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Localization of a feline autosomal dominant dwarfism locus: a novel model of chondrodysplasia.

Running title: Feline heritable chondrodysplasia

L.A. Lyons[†,‡,*], D.B. Fox[†], K.L. Chesney[†], L.G. Britt[§], R.M. Buckley[†], J.R. Coates[†], B. Gandolfi[†,‡], R.A. Grahn[‡,‖], M.J. Hamilton[‡,¶], J.R. Middleton[†], S.T. Sellers[†], N.A. Villani[†,‡], S. Pfleuger[#] and the 99 Lives Consortium

[†]*Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri, Columbia, MO, USA*

[‡]*Department of Population Health and Reproduction, School of Veterinary Medicine, University of California - Davis, Davis, CA, USA*

[§]*All Creatures Teleradiology, LLC*

[‖]*Veterinary Genetics Laboratory, University of California – Davis, Davis, CA, USA*

[‖]*Department of Cell Biology and Neuroscience, Institute for Integrative Genome* [¶]*Biology, Center for Disease Vector Research, University of California - Riverside, Riverside, CA, USA*

[#]*Veterinary Medical Diagnostic Laboratory College of Veterinary Medicine University of Missouri Columbia, MO, USA*

[#]*In memoriam*

Leslie A. Lyons – lyonsla@missouri.edu

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Derek B. Fox - foxdb@missouri.edu

Kari L. Chesney - chesneyk@mizzou.edu

Lisa G. Britt - lgb1991heart@gmail.com

Reuben M. Buckley – bucklyrm@missouri.edu

Joan R. Coates - coatesj@missouri.edu

Barbara Gandolfi – Barbara.Gandolfi@Idexx.com

Robert A. Grahn – ragrahn@ucdavis.edu

Michael J. Hamilton - mhami004@ucr.edu

John R. Middleton - middletonjr@missouri.edu

Samantha T. Sellers - ststgb@mail.missouri.edu

Natalie A. Villani - villanin@missouri.edu

Solveig Pfleuger – not available

*Corresponding author:

E-mail: lyonsla@missouri.edu

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Abstract

Despite the contribution of a few major genes for disproportionate dwarfism in humans, many dwarf patients are yet genetically undiagnosed. In domestic cats, disproportionate dwarfism has led to the development of a defined breed, the Munchkin or Minuet. This study examined the genetic aspects of feline dwarfism to consider cats as a new biomedical model. DNA from dwarf cats was genetically analyzed using parentage, linkage, and genome-wide association studies as well as whole genome sequencing. Each genetic approach localized the dwarfism phenotype to a region on cat chromosome B1. No coding variants suspected as causal for the feline dwarfism were identified but a critical region of ~5.7 Mb from B1:170,278,183-175,975,857 was defined, which implicates a novel gene controlling disproportionate dwarfism. A yet unidentified but novel gene variant, likely structural or regulatory, produces disproportionate dwarfism in cats, which may define undiagnosed human patients.

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Introduction

Dwarfism is a genetic and or endocrine abnormality causing an animal to be less than normal size and lacking the capacity for normal growth. In humans, any person less than 147 cm for adult height is considered a dwarf[1]. Two general categories of dwarfism are defined, disproportionate and proportionate dwarfism. Disproportionate dwarfs possess shortened limbs with a normal trunk while proportionate dwarfs are uniformly small[2,3]. Disproportionate dwarfs result from genetic disorders involving bone and or cartilage, while the majority of instances of proportionate dwarfism result from hormonal abnormalities[4,5].

In humans, over 200 different forms of dwarfism are defined and approximately 1 in 20,000 newborn infants display congenitally shortened limbs, i.e. disproportionate dwarfism. DNA variants in one gene, *fibroblast growth factor receptor 3* (*FGFR3*), account for a majority of human disproportionate dwarfism with hypochondrodysplasia (HCH) (OMIM #146000) or achondroplasia (OMIM #100800) constituting the majority of diagnosed cases. The *FGFR3* G1138M variant accounts for 99% of all ACH[6-8] while an estimated 70% of HCHs result from variants in *FGFR3* (see reviews[9,10]). However, many forms of disproportionate human dwarfism are still undefined.

Feline disproportionate dwarfism (OMIA 000299-9685) has only briefly been mentioned in the scientific literature and has not been clinically characterized[11]. Breeds of cat have developed from disproportionate dwarf cats, termed Munchkins, Napoleons or Minuets (**Fig. 1**)[12]. The cats are at least mesomelic, with shortened forelimbs and hind limbs, implying the humerus, the radius and ulna and the femur, the tibia and fibula have deficient growth. Pre-mature ossification of epiphyseal plate cartilage is unknown. As reported by breeders, the cats have no indication of gender bias in the deformity and no

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indication of homozygotes. The feline phenotype lacks the frontal bossing and other maladies associated with achondroplasia[13], although the clinical features of the dwarf cats have not been extensively defined. An autosomal dominant mode of inheritance has been suggested. Thus, feline dwarfism closely parallels the human HCH phenotype, although the genetic cause of feline dwarfism is undetermined. The cat may be an important biomedical model for human chondrodystrophic disorders and potentially osteoarthrosis and degenerative joint disease.

To genetically define the disproportionate dwarfism in the domestic cats and implicate candidate genes for this biomedical model, genetic studies were conducted in dwarf cats. Linkage analyses and genome-wide association localized the dwarfism phenotype to a region on cat chromosome B1, which has homology to human chromosome 4 but exclusive of the region of *FGFR3*, supporting the plausibility of cat disproportionate dwarfism as a novel biomedical model to help identify the approximately 30% of HCH human cases that do not yet have gene associated mutations.

