activity of cardiac muscle cells
  - Dysfunction can cause arrhythmias
JDCM in Toy Manchester Terriers - Frequency

- Test Population
  - 191 Toy Manchester Terriers
    - 133 clear of the mutation
    - 43 carriers = ~23%
    - 15 homozygous
TESTING & BREEDING DECISIONS
Submitting Samples

- Types
  - Blood
  - Cheek Swab
  - Dew Claw & Tail Docking
  - Semen

- Information and submission forms can be found on our websites:
  - http://z.umn.edu/jdcm
  - http://z.umn.edu/xanthinuria
Submitting Cheek Swabs

- Place completed swabs directly into a paper envelope and seal it.
- Submission form and envelope with swabs go in a larger envelope.
- Complete instructions on our websites
Test Results

University of Minnesota
Juvenile Dilated Cardiomyopathy (JDCM)

Canine Genetics Laboratory
295 Animal Science/Veterinary Medicine
1988 Fitch Avenue
St. Paul, MN 55108

Sample Number: TMT 000
Owner: TMT Fan
Address

Report Generated: Sep 16, 2016

Registered Name: Cutest TMT Ever
Breed: Toy Manchester Terrier

With Registration Number:
Sex: F
DOB: 09/16/16

Permanent ID:
ID verified:

Juvenile Dilated Cardiomyopathy (JDCM): Affected (D/D) - Two copies of the JDCM mutation

Orthopedic Health Foundation (OFA) Database:
To register these results with OFA, make a copy of this result page, sign below, enclose fee (if any) and send to:
Test Results

- Clear (N/N), Carrier (D/N), Affected (D/D)
- Fully penetrant
- Recessive

- So now what?
Breeding Outcomes

- Clear (N/N) x Clear (N/N) = 100% Clear (N/N)
Breeding Outcomes

- Clear (N/N) x Carrier (D/N) = 50% Clear (N/N), 50% Carrier (D/N)
Breeding Outcomes

- Carrier (D/N) x Carrier (D/N) = 25% Clear (N/N), 50% Carrier (D/N), 25% Affected (D/D)
In Reality…
Breeding Outcomes

- Affected (D/D) x Affected (D/D) = 100% Affected (D/D)
Take Home Message

- 18% carriers for Xanthinuria
- 23% carriers for JDCM
- Can’t just use clear dog
  - small number of breeding stock
- Breed conditions out over many generations
  - Test and replace
  - Keep carriers
Acknowledgements

- Dr. Eva Furrow
- University of Minnesota Canine Genetics Laboratory
  - Katie Minor
  - Kasey Petersen
  - Shannon Larrabee
  - Dr. Jim Mickelson
  - Dr. Jody Lulich
- Veterinarians that submitted samples
  - Dr. JD Foster
  - Dr. Michael Koch
  - Dr. Kate Byrne
  - Dr. Tim Kuhnmuench
- Dr. Paula Henthorn
- Dr. Shannon Martinson
- Dog Biomedical Variant Database Consortium
- Study participants, owners, breeders and breed associations
Questions?