Dwarfism in the Great Pyrenees & The Dwarf Marker Project with UC Davis School of Veterinary Medicine

Submitted by:
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What is Dwarfism?
The Great Pyrenees defect is a disproportionate dwarfism; the primary defect is likely tied to abnormal metabolism within cells that produce and maintain cartilage (which is remodeled into bone during skeletal maturation). An earlier study (Bingel & Sande, 1994) identified two tell-tale signs of chondrodysplasia: (1) chondroitin sulfate in the urine, and (2) dilated rough endoplasmic reticulum in the cytoplasm of chondrocytes. These are hallmark features of non-hormonal dwarfism in humans. Once a region of the dog genome has been linked to this disease, the previously published diagnostics will likely implicate one or a few obvious candidate genes.

What causes Dwarfism?
The cause of dwarfism in Great Pyrenees is unknown, though the origins are thought to be genetic and tied to just one gene. Informal pedigree analysis (owing to unknown ascertainment biases) is strongly suggestive of an autosomal recessive mode of inheritance; it is also consistent with a Mendelian (single gene) heredity. If true, then current approaches in the laboratory would allow mapping the region of the genome that causes Great Pyrenees dwarfism with DNA from just 12-24 affected dogs (and many more unaffected dogs to serve as a 'normal' genetic baseline).

The History of Dwarfism Studies in the Great Pyrenees
The earliest dwarfism in the breed is not known. There are references to dwarfism in breed club newsletters in the early 1970s. Prior to that, there were descriptions of "small" Great Pyrenees in the 1960s, and wonders whether they might be desirable pets.

The first scientific article on Great Pyreenes dwarfism was published in 1994 by Bingel & Sande. A broad range of diagnostics were used to describe the etiology and pathology of the dwarfism. In the late 1990s, Dr. Neff was interested in trying to map the basis of the defect using conventional family-based gene mapping. Unfortunately, the number of DNAs from affected dogs was insufficient (3 dwarfs were collected).

Dwarfism Today
More effective tools are available today that obviate the need for collecting DNAs from 3-generation families. Now, gene mapping can be performed with unrelated dogs. In addition, gene mapping can be performed with blood samples, which can be obtained by your local veterinary clinic. Though cheek swabs can also achieve the same results, Blood Draws are "preferred" due to the fact that they have longevity and more information can be obtained from them. For this Study – Blood Draws are required.

With a sufficient number of DNA samples, researchers will search for a molecular marker that is shared among affected dogs, but that is present at a much lower frequency in unaffected dogs. Dr. Neff's laboratory has mapped four different genes in the past 3 months using this approach, including beagle dwarfism (which is a similar chondrodysplasia).

The Dwarf Marker Project with UC Davis School of Veterinary Medicine

GPCA Participation

Institution: UC Davis School of Veterinary Medicine

Investigator / Researcher: Dr. Mark Neff, PhD
Associate Director
VGL Canine Genetics
UC Davis School of Veterinary Medicine

GPCA Project: Dwarfism Marker – Great Pyrenees

Year Project Began: December 2006

Funding: *NONE REQUESTED*

GPCA Lead Contact: Peggy Watson
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Summary

Disproportionate dwarfism in the Great Pyrenees appears to stem from a single ancestral mutation. The pattern of inheritance is consistent with a simple autosomal recessive inheritance. Whole genome association with a 12:25 design and a 1000-marker genome scanning set is expected to reveal the region of the genome harboring the causative gene. Previously published diagnostics (biochemical and histological) point to a classical chondrodysplasia cause – a mapped region is expected to contain strong candidate genes for effective interrogation. Identifying the causal mutation will translate into a DNA test for breeders that will help eliminate the defect from the breed. The root cause of the disease will shed light on human skeletal dysplasias, thereby improving human health as well.

Investigator

Mark Neff, PhD, is Associate Director at the Center for Veterinary Genetics at the UC Davis School of Veterinary Medicine.

Academic Training

Ph.D. (Yeast Genetics) University of Virginia, Charlottesville 1987-1993
Postdoc (Canine Genetics) University of California, Berkeley 1993-2000

Research Interests

Dr. Neff's interests are three-fold: (1) resolving genetic diseases in the dog to improve canine and human health; (2) understanding the basis of model adaptations in the dog to illuminate the evolution of form and function; (3) probing the brain and behavior with natural variation of selected action patterns (pointing, herding, retrieving, etc).

Selected Publications

Neff MW, Robertson KR, Wong AK, Safra N, Broman KW, Slatkin M, Mealey KL, and Pedersen N. (2004) Breed distribution and history of canine mdr1-1Δ, a pharmacogenetic

mutation that marks the emergence of breeds from the collie lineage. *PNAS*. 2004 Aug;101(32):11725-11730.

