

IDENTIFICATION OF GENETIC RISK FACTORS UNDERLYING PRIMARY HYPOADRENOCORTICISM IN DOGS

by

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(Under the Direction of Leigh Anne Clark)

ABSTRACT

Dogs offer a unique population structure that can be exploited to identify genetic risk factors of complex disease. Herein, I used the canine model to investigate the genetic underpinnings of primary hypoadrenocorticism, a rare endocrine disorder of the adrenal gland. Primary hypoadrenocorticism occurs naturally in dogs and with increased incidence in certain breeds. Affected dogs and people experience similar clinical signs, disease progression, and treatment responses, thereby making the dog an excellent comparative genetics model. To characterize the genetic risk factors associated with primary hypoadrenocorticism, I employed next-generation and Sanger sequencing technologies in two high-risk breeds: the Portuguese Water Dog and the Standard Poodle. I first generated low-coverage whole genome sequencing data from unrelated cases and controls. Based on a multi-breed reference panel, I imputed low-coverage genomes for increased coverage and genotype accuracy. With these data, I performed a genome-wide association study and cross-population extended haplotype homozygosity testing in Standard Poodles. I identified a novel locus associated with primary hypoadrenocorticism on chromosome 17, and two additional risk loci on chromosome 27 containing signatures of selection unique to cases. Notably, all three loci contain genes canonically related to the central nervous system.

I also uncovered shared and breed-defining genetic factors that may contribute to the high frequency of primary hypoadrenocorticism in these breeds. Runs of homozygosity and F_{ST} analyses revealed shared signatures of selection over six loci containing genes that may have pleiotropic effects related to adrenocortical dysfunction. Because it has been clearly linked to human primary hypoadrenocorticism, I next evaluated the major histocompatibility complex (MHC) class II genes and found that the two breeds have different haplotype compositions, where only Portuguese Water Dogs possess a clear risk haplotype. Finally, I filtered for unique variants based on minor allele frequencies in high-coverage data and identified four missense mutations associated with primary hypoadrenocorticism, within *ARID5B* and *SMYD1* for Standard Poodles and within *MYPN* and *ASCC3* for Portuguese Water Dogs. Collectively, these data highlight the genetic complexity underlying disease risk while also implicating the immune system, and for the first time, the central nervous system in primary hypoadrenocorticism etiology.

INDEX WORDS: Dog, Low-pass, Adrenocortical dysfunction, *LRRTM4*, *CACNA1C*, *ANO2*, Major histocompatibility complex, Addison's disease, Canine model

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For all the dogs affected by adrenal insufficiency.

*For my beloved uncle, Donald Arden, and my dear longtime friend, Kelsey Lewis,
who were taken in October 2024 much too soon. Love you both.*

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CHAPTER 1

INTRODUCTION

DISSERTATION OBJECTIVES

The goal of this work was to identify genetic risk factors underlying primary hypoadrenocorticism in two highly affected dog breeds: the Portuguese Water Dog and the Standard Poodle. The breeds are closely related¹ and have the greatest incidence of disease compared to any other dogs². In the first half of my dissertation, I describe an imputed low-coverage sequencing approach used to generate a dense, unbiased dataset of variants. I perform a genome-wide association study (GWAS) for primary hypoadrenocorticism in Standard Poodles and identify a novel locus associated with the disease, as well as two additional loci with extended haplotype homozygosity unique to cases. No candidate variants are found in coding regions upon scanning high-coverage genomes, but six variants intronic to *CACNA1C* and *ANO2* are identified at conserved positions and are associated with primary hypoadrenocorticism in the GWAS cohort.