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Materials and Methods

DNA analyses - pedigree and DNA extraction

Buccal swabs or EDTA anti-coagulated whole blood samples from cats were solicited from owners of dwarf cats for DNA isolation over a period of twenty years. The familial relationships and dwarfism phenotypes were reported by the owners and breeders. DNA was isolated using the Qiagen DNAeasy kit according to the manufacturers protocol (Qiagen, Inc. Hilden, Germany) or standard organic extraction. All sample collections were conducted in accordance with an approved University of California, Davis Institutional Animal Care and Use protocols 11977, 15117, and 16691 and University of Missouri protocols 7808 and 8292.

DNA Analyses – Short Tandem Repeat (STR) Analysis

To develop a pedigree, parentage of the cats were verified with a panel of feline-derived short tandem repeats (STRs) as previously described[14]. STR fragment sizes were determined using STRand analysis software[15].

DNA Analyses – Linkage Analysis

Two-point linkage between the STRs and the dwarfism phenotype was conducted as previously described[16] using the LINKAGE and FASTLINK software programs[17-19]. Loops in the pedigree were broken by duplication of individuals. The dwarfism phenotype was coded as a fully penetrant autosomal dominant trait with non-variable expression. All matings were between a dwarf and a non-dwarf cat. No homozygous cats were predicted by the breedings nor have been reported by breeders, thus dwarf cats were assumed to be heterozygous. STR positions were determined by aligning the unique sequence flanking of the repeats to cat reference genome Felis_Catus_9.0 (GCF_000181335.3/).

DNA Analyses – Genome-wide association

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The initial dataset for the SNP array genome-wide analysis comprised 95 cats, including 26 affected dwarf cases that were unrelated to the third generation from provided pedigree information, 11 related non-dwarf cats, and cats from the closely related breeds, Scottish fold (n = 34), British shorthair (n = 14) and Selkirk rex (n = 10) for controls[20]. Approximately 600 ng of genomic DNA was submitted to Neogene, Inc (Lincoln, NE, USA) for genotyping on the Illumina Infinium Feline 63K iSelect DNA array (Illumina, Inc., San Diego, CA). Genotyping and analysis was performed as previously described[21]. SNP genotyping rate and minor allele frequency was evaluated using PLINK[22]. SNPs with a MAF < 5%, genotyping rate < 90%, and individuals genotyped for < 90% of SNPs were excluded from downstream analyses. Inflation of p-values was evaluated by calculating the genomic inflation factor (λ). The $\hat{P}$ for each individual, an identity by descent analysis, and multidimensional scaling (MDS) was calculated using PLINK to evaluate population substructure within cases and controls (data not shown). To reduce λ, cats not tightly clustered and/or highly related with a $\hat{P} > 0.4$ were removed from downstream analyses. Selection for each case to the closest control using the values from the MDS dimensions was attempted.

Whole genome sequencing

Three unrelated dwarf cats were submitted for whole genome sequencing as part of the 99 Lives Cat Genome Sequencing Consortium as previously described[23-26] (BioProject PRJNA308208, PRJNA288177; BioSamples: SAMN05980349, SAMN05980348, SAMN05980352). Reads were mapped to Felis_catus_9.0 (GCF_000181335.3/) and assigned to read groups using BWA-MEM from Burrows-Wheeler Aligner version 0.7.17[27]. Duplicate reads were marked using MarkDuplicates

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from Picard tools version 2.1.1 (http://broadinstitute.github.io/picard/), with OPTICAL_DUPLICATE_PIXEL_DISTANCE set at 2500. Genome Analysis Toolkit version 3.8 (GATK 3.8) were used to further process the sequence data[28]. Indel realignment was performed with RealignerTargetCreator and IndelRealigner[29] and SNPs, and Indels were called using HaplotypeCaller in gVCF mode (-ERC GVCF)[30]. The gVCFs were combined into groups of ~20 individuals using CombineGVCFs and were genotyped simultaneously using GenotypeGVCFs. Throughout, Samtools version 1.7 sort, index, view, and cat functions were used to process BAM files between individual tasks[31]. Together these processes produced a single VCF comprised of 195 cats for downstream analysis. DNA variants were viewed, filtered and annotated using VarSeq (Golden Helix, Boseman, MT) with the Ensembl Release 94 Felis_catus_9.0 genome annotation[32]. For variant prioritization, candidate variants were required to be within the region implicated by the GWAS (chr B1 170 – 187 Mb), heterozygous in all three dwarf cats, and absent in 71 normal cats also in the 99 Lives dataset (PRJNA308208).

Results

Pedigree Analysis

The dwarfism phenotype in the affected Munchkin cats is unique and distinct, with only mild variations in presentation, therefore diagnosis of affected kittens is not confounded by other congenital birth defects in cats (**Fig 1**). A six-generation, 83-member pedigree (65 informative meioses) was created based upon owner supplied pedigrees, parentage analyses and phenotypes (**Fig. 2**). The parentage analysis confirmed reported relationships of the cats (data not shown). Sires and dams bred into the pedigree were, in general, of random bred stock and were not related. All matings and all dwarf offspring

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in the pedigree had at least one dwarf parent. Complete litter data was available for nine matings, one was a breeding of two dwarf cats that produced six kittens, including one dwarf male kitten, three normal male kittens and two normal female kittens. Eight matings had one dwarf parent, producing eight of 19 dwarf male kittens and seven of 17 dwarf female kittens. Matings that had complete litter information showed no sex bias with 39% of males and 37% of females displaying the dwarf phenotype. No litter produced all dwarf kittens, thus the dwarf parents are expected to be heterozygous. A heterozygous affected by normal mating would predict 50% affected offspring, 42% of progeny displayed the dwarf phenotype in the pedigree. For the 10 matings with both parents having dwarfism, none of the Munchkin offspring (n = 6) are homozygous for the STR in complete linkage with the dwarf phenotype. Also, normal sized cats were produced from these matings, further excluding a recessive mode of inheritance.

Linkage analysis

One STR genotyped to confirm parentage, *FCA149,* indicated significant linkage (Z = 5.43. θ = 0.05) to the dwarfism phenotype and is located on feline chromosome B1[33]. Additional publicly available regional STRs (n = 8)[34-36] were genotyped to refine the linkage region (**Table 1**). Marker *FCA827* was completely linked to the dwarfism phenotype, Z = 15.05, θ = 0.00, which is positioned at B1:174,566,680 – 174,566,701. Recombinants were detected with flanking markers *FCA149* and *FCA152*, defining a minimal critical region from B1:167,386,513 – 179,961,345, a 12 Mb as based on STR positions on the cat genome assembly.

Genome-wide association

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A genome-wide case-control study was conducted on 26 cases and 50 controls. All samples passed genotype rate (MIND > 0.2) and 49,424 SNPs were analyzed after missingness (GENO > 0.2) and the frequency test (MAF < 0.05). The genomic inflation (ʎ) was 2.95, suggesting inflation is due to the population substructure as suggested by the MDS (**Fig. 4**). The highest significant association was identified on cat chromosome B1 at position 179,190,128 (**Fig. 3**). The P-values and positions of the 36 most associated SNPs are presented in **Table 2**. A majority of the highly associated SNPs reside on cat chromosome B1, from position 170,786,914 - 186,605,881, a ~16 Mb critical region. Considering the linkage boundary of STR *FCA152* (B1:179,961,345), the critical region reduces to ~ 9.2 Mb B1:170,786,914 – 179,961,345.

Whole genome sequencing

Approximately 30x genome coverage was produced from the three dwarf cats. An ~17 Mb region containing 369,708 variants was examined. Only 65 candidate variants were identified after considering the dwarf cats to be heterozygous and the variant absent in the 192 additional cats in the 99 Lives dataset. However, no variants were coding nor protein altering, including 33 intergenic and 32 intronic variants found within the eight genes, including, *LIMCH1*, *APBB2*, *RBM47*, *CHRNA9*, *UGDH*, *RFC1*, *WDR19*, and *TMEM156* (**STable 1**). These variants encompassed the 5.7 Mb region of B1:170,278,183 - 175,975,857, further refining the critical region to B1:170,786,914 – 175,975,857, ~5.2 Mb. Overall, 48 genes and transcripts are defined within this critical region (**STable 2**).

Discussion

The domestic cat is one of the few species with an autosomal dominant mode of inheritance for dwarfism that does not have other syndromic features, a strong model for

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HCH. The Munchkin cat is a relatively new breed of domestic cat and has developed from random bred dwarf cats. A random bred, short-limbed pregnant female was found in Louisiana in 1983[37,38]. The resulting litter also possessed short-limbed cats, one of which was used as a breeding male from which all Munchkins are supposedly derived. This recent de novo mutation could explain some of the high genomic inflation in the GWAS. Other spontaneous dwarf cats have been reported in the lay literature, but their contribution in the Munchkin breeding program is speculative. Within ten years, the breed has sufficiently grown in popularity to be accepted for championship show status by The International Cat Association (TICA) in 1994[31], but is banned from registration in many other cat fancy registries, thus, is mainly bred in the USA. The segregation in the pedigree suggested an autosomal dominant mode of inheritance for feline dwarfism in the Munchkin cat breed. No individuals from six matings of two dwarf parents were homozygous for the linked marker, which suggests lethality *in utero*. An autosomal recessive mode of inheritance was also eliminated as two dwarf parents produced offspring with normal limb length.

Nearly 4000 human infants are born each year with some form of dwarfism. Disproportionate dwarfism constitutes the vast majority of congenital dwarfism and has both sex-linked and autosomal dominant modes of inheritance. The cat autosomal dominant disproportionate dwarfism most closely resembles human HCH as the cat has no noted health concerns other than the limb abnormalities. However, the genetic studies did not implicate *FGFR3* in cats and Sanger sequencing of the coding region of *FGFR3* (data not shown) did not identify any associated variants. In dogs, *FGF4* retrogene is responsible for autosomal recessive chondroplasia in 19 canine dwarf breeds[39].

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Additional variants in canine homologs for *Cartilage specific integrin alpha 10 (ITGA10)*[40], *collagen alpha-2(XI) chain (COL11A1)*[41], and two *collagen type IX* genes (*COL9A2* and *COL9A3*)[42] cause an autosomal recessive chondrodysplasia affecting the Norwegian Elkhound and Karelian Bear Dog breeds, a mild form of disproportionate dwarfism in Labrador Retrievers, which is not associated with any obvious health problems such as secondary arthrosis, and an oculoskeletal dysplasia in Labrador retrievers and Samoyed dogs, respectively. These canine dwarfism genes are not on a chromosome that shares synteny with cat chromosome B1.

Three complementary and independent genetic analyses, including a familial-based linkage analysis, a GWAS and whole genome sequencing refined a critical region to ~5.7 Mb from B1:170,278,183-175,975,857, which has no genes causal for dwarfism and thereby implicating a novel gene for dwarfism. Although on the same chromosome, *FGFR3* (B1:207161233 - 207179684) is not near this area of association. At least 46 genes were annotated within the critical region for feline dwarfism. Unfortunately, no coding or splice variants were identified within these genes in the region. One gene, *replication factor C, subunit 1* (*RFC1*) has a pathway associated with Hutchinson-Gilford Progeria Syndrome (OMIM: 176670), which is a rare disorder characterized by short stature, low body weight, early loss of hair, lipodystrophy, scleroderma, decreased joint mobility, osteolysis, and facial features that resemble aged persons[43]. As for all WGS-based approaches, the analyses were limited by annotation, correct genome assembly, and the ability to identify more complex variants, such as structural variants and variants that influence gene regulation. Therefore, structural or regulatory variants should be

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examined within these regions to further implicate one of the regional candidate genes or unannotated transcripts.

Surveillance for animal welfare concerns resulting from pedigree animal breeding practices has increased since the BBC documentary *Pedigree Dogs Exposed (2008)*[44]. Although cats do not have the same extreme conformational ranges as dogs, heightened scrutiny of breeding practices has extended to cats. Orthopedic diseases are commonly associated with dog breed conformation, but far less so with domestic cat breeds[45,46]. Hip dysplasia is a concern of the Maine Coon breed[47], osteochrondrodysplasia is an inherent condition of the Scottish Fold breed, and osteoarthritis, particularly of the elbow, is now recognized as a common condition of aged cats[48,49]. The Scottish Fold, which has varying degrees of osteochondrodysplasia, has been banned from several cat registries. The Manx, which can suffer from various conditions resulting from sacral and caudal vertebral agenesis, has heightened the concern for acceptance of other cat breeds with tail abnormalities. Thus, welfare concerns have encircled the acceptance of chondrodysplastic cats as a recognized breed.

Controversy regarding the immediate and long-term health of the chondrodysplastic cats focuses on the potential for impaired ambulation, secondary osteoarthritis[50] and intervertebral disc disease[51,52] , which is common to many chondrodysplastic dog breeds. Biapical deformities are common in dogs with limb deformities, particularly chondrodystrophic dogs[53]. *Fibroblast growth factor 4 (fgf4*) is strongly associated with autosomal recessive chondrodysplasia in at least 19 dog breeds including dachshund, corgi, and basset hound[39]. The *FGF4* variant has also been shown to be the leading cause for intervertebral disc degeneration in the chondrodysplastic dogs[54], thus, since

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the cats do not have this variant, disc disease is a less likely concern. However, poor breeding practices, such as striving for the shortest legs or longest body, could lead to similar health concerns in the cats to those that plague the dwarf dog breeds[55].

Although many chondrodysplastic dog breeds have the *FGF4* variant, selection by breeders can lead to longer straighter legs as found in several chondrodysplastic dog breeds or the severely dismorphic limbs of basset hounds. The shortest documented cat stands at 5.25 in (13.34 cm), while other cat breeds, measured from ground to withers, range from 8 – 14 in (20.32 – 35.56) (LA Lyons, personal communication). Selection by cat breeders and cat show judges will ultimately control the health and quality of life of domestic cats with dwarfism. More detailed studies demonstrating the morphological variation should further enlighten the concerns for impaired ambulation and secondary osteoarthritis in the dwarf cat breed. Regulatory and structural variant analyses are required to further elucidate the variant causing disproportionate dwarfism in the cat.

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Author contributions

- Conception and design – LAL, DBF, SP
- Provision of study materials or patients – LAL, RAG, BG, MJH, NAV
- Collection and assembly of data – LAL, RAG, MJH, BG, RMB, KLC, SS, NAV
- Analysis and interpretation of the data – KLC, RAG, MJH, BG, RMB, JRC, DBF
- Drafting of the article – LAL, RMB
- Statistical expertise – JRM, RMB
- Obtaining of funding – LAL, KLC
- Critical revision of the article for important intellectual content – LAL, RMB
- Final approval of the article – all authors except SP.

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Conflict of interest

The authors declare no conflict of interests pertaining to this research.

Studies involving humans or animals

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The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. All sample collection and cat studies were conducted in accordance with an approved University of California, Davis Institutional Animal Care and Use protocols 11977, 15117, and 16691 and University of Missouri protocols 7808 and 8292.

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Figure legends

Figure 1. Dwarfism in domestic cats. Identified in random bred cats, dwarfism in cats presents as varying degrees of shorted long bones. The random bred cats have been bred to Persians and other breeds and have various breed names, such as, Napoleons, Minuets or Munchkins. Although the breed is controversial due to stature, additional adverse health problems have not been documented. A variety of hair coats and pelage colorations are accepted in the breed standard in The International Cat Association (TICA). Image courtesy of Terri Harris.

Figure 2. Six Generation 83-member pedigree segregating for the dwarf phenotype. Squares represent males, circles females. Open shapes are wildtype, half-filled symbols are phenotypically dwarf cats. Cross hatched symbols were not available for typing. Four-digit numbers under each symbol are animal ID numbers. Alleles for STRs *FCA149*, *FCA827* and *FCA152* are under each identifier. Inferred types are in parenthesis. Recombinants (N = 6) are indicated by R.

Figure 3. Manhattan plot of genome-wide association for feline dwarfism. Manhattan plots of the Munchkin GWAS. The plot represents the P_{raw} values of each SNP included in the case-control association study. The association study compared the Munchkin cats to non-standard Munchkin cats, British shorthair, Selkirk rex and Scottish fold. A significant association was found with chromosome B1. Over 20 SNPs show association on cat chromosome B1 from 170 – 186 Mb. Chromosome 4 corresponds to cat chromosome B1.

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Figure 4. Multi-dimensional scaling (MDS) in two dimensions of samples that passed quality control for dwarf cat analysis. Left) All cats, all breeds in the preliminary analysis. Right) MDS of cases and controls included in the analysis, indicating substructure of the cats.

Table 1. Chromosome B1 STRs with linkage to feline dwarfism.

STR	LOD (Z)	Theta (Θ)	Start	End
FCA820	0.03	0.40	chrB1:97271192	chrB1:97271050
FCA730	1.42	0.20	chrB1:182979793	chrB1:182979657
FCA097	0.39	0.30	chrB1:154184908	chrB1:154184757
FCA257	0.22	0.40	chrB1:158429698	chrB1:158429838
FCA149	5.43	0.05	chrB1:167386536	chrB1:167386414
FCA827	**10.34**	**0.00**	chrB1:174566701	chrB1:174566475
FCA152	6.22	0.05	chrB1:179961324	chrB1:179961465
FCA826	1.84	0.10	chrB1:168743712	chrB1:168743712
FCA830	unlinked	0.40	chrB1:200676672	chrB1:200676788

*Positions determined from cat genome assembly Felis_Catus_9.0 (GCF_000181335.3/).

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Table 2. Chromosome B1 SNVs associated with feline dwarfism.

SNV ID	Position†	Association	Bonferroni
chrUn13.10177665	170786914	1.06E-07	0.005259
chrUn13.9960308	170921912	5.44E-11	2.69E-06
chrC1.27022876	173720688	2.08E-07	0.01029
chrB1.198320842	175364385	1.34E-08	0.000664
chrB1.198662234	175659243	3.88E-07	0.0192
chrB1.198999098	175941649	1.87E-07	0.009242
chrB1.199182095	176101920	1.45E-07	0.007147
chrB1.199265607	176174430	1.06E-09	5.23E-05
chrB1.199329953	176218315	3.24E-09	0.00016
chrB1.200056289	176813860	1.13E-08	0.000561
chrB1.202493738	178828246	5.58E-10	2.76E-05
chrUn.39080896	178869896	4.28E-07	0.02113
chrUn3.12360067	**179190128**	**8.58E-13**	**4.24E-08**
chrUn3.12992679	179811107	7.35E-08	0.003632
chrUn3.13370407	**180186422**	**1.08E-12**	**5.34E-08**
chrUn3.13714600	180539664	4.47E-08	0.002209
chrUn3.14277294	181353865	5.02E-07	0.02479
chrUn3.14308750	181384642	3.88E-07	0.0192
chrB1.214247550	182582638	1.84E-09	9.11E-05
chrB1.214054453	182742951	5.80E-07	0.02867
chrUn.55868800	183444232	8.26E-10	4.08E-05
chrB1.212700379	183856801	1.64E-09	8.09E-05
chrB1.212633662	183910988	2.67E-07	0.01321
chrB1.212510316	184016410	6.51E-07	0.03217
chrB1.211909881	184489915	4.40E-07	0.02176
chrB1.211304362	184973685	1.36E-07	0.006704
chrB1.209176524	186605881	1.31E-08	0.000647
chrB1.172384899	142661477	8.56E-08	0.00423
chrB1.174385551	144305624	4.55E-07	0.0225
chrUn32.1463518	144955066	3.75E-07	0.01856
chrUn.25638158	145107438	6.75E-08	0.003338
chrUn32.1207596	145210630	6.75E-08	0.003338

†Positions determined from cat genome assembly Felis_Catus_9.0 (GCF_000181335.3/). The two highest associated SNVs are presented in **BOLD**. A majority of the association is with SNVs between 170 – 186 Mb

Figure 1. Dwarfism in domestic cats.

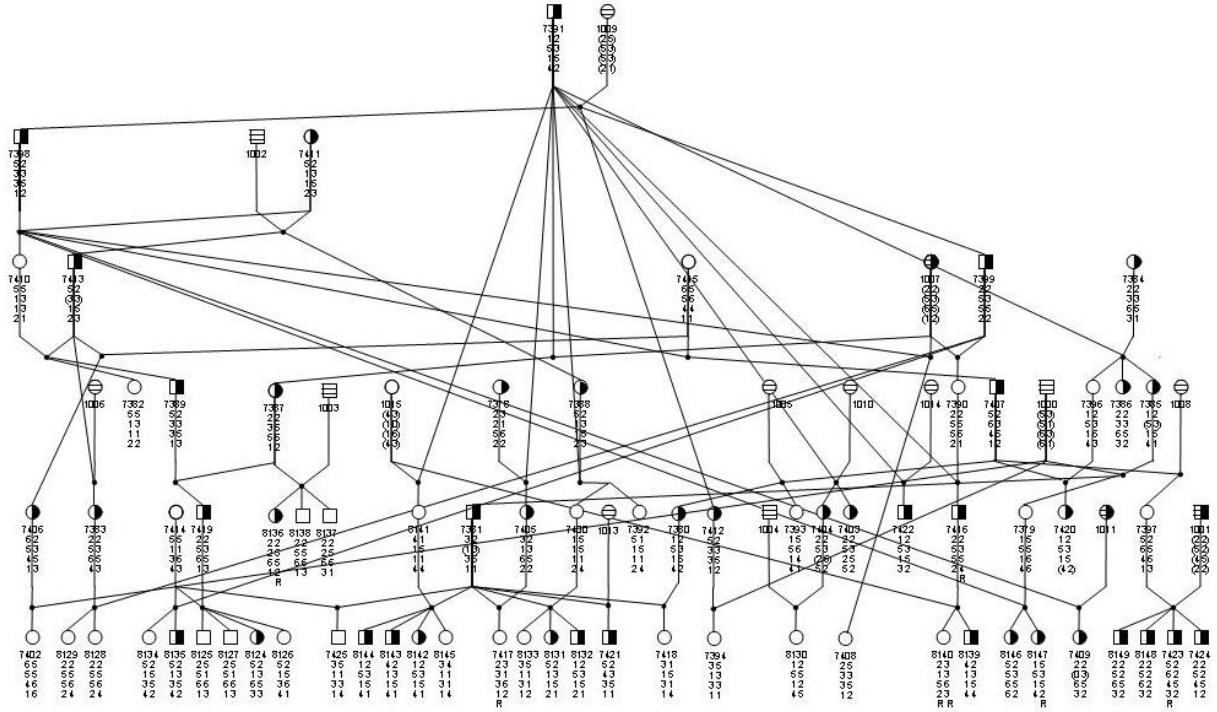

Figure 2. Six generation 83-member pedigree segregating for the dwarf phenotype.

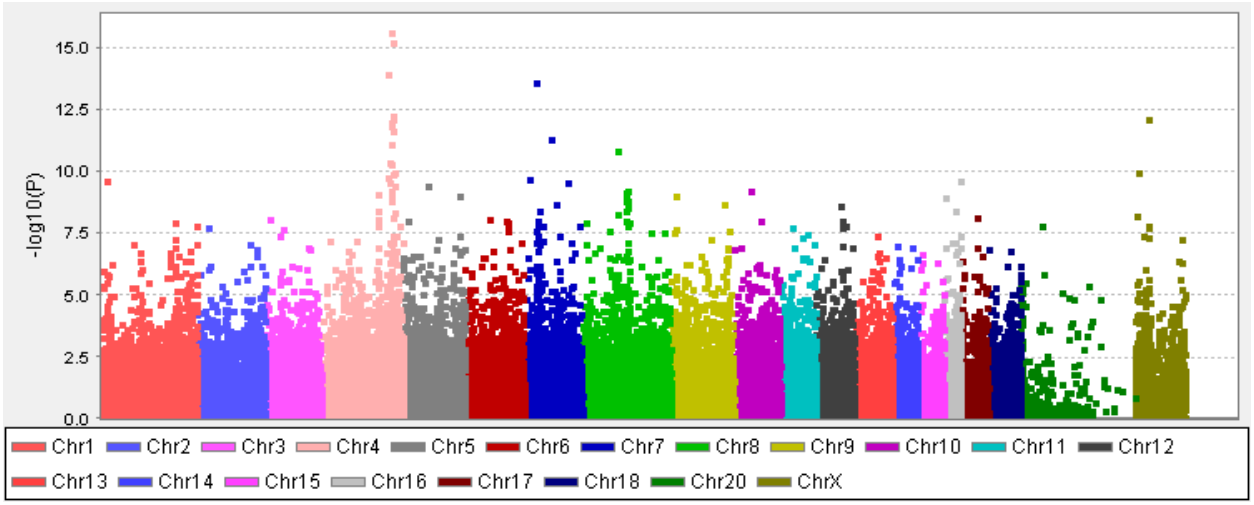

Figure 3. **Manhattan plot of genome-wide association for feline dwarfism.**

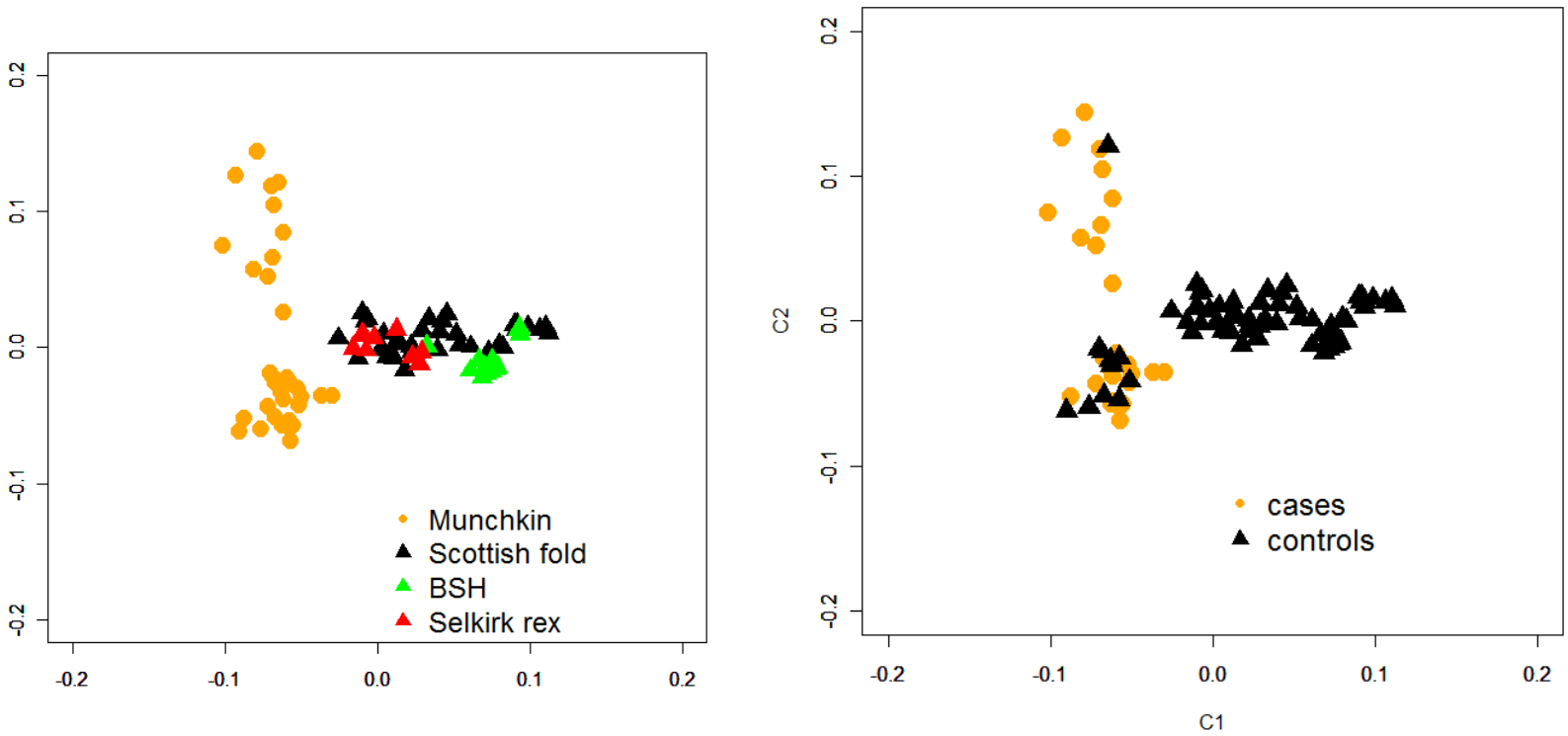

Figure 4. Multi-dimensional scaling (MDS) in two dimensions of samples that passed quality control for dwarf cat analysis.

Supplementary Table 1. Variants identified by whole genome sequencing within the critical region identified by genome-wide association study.

Chromosome: Position	Reference/ Alternative	Gene	Gene Position	Transcript Name	HGVS c. (Clinically Relevant)
B1:167386513		**FCA149**	**intergenic_STR**		
B1:170278183	C/T		intergenic_variant		
B1:170786914			intergenic_variant		
B1:171215074	T/A		intergenic_variant		
B1:171486710	G/A		intergenic_variant		
B1:171524991	C/T		intergenic_variant		
B1:172038327	A/C		intergenic_variant		
B1:172906886	A/G		intergenic_variant		
B1:173097092	T/C	LIMCH1	intron_variant	ENSFCAT00000047977	ENSFCAT00000047977:c.237+270A>G
B1:173099638	-/AAATA	LIMCH1	intron_variant	ENSFCAT00000047977	ENSFCAT00000047977:c.168-2211_168-2207dupTATTT
B1:173103057	T/A	LIMCH1	intron_variant	ENSFCAT00000047977	ENSFCAT00000047977:c.168-5626A>T
B1:173137458	-/T	LIMCH1	intron_variant	ENSFCAT00000047977	ENSFCAT00000047977:c.97-16755dupA
B1:173285632	G/A		intergenic_variant		
B1:173391984	-/A	APBB2	intron_variant	ENSFCAT00000022248	ENSFCAT00000022248:c.-177+27299dupA
B1:173436205	T/G	APBB2	intron_variant	ENSFCAT00000022248	ENSFCAT00000022248:c.-176-44053T>G
B1:173497493	A/C	APBB2	intron_variant	ENSFCAT00000022248	ENSFCAT00000022248:c.-70-13022A>C
B1:173615935	AGAA/-	APBB2	intron_variant	ENSFCAT00000022248	ENSFCAT00000022248:c.863-8872_863-8869delAAAG
B1:173848028	T/G		intergenic_variant		
B1:173936171	G/T	RBM47	intron_variant	ENSFCAT00000012401	ENSFCAT00000012401:c.-32+31359G>T
B1:173949358	TTTAT/-	RBM47	intron_variant	ENSFCAT00000012401	ENSFCAT00000012401:c.-32+44578_-32+44582delTATTT
B1:173949362	TTTTA/-	RBM47	intron_variant	ENSFCAT00000012401	ENSFCAT00000012401:c.-32+44578_-32+44582delTATTT
B1:173951124	G/A	RBM47	intron_variant	ENSFCAT00000012401	ENSFCAT00000012401:c.-32+46312G>A
B1:173970209	C/T	RBM47	intron_variant	ENSFCAT00000012401	ENSFCAT00000012401:c.-32+65397C>T

B1:173978144	G/C	RBM47	intron_variant	ENSFCAT00000012401	ENSFCAT00000012401:c.-32+73332G>C
B1:173978205	C/T	RBM47	intron_variant	ENSFCAT00000012401	ENSFCAT00000012401:c.-32+73393C>T
B1:173980454	A/G	RBM47	intron_variant	ENSFCAT00000012401	ENSFCAT00000012401:c.-31-74347A>G
B1:173990664	T/G	RBM47	intron_variant	ENSFCAT00000012401	ENSFCAT00000012401:c.-31-64137T>G
B1:174053810	C/A	RBM47	intron_variant	ENSFCAT00000012401	ENSFCAT00000012401:c.-31-991C>A
B1:174071994	C/T		intergenic_variant		
B1:174076407	C/A		intergenic_variant		
B1:174077557	G/A		intergenic_variant		
B1:174077762	G/A		intergenic_variant		
B1:174078299	A/G		intergenic_variant		
B1:174079184	GAGA/-		intergenic_variant		
B1:174079207	C/A		intergenic_variant		
B1:174079731	A/G		intergenic_variant		
B1:174080146	AGAG/-		intergenic_variant		
B1:174080721	C/T		intergenic_variant		
B1:174081820	G/C		intergenic_variant		
B1:174081969	T/A		intergenic_variant		
B1:174082694	T/G		intergenic_variant		
B1:174084958	A/G		intergenic_variant		
B1:174085059	G/A		intergenic_variant		
B1:174085166	CT/-		intergenic_variant		
B1:174085855	C/T		intergenic_variant		
B1:174087078	C/T		intergenic_variant		
B1:174089147	T/C		intergenic_variant		
B1:174096760	A/T		intergenic_variant		
B1:174105763	C/T		intergenic_variant		
B1:174127194	AGTC/-	CHRNA9	intron_variant	ENSFCAT00000042269	ENSFCAT00000042269:c.366-145_366-142delGACT
B1:174131921	G/A	CHRNA9	intron_variant	ENSFCAT00000042269	ENSFCAT00000042269:c.365+2136C>T
B1:174132207	A/C	CHRNA9	intron_variant	ENSFCAT00000042269	ENSFCAT00000042269:c.365+1850T>G
B1:174132368	G/A	CHRNA9	intron_variant	ENSFCAT00000042269	ENSFCAT00000042269:c.365+1689C>T

B1:174133775	G/C	CHRNA9	intron_variant	ENSFCAT00000042269	ENSFCAT00000042269:c.365+282C>G
B1:174566680		**FCA827**	**intergenic_STR**		
B1:174847189	G/T		intergenic_variant		
B1:174847190	A/C		intergenic_variant		
B1:174860626	T/G	UGDH	intron_variant	ENSFCAT00000009602	ENSFCAT00000009602:c.-7-1593T>G
B1:174867022	T/-	UGDH	intron_variant	ENSFCAT00000009602	ENSFCAT00000009602:c.163-439delT
B1:174999000	A/T	RFC1	intron_variant	ENSFCAT00000001781	ENSFCAT00000001781:c.135+5393A>T
B1:175078887	A/G	WDR19	intron_variant	ENSFCAT00000001779	ENSFCAT00000001779:c.*13+3682T>C
B1:175078920	A/G	WDR19	intron_variant	ENSFCAT00000001779	ENSFCAT00000001779:c.*13+3649T>C
B1:175078933	T/C	WDR19	intron_variant	ENSFCAT00000001779	ENSFCAT00000001779:c.*13+3636A>G
B1:175078947	C/T	WDR19	intron_variant	ENSFCAT00000001779	ENSFCAT00000001779:c.*13+3622G>A
B1:175078953	T/C	WDR19	intron_variant	ENSFCAT00000001779	ENSFCAT00000001779:c.*13+3616A>G
B1:175349169	A/G	TMEM156	intron_variant	ENSFCAT00000031918	ENSFCAT00000031918:c.89-5273A>G
B1:175975857	G/C		intergenic_variant		
B1:179961345		**FCA152**	**intergenic_STR**		
B1:186605881			intergenic_variant		

21
22

Supplementary Table 2. Critical region genes for feline dwarfism on cat chromosome B1:170278183-175975857.

Gene ID	Name	Start	End	GeneCard associated Diseases
ENSFCAG00000028486	*GNPDA2*	170293762	170322496	Obesity
ENSFCAG00000028580	*GUF1*	170325353	170346889	Epileptic Encephalopathy, West Syndrome
ENSFCAG00000006282	*YIPF7*	170366863	170394543	De Quervain Disease, Epicondylitis.
ENSFCAG00000029885		170488906	170489280	
ENSFCAG00000030570	*KCTD8*	170589687	170845851	Sweet Taste Signaling, Neuropathic Pain-Signaling in Dorsal Horn Neurons
ENSFCAG00000034150	*RF00100*	171550935	171551217	
ENSFCAG00000018569	*GRXCR1*	171751919	171878987	Deafness, Branchiootic Syndrome 1
ENSFCAG00000036356		171990790	171991881	
ENSFCAG00000015213	*ATP8A1*	172062098	172289239	Cerebellar Ataxia, Mental Retardation, Dysequlibrium Syndrome, Robinow Syndrome
ENSFCAG00000043473	*SHISA3*	172299898	172305862	Tumor suppressor
ENSFCAG00000033789	*RF00026*	172345184	172345284	
ENSFCAG00000044789		172396346	172417546	
ENSFCAG00000043262		172442984	172449907	
ENSFCAG00000044080	*BEND4*	172498442	172530596	Follicular Lymphoma
ENSFCAG00000024533	*SLC30A9*	172564833	172650293	Birk-Landau-Perez Syndrome
ENSFCAG00000040948	*TMEM33*	172673293	172693525	Congenital Ichthyosis
ENSFCAG00000045230	*PHOX2B*	172854075	172859113	Central Hypoventilation Syndrome, Congenital Neuroblastoma 2.
ENSFCAG00000042497		172866353	172866487	
ENSFCAG00000046477		172869997	172882934	
ENSFCAG00000007444	*LIMCH1*	172914742	173249269	Lung cancer, Hepatosplenic T-Cell Lymphoma
ENSFCAG00000025457	*UCHL1*	173311731	173327417	Parkinson disease
ENSFCAG00000012843	*APBB2*	173364437	173753735	Alzheimer Disease
ENSFCAG00000012841	*NSUN7*	173754945	173809607	Infertility
ENSFCAG00000042869		173865395	173885964	
ENSFCAG00000012399	*RBM47*	173904131	174069382	Breast, Colorectal Cancer
ENSFCAG00000035547	*CHRNA9*	174118937	174135747	Deafness, Breast cancer

ENSFCAG00000012394	*RHOH*	174208322	174208897	T-Cell Immunodeficiency with Epidermodysplasia Verruciformis
ENSFCAG00000024887	*N4BP2*	174283177	174356646	
ENSFCAG00000037355	*RF00026*	174304986	174305092	
ENSFCAG00000003209	*PDS5A*	174441923	174579837	
FCA827	*FCA827*	174566680	174566701	
ENSFCAG00000033193	*UBE2K*	174615267	174689895	Huntington Disease
ENSFCAG00000038568	*RF00007*	174675118	174675271	
ENSFCAG00000024033		174747387	174747617	
ENSFCAG00000032694	*SMIM14*	174760874	174841113	
ENSFCAG00000009600	*UGDH*	174853638	174885557	Deafness, biosynthesis of glycosaminoglycans such as hyaluronan, chondroitin sulfate, and heparan sulfate
ENSFCAG00000023567	*LIAS*	174892614	174907965	Hyperglycinemia, Lactic Acidosis, Seizures, Lipoic Acid Synthetase Deficiency.
ENSFCAG00000012284	*RPL9*	174908042	174912983	Lipoic Acid Synthetase Deficiency.
ENSFCAG00000026771	*KLB*	174918899	174953922	Hypogonadotropic Hypogonadism
ENSFCAG00000001781	***RFC1***	**174993455**	**175063047**	**Hutchinson-Gilford Progeria Syndrome**
ENSFCAG00000001779	*WDR19*	175062084	175177435	Disorders affecting function of the cilium
ENSFCAG00000003534	*KLHL5*	175208337	175296713	
ENSFCAG00000028887	*TMEM156*	175327852	175381406	Follicular Lymphoma
ENSFCAG00000027380	*FAM114A1*	175397428	175467463	Mixed Germ Cell Cancer
ENSFCAG00000043678	*RF00026*	175459211	175459317	
ENSFCAG00000040731		175493242	175495632	
ENSFCAG00000031748		175521624	175523997	
ENSFCAG00000007666	*TLR10*	175549356	175551785	Crimean-Congo Hemorrhagic Fever, Theileriasis.
ENSFCAG00000028338	*KLF3*	175613723	175648997	Transcriptional misregulation in cancer