Neff MW, Broman KW, Mellersh CS, Ray K, Acland GM, Aguirre GD, Ziegle JS, Ostrander EA, Rine J. (1999) A second-generation genetic linkage map of the domestic dog, Canis familiaris. *Genetics*. 1999 Feb;151(2):803-20.

Purpose of the Dwarfism Marker Project

To identify the causative gene for dwarfism in Great Pyrenees, and to develop a DNA test that breeders can use to eliminate the defect from their bloodlines, and ultimately from the gene pool.

Goals

1) To map the region of the dog genome that harbors the causative gene
1) To identify the causal mutation in the gene
2) To develop a DNA test for genotypic selection

Obstacles

The primary obstacle is collecting DNA samples from enough affected dogs. Dwarfism is not common, so there are not that many dogs available. A secondary obstacle is collecting DNA samples from unaffected dogs while avoiding population stratification.

Ownership of Samples

DNA samples submitted to the VGL Canine Genetics Laboratory at UC Davis are necessarily owned by the University. Dr. Neff is delighted to share or return samples (if the OWNER makes a request), but this can only be done informally. Material (DNA) will get used during the research.

Methods / Procedure

An unbiased, whole genome association will be performed using a conventional case: control experimental design. The minimal sample sizes will be 12 affecteds and 25 unaffecteds, though 25 affecteds would be highly preferable. Using a high-density scanning set (1000 DNA markers), there is a 99% chance of successfully mapping the dwarfism IF it is tied to a single gene defect.

Anticipated Costs

The average manuscript in academic biology costs $200,000 to complete. This is a reasonable anticipated cost for this research (salaries, equipment, and consumables). Because of intramural funding, the VGL Canine Genetics laboratory is NOT requesting funds from the GPCA. Assistance in sample collection is all that is needed.

However, if a region of the dog genome is indeed successfully mapped, the laboratory may ask the GPCA to co-sponsor an AKC-CHF Acorn grant. This funding mechanism involves matching funds from the breed club ($4-6k). These funds are matched by the AKC-CHF ($6k), and are also matched by the UC Davis CCAH ($7500). These funds would be used to identify the causal mutation and develop a DNA test.

Timeline

The research will begin as soon as 12 definitively diagnosed dwarfs have been collected. It is expected that a region would be mapped within 2 months. The discovery of the causal mutation could then take up to one year. Development of a DNA test usually takes 2 months.

Ensuring Confidentiality

All information received by Peggy Watson and Dr. Neff will be held in confidence. To ensure that confidence, when a sample is received, Peggy will assign it an ID #, date, time

and shipping date. She will reference this number on the "Shipping Label" and will make that notation on the Receipt. The form will then be sent to Flo Laicher, Health Committee Chair for reimbursement approval, and she will submit to GPCA Treasurer.

Owners who have their Veterinarian do collections, will contact Peggy prior to and Peggy will coordinate with their Veterinarian and provide them with an ID #. Veterinarians will provide Owner or Peggy with the receipt.

In the case of a clinic situation, or bulk submission, Peggy will assign a Clinic # on the shipping label but will submit to the GPCA Health Chair a Log with assigned ID # which were included in the shipment for reimbursement.

Reporting / Follow Up

Updates

Dr. Neff will provide Peggy Watson with updates upon request, which will also be submitted to the GPCA Health Committee. The GPCA Health Committee will format & record all updates and forward to the Editor of the GPCA Newsletter for publishing. All updates will also be available on-line at the www.gpcahealth.org

Results

Dr. Neff will provide the GPCA with a summary of findings, and a copy of the final research manuscript.

Conclusion and Clinical Relevance

Dr. Neff will provide Peggy Watson with a detailed "conclusion" when the Project is completed. This will be available following the procedures for "Reporting".

Information on How to Submit Blood Samples (Peggy complete)

What you will need (dog information, signed release form*)

Information for your Veterinarian

Collect whole blood using an EDTA or ACD vacutainer tube (lavender or yellow top)
Between 3-5 mls of blood is sufficient
Samples can be shipped using STANDARD overnight at ambient temperature (NO ICE)
Use FedEx #2527-7516-1 (check "bill recipient")
Please ship samples to:

Dr. Mark Neff (GP Dwarfism)
VGL Canine Genetics
CCAH/CVG Bldg 2nd Floor
UC Davis School of Veterinary Medicine
Davis, CA 95616
(530) 752-1381

For More Information

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