The latter half of my dissertation investigates the genetic backgrounds of Portuguese Water Dogs and Standard Poodles in efforts to understand what factors are driving their high risk, a 29-fold and 17-fold increased risk respectively, for primary hypoadrenocorticism compared to other dogs². I discover shared signatures of selection over six genomic regions, including the loci responsible for the furnishings trait observed in both breeds. Additional signatures of selection distinguish the breeds, and I perform functional enrichment analyses

using genes mapped from the loci. I reveal an overrepresentation of genes related to the immune system regulator IL-1 in Portuguese Water Dogs but not in Standard Poodles. Major histocompatibility complex (MHC) class II three-locus haplotypes also differ between the breeds, and a haplotype associated with risk is identified in Portuguese Water Dogs but not in Standard Poodles. Using high-coverage whole genome sequence from Standard Poodles, Portuguese Water Dogs and 2,692 dogs from 384 other breeds, unique coding variants in the Standard Poodle and Portuguese Water Dog breeds, where I discover four damaging mutations that have an association with primary hypoadrenocorticism.

From the aforementioned results, a better understanding of the genetic risk factors underlying primary hypoadrenocorticism is gained, which can help identify novel human contributors as well as aid dog breeders with selection to decrease the frequency of disease.

THE CANINE MODEL

Dogs are the earliest domesticated species and have undergone at least two major genetic bottleneck events: one during early domestication from gray wolves and another during breed formation³⁻⁶. The latter resulted in extensive linkage disequilibrium (LD) approximately 100X longer than in humans, as dogs underwent artificial selection for breed-forming traits, such as for size, coat type, and behavior³⁻⁷. Furthermore, selection for popular sires, founder effects, and breeding practices allowing for closely related mate-pairs have prompted especially large amounts of homogeneity within breeds, while dogs across breeds remained genetically diverse⁵⁻⁸. As a result, dogs have a unique population structure consisting of long LD within breeds and narrow LD across breeds, making them an ideal model for identifying novel loci compared to heterogeneous human populations, while still enabling the discovery of causative variants with their vast diversity observed across breeds.

Canine GWASs for complex traits need only a fraction of the individuals required in human GWASs. A study sample may comprise of less than 100 dogs but still succeed in identifying novel variants underlying disease⁹. Many complex diseases in humans occur naturally in dogs or have an analogous human counterpart⁹. At the time of this publication, there are over 600 heritable phenotypes in dogs that can serve as potential models for human disorders¹⁰ (Online Mendelian Inheritance in Animals 2024; <https://omia.org/>). Additionally, the availability of samples from pet populations, likely with medical records or family histories, eliminates the need to induce conditions and establish costly research colonies¹¹.

Finally, similar physiologies, immune systems, and environmental exposures make dogs an excellent model for studying human complex diseases^{9,11,12}. Large organ sizes and comparable immunological profiles facilitate translation into human medicine^{9,12}. The dog model especially trumps murine models for immune disorders because the dog major histocompatibility complex (MHC) involves many of the same functional class II genes as humans, including DQA1, DQB1, DRA, and DRB1¹³. Class I genes are also shared, with dog leukocyte antigen (DLA) -88 corresponding to human leukocyte antigen (HLA) -C, and DLA-64 corresponding to HLA-B¹⁴. On the other hand, murine histocompatibility (H2) lacks DQA1 and DRA human counterparts, limiting the species' usefulness as a model¹⁵.

PRIMARY HYPOADRENOCORTICISM

Presentation. Primary hypoadrenocorticism is a complex disorder involving the destruction of the outermost layer of the adrenal glands, the adrenal cortex. The adrenal cortex is responsible for the chief production of two essential hormones: aldosterone and cortisol. Aldosterone maintains fluid and salt homeostasis in the body by promoting sodium absorption, potassium excretion, and water retention in the kidneys^{16–18}. Lack of aldosterone therefore prompts low

blood sodium levels (hyponatremia), which at worst, can cause brain inflammation, seizures, and severe cognitive impairment¹⁹. Additionally, aldosterone insufficiency causes high blood potassium levels (hyperkalemia) that can affect the muscles of the heart, possibly triggering a heart attack^{18,20}. The second hormone, cortisol, is a major component of the Hypothalamic Pituitary Adrenal (HPA) axis, which governs the body's response to stress. Cortisol acts on all levels of the HPA-axis²¹⁻²³ and when released, can modulate diverse signaling cascades, including those of the cardiac system, hepatic system, reproductive pathway, and brain-gut axis²⁴⁻²⁷. Lack of these adrenocortical hormones in the dog causes nonspecific clinical signs including lethargy, vomiting, and dehydration²⁸. Treatment is life-long and often costly, involving continued replacement of these adrenocortical hormones, but diagnosis at an early stage can allow a more successful long-term prognosis^{28,29}.

Diagnosis. Diagnosis of primary hypoadrenocorticism requires an adrenocorticotropin hormone (ACTH) stimulation test that compares cortisol levels before (baseline) and after ACTH administration²⁹. Blood electrolyte levels are also used, with low sodium and high potassium corresponding to the typical form of the disease. Extremely rare in people but more common in some dog breeds, another form known as atypical primary hypoadrenocorticism can occur, which presents with normal electrolyte levels because the outermost layer of the adrenal cortex, where aldosterone is produced, remains intact^{28,29}. In people, the most common etiology of primary hypoadrenocorticism is autoimmune and diagnosed via the detection of autoantibodies against a major steroid-producing enzyme, 21-hydroxylase³⁰⁻³². To date, one study in dogs has investigated 21-hydroxylase, but found no evidence of immunoreactivity³³. The study did observe reactivity against P450 side-chain cleavage enzymes³³; however, the investigators do not specify if Portuguese Water Dogs or Standard Poodles were among the breeds with the reaction.

Human genetics. Most research on human primary hypoadrenocorticism has involved candidate gene approaches in genes previously associated with autoimmune diseases. The involvement of MHC genes in autoimmune disease and in primary hypoadrenocorticism is among the most extensively studied^{34–37}. MHC class II haplotypes HLA-DRB1*003:01/DQA1*005:01/DQB1*002:01 and HLA-DRB1*004:04/DQA1*003:01/DQB1*003:02 have been associated with increased risk, with their presence in heterozygosity increasing a person's likelihood of disease by 23-fold^{34,35}. Haplotypes containing HLA-DQB1*003:01 and HLA-DQB1*004:02 also conferred risk³⁷, and upon further dissection, Eriksson et al.³⁷ found that the DQB1 alleles alone explain haplotype associations. Regression modeling of class I and II genes revealed DQB1 as the major genetic determinant of primary hypoadrenocorticism and also implicated class I alleles encoding Asp at position 74 or 156 in HLA-B³⁷. The aforementioned HLA-DQB1 and HLA-B alleles include mutations that encode amino acid residues located within the peptide binding pocket of MHC molecules³⁸.

Several investigations have also associated mutations in *CTLA-4*, encoding cytotoxic T lymphocyte antigen 4, with primary hypoadrenocorticism risk^{39–41}. Normal functioning CTLA-4 prevents T-cell autoreactivity and has been implicated as a key regulator in autoimmune disease⁴². Thirteen additional genes have been noted as candidates from different investigators³⁸. Only one GWAS on primary hypoadrenocorticism in humans has been published, which identified 9 significantly associated regions, including the MHC locus³⁷.

Dog genetics. Three-locus haplotypes comprising of the most polymorphic MHC class II genes (DRB1, DQA1, and DQB1) have been associated with primary hypoadrenocorticism in 8 dog breeds: Bearded Collies, Nova Scotia Duck Tolling Retrievers, Cocker Spaniels, Springer Spaniels, Jack Russell Terriers, West Highland White Terriers, Labrador Retrievers, and

Standard Poodles^{43–46}. In Standard Poodles, two separate investigations^{45,46} found contradictory results (risk versus protective) for the haplotype DLA-DRB1*015:01/DQA1*006:01/DQB1*023:01. Treeful et al.⁴⁶ found that the haplotype conferred risk, while Massey et al.⁴⁵ determined that the haplotype was protective against primary hypoadrenocorticism. Massey et al.⁴⁵ also associated another haplotype with risk, which differs from the former by a single amino acid at position 90.

Although Portuguese Water Dogs have the greatest risk for primary hypoadrenocorticism, the MHC has not been investigated in the breed. Pedigree-based heritability analysis in Portuguese Water Dogs revealed an estimate of heritability of 0.49; however, the investigators noted that 2,051 out of 2,077 dogs in the study were derived from one large family⁴⁷, which is not surprising given the current Portuguese Water Dog population can be traced back to 31 founders⁴⁸. The second study focused on late-onset primary hypoadrenocorticism and performed a genome-wide scan in 57 cases and 749 controls using microsatellite markers⁴⁹. Quantitative trait loci (QTLs) were identified on chromosome 12 around the DLA region and on chromosome 37 around *CTLA-4*. No other research on the genetic factors underlying the breed's high incidence of primary hypoadrenocorticism has been published since these reports from 2006.

In Standard Poodles, a GWAS performed in 61 cases and 72 controls using SNP array datasets did not identify any significantly associated loci⁵⁰. Originally, the disease in Standard Poodles was thought to follow an autosomal recessive inheritance pattern⁵¹. One locus may still exhibit this inheritance pattern, but findings from the GWAS indicate the likely involvement of multiple loci with complex gene interactions⁵⁰. One other GWAS was performed in a different

high-risk breed, the Bearded Collie, that found an association on chromosome 18, but no candidate variants were identified⁵².

Additional risk factors. Environmental risk factors have not been identified in humans, but several studies correlated gonadectomy with increased risk of primary hypoadrenocorticism in dogs^{53–55}. Treeful et al.⁵⁵ found that specifically in Standard Poodles and Portuguese Water Dogs, gonadectomy increases risk 3.6-fold in females and 6.6-fold in males. Common environmental triggers implicated in complex disease, such as cigarette smoke and seasonal variation⁵⁶, were also studied in Portuguese Water Dogs and Standard Poodles but only gonadectomy was associated with increased risk⁵⁵.

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CHAPTER 2

GENOMIC ANALYSES OF PRIMARY HYPOADRENOCORTICISM IN STANDARD POODLES USING IMPUTED LOW-PASS WHOLE GENOME SEQUENCING

ABSTRACT

Primary hypoadrenocorticism is an endocrine disorder characterized by the deficiency of cortisol and aldosterone, necessitating lifelong hormone replacement therapy. The disease occurs naturally in dogs and is significantly overrepresented in Standard Poodles, indicating a genetic predisposition. Gonadectomy is a major environmental risk factor in dogs that, to date, has not been considered in studies to identify genetic contributors to the disease. Here, we performed a genome wide association study, Bayesian effect size modeling, and extended haplotype homozygosity testing using imputed low-coverage whole genome sequencing data from 93 gonadectomized Standard Poodles. We identified a single region of association with low-to-moderate effect on chromosome 17 (chr17:47,719,566; $p = 1.9 \times 10^{-8}$) and detected a signature of selection over this locus and at two additional loci on chromosome 27. These regions harbor genes canonically associated with the central nervous system, behavior, and domestication, which have not been previously implicated in the etiology of primary adrenocortical dysfunction. We did not identify candidate variants in coding regions, but found variants in highly conserved positions that may affect gene regulation. The absence of a detectable major locus suggests that fixed genetic effects may underlie the increased risk of primary hypoadrenocorticism in Standard Poodles.

INTRODUCTION

Primary hypoadrenocorticism, also known as Addison's disease, is an endocrine disorder in which the adrenal cortex fails to produce sufficient cortisol and aldosterone, hormones that are essential for life. Symptoms include lethargy, nausea, musculoskeletal pain, weight loss, and hyperpigmentation and are generally nonspecific¹, complicating diagnosis². Lack of appropriate treatment with replacement hormones can cause a fatal Addisonian crisis, where severe

dehydration, circulatory failure, hyponatremia, and hyperkalemia can lead to hypovolemic shock or cardiorespiratory arrest^{1,3}. The prevalence of primary hypoadrenocorticism in humans ranges from 5-10 per million in Asian and American populations to upwards of 221 per million in Scandinavian populations⁴⁻⁶. Nearly all human patients with primary hypoadrenocorticism develop autoantibodies against 21-hydroxylase⁷⁻⁹, which strongly suggests an autoimmune etiology. Accordingly, genetic studies have identified associations with multiple immune genes, including the major histocompatibility complex (MHC) and the autoimmune regulator (AIRE) genes¹⁰⁻¹⁴.

Primary hypoadrenocorticism occurs naturally in dogs, with increased prevalence in certain breeds. Standard Poodles, Portuguese Water Dogs, and Bearded Collies have a 7 to 29-fold increased risk of developing the disease compared to other breeds, which is strongly indicative of a genetic component^{15,16}. Clinical signs, disease progression, and treatment strategies are nearly identical between dogs and humans^{17,18}. These similarities, coupled with the high disease prevalence in certain breeds, make the dog a potentially outstanding model organism for better understanding the human condition and developing novel therapeutic options across species.

Presently, the genetic risk factors and molecular mechanisms that cause adrenal dysfunction in canine primary hypoadrenocorticism are unknown. A published GWAS for primary hypoadrenocorticism in Standard Poodles did not identify any associations and suggested a complex inheritance pattern¹⁹. A similar study in Bearded Collies revealed a single associated locus but no strong candidate genes²⁰. Several studies have found associations between certain MHC class II haplotypes and primary hypoadrenocorticism in specific breeds²¹⁻²³, although other authors have suggested the candidate gene approach may cause spurious

associations²⁴. One immunological study in dogs could not identify an autoantibody biomarker for the disease in over 75% of cases²⁵, suggesting that an immune-mediated mechanism for adrenocortical dysfunction in primary hypoadrenocorticism may not be universal across dog breeds.

A consistent finding in canine primary hypoadrenocorticism is that gonadectomy is a major non-genetic risk factor^{26–28}. Further, gonadectomy confers greater risk for neutered males (6.6-fold) than for spayed females (3.6-fold)²⁸, potentially implicating the loss of androgens in the disease pathogenesis. In this study, we performed GWAS, Bayesian mixture modeling, and extended haplotype homozygosity testing with imputed low-coverage whole genome sequencing data to identify genetic risk factors of primary hypoadrenocorticism in Standard Poodles. To mitigate the impact of gene-environment interactions, all dogs in our study cohort were neutered males or spayed females. We identified three risk loci that harbor genes associated with the central nervous system, behavior, and domestication, which to date, has not been implicated in the etiology of adrenocortical dysfunction. Our inability to detect a major locus suggests that a significant component of disease risk in Standard Poodles may be due to fixed alleles, meriting further investigation.

RESULTS

Genome-wide association studies. For GWAS, we defined a cohort of 93 Standard Poodles, comprising 56 cases (35 female, 21 male) and 37 controls (25 female, 12 male). All individuals were gonadectomized and unrelated within three generations based upon pedigrees. Dogs were balanced for North American and European ancestry across case and control populations. We performed low-coverage whole genome sequencing with genotype imputation to high coverage, and we filtered our imputed dataset of 8,864,770 confidently called bi-allelic SNVs for MAF and

HWE, leaving 6,561,166 SNVs. Non-reference genotype concordances were above 98% for each of 10 Standard Poodles from which both low- and high-coverage data were generated. After removing SNVs in high LD ($r^2 < 0.99$), 1,618,820 SNVs remained.

Numeric regression analyses were performed with this dataset, which we first validated through a GWAS for eumelanin vs. pheomelanin coat colors, a trait known to be controlled by a SNV in *Melanocortin 1 Receptor* (*MC1R*) on chromosome 5 at position 64,186,728 bp²⁹. This GWAS only included dogs whose coat color was provided by the owner ($n = 88$) and compared 60 dogs having eumelanin (black, brown, blue, gray, and silver) to 28 dogs having only pheomelanin (red, apricot, cream, and white). The lead SNV (chr5:64,167,306; $p = 2.3 \times 10^{-21}$) was located 19 kb downstream of *MC1R* (Fig 1). A weaker signal on chromosome 16 tagged *beta-defensin 103* (*CBD103*), another locus controlling pigment type in poodles^{30,31}.

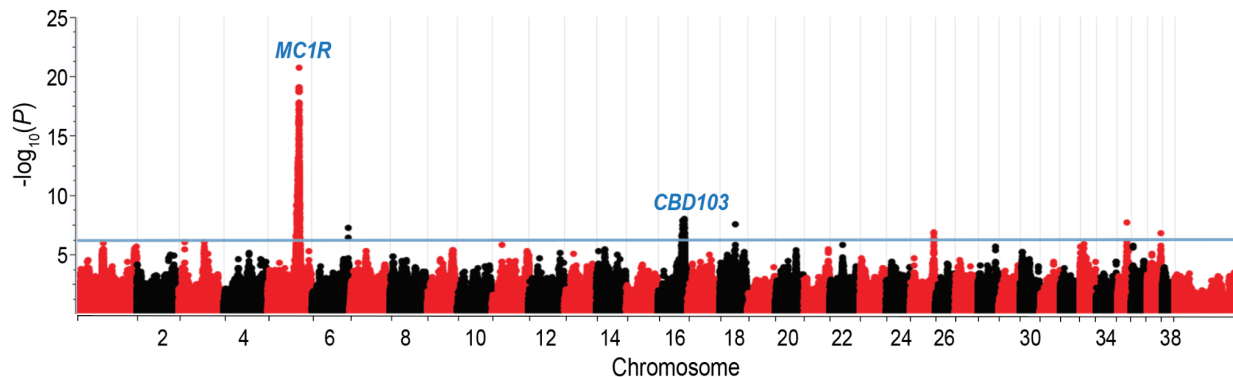


Fig 1. Manhattan plot depicting GWAS results for eumelanin coat color using 60 eumelanin and 28 pheomelanin Standard Poodles. Signals on chromosome 5 and 16 mark genes controlling pigment type, *MC1R* and *CBD103*, respectively. Blue line denotes Bonferroni-corrected statistical significance.

We next performed a GWAS for primary hypoadrenocorticism with 56 cases and 37 controls and identified a single region of association on chromosome 17 (chr17:47,719,566; $p = 1.9 \times 10^{-8}$, Fig 2A). In the unpruned dataset, 35 SNVs exceeded Bonferroni-corrected significance levels (1×10^{-7}). All significantly associated SNVs had a MAF of at least 0.34 in a database of whole genome sequences from 2,771 dogs, suggesting they are common polymorphisms.

Pairwise LD analysis with the lead SNV revealed a narrow region of LD spanning 163 kb ($r^2 > 0.6$) between *leucine-rich repeat transmembrane neuronal 4 (LRRTM4)* and *GC-rich sequence DNA-binding factor 2 (GCFC2)* (Supplemental Fig 2.1). Effect size analysis using BayesR showed that this locus had a low-to-moderate effect on disease phenotype and did not reveal additional suggestive loci (Fig 2b).

A 107 kb window (chr17:47,504,600-47,611,750) adjacent to the 163 kb associated region was not imputed because of low quality variants that were omitted from the imputation reference panel. Visual inspