# The Munchkin Cat

# Phenotypic and Genotypic Characterization

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## Introduction:

Dwarfism in cats has been recorded as early as the 1930s, but disappeared sometime during World War II. Dwarf cats were rediscovered in 1983 and established into a recognized breed, called Munchkin, in 1994 (1). To date, the Munchkin breed has not been fully clinically and genetically characterized (**Figure 1**). In human achondroplasia, a mutation in the *FGFR3* gene, is the most common form of human dwarfism that occurs 1 in 15,000 live births (2). There are still many unknown causes of inherited dwarfism in people. Finding the gene responsible for bone development and growth, in these cats, may reveal a new function of one of the genes and may suggest a gene implicated with dwarfism in other species. A case-control genome wide association study localized a dwarfism locus to a 16Mb critical region on cat chromosome B1.

**Figure 1: Munchkin Cat** – characterized by short limbs.

**Figure 2: The Napoleon** – a subtype of Munchkin that occurs when breeding a Munchkin to a Persian. All of the affected cats used for the genome-wide case-control study were Napoleons. Persians, as well as unaffected related cats, were used as controls for the GWAS.

## Materials and Methods:

- 7 Munchkin cats were evaluated with MRI, CT and/or radiography to assess variability in limb length and for other congenital defects that may be associated with dwarfism.
- Breeding studies confirmed an autosomal dominant mode of inheritance.
- The genome-wide case-control study was performed using PLINK (3) on a group of 26 affected cases and 70 unaffected controls (**Figure 2 & 3**).
- Haplotype analysis identified a 16 Mb critical region on cat chromosome B1, between base pairs 168,000,000 and 184,000,000.

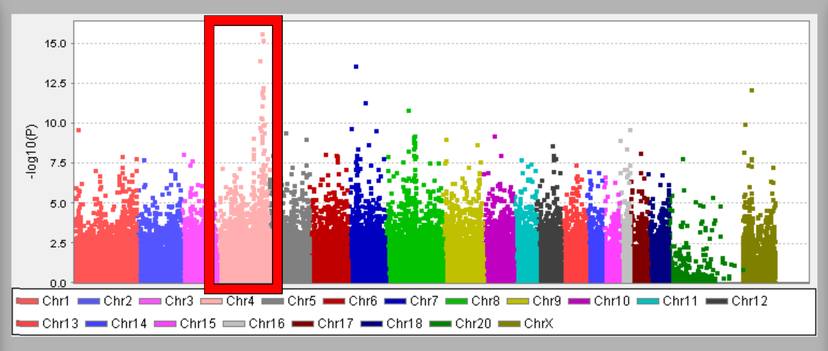


**Figure 3: Manhattan plot summarizing the case–control GWAS.** A significant association with dwarfism was obtained with SNPs making up a 16Mb critical region on chromosome B1 (represented by chromosome 4 above).

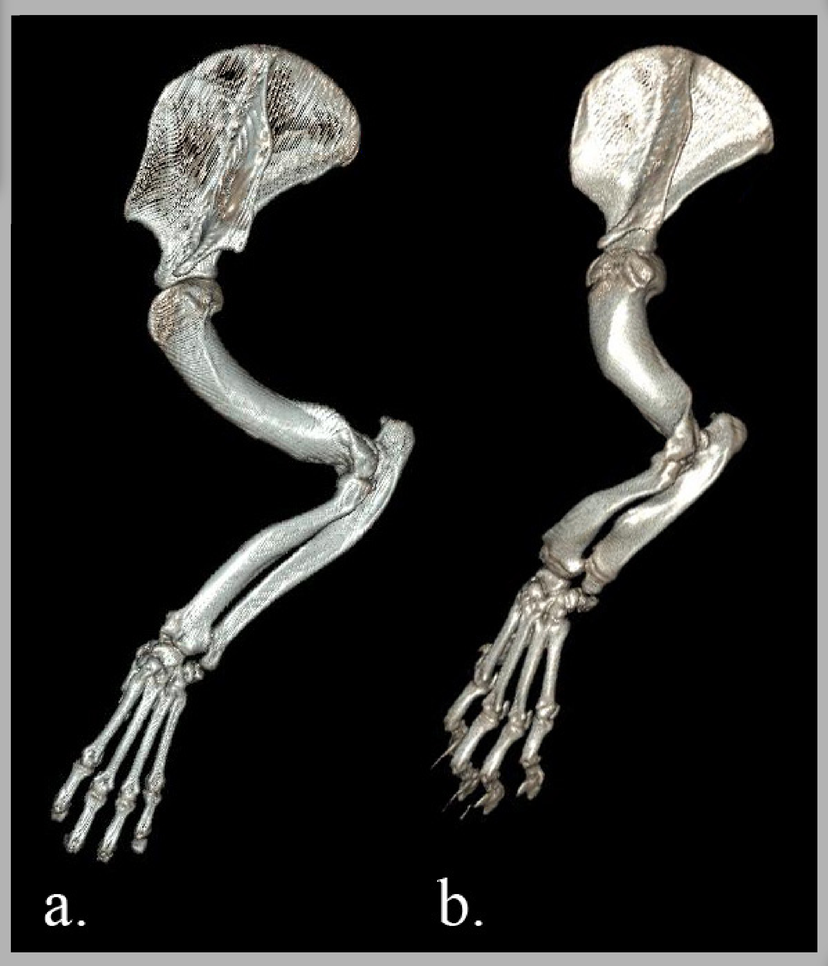


**Figure 4: 3-D reconstructed CT images of left thoracic limb.** a) Mildly affected Munchkin; b) Severely affected Munchkin. Note the angular limb deformity and shortened bone lengths of the humerus, radius and ulna.

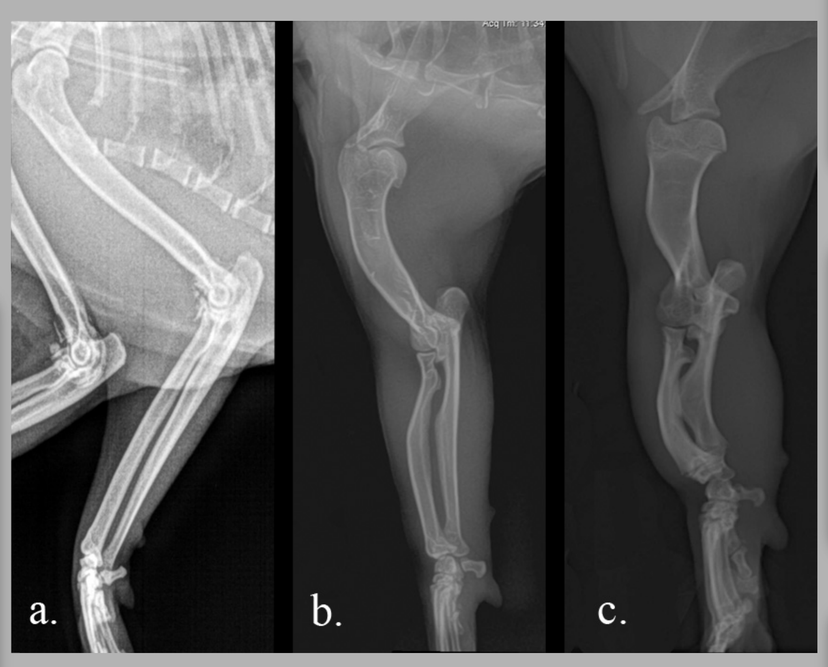


**Figure 5: Radiographs of left thoracic limb.** a) Normal cat; b) Mildly affected Munchkin; c) Severely affected Munchkin. Note the severity of angular limb deformities and shortened bone lengths of the humerus, radius and ulna.

## Results:

- Clinical evaluations of affected cats' shortened bone lengths are more notable in the thoracic limbs compared to pelvic limbs (**Figures 4, 5 & 6**).
- MRI of 1 older cat revealed intervertebral disc degeneration at 2 sites, which was considered age-related.
- GWAS revealed a strong association of a 16Mb critical region on chromosome B1.
- The region contained 60 annotated genes. After visual inspection of the associated region and literature review, none of the loci in the interval were associated with any form of dwarfism.

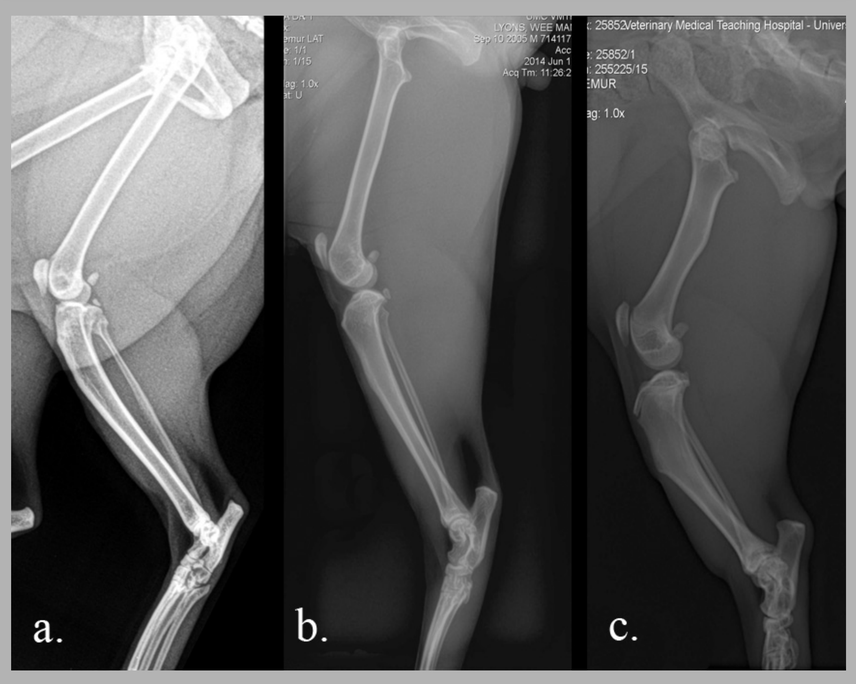


**Figure 7: Radiographs of the left pelvic limb.**
a) Normal cat; b) Mildly affected Munchkin; c) Severely affected Munchkin. Note the angular limb deformity and altered limb length that is more obvious in the severely affected cat.

## Conclusions:

**<u>This project represents the first phenotypic and genotypic characterization of the Munchkin breed, a successful GWAS study, and suggests a region of investigation for dwarfism.</u>** Currently a trio of cats is being whole genome sequenced and the 16 Mb region will be reevaluated for the presence of mutations associated with dwarfism.

## Acknowledgements:

This project was funded in part previously by the National Center for Research Resources R24 RR016094 and is currently supported by the Office of Research Infrastructure Programs OD R24OD010928, the Winn Feline Foundation and the Cat Health Network.

**References:**

**1** "Munchkin." *TICA Munchkin Breed Introduction*. Web. 3 July 2014.

**2** He L., Shobnam N., Wimley, W. C., Hristova, K. J. (2011) *FGFR3 Heterodimerization in Achondroplasia, the Most Common Form of Human Dwarfism*, *Biol. Chem.*, 286.

**3** Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, Maller J, Sklar P, de Bakker PIW, Daly MJ & Sham PC (2007) PLINK: a toolset for whole-genome association and population-based linkage analysis. *Am J Human Genet*, 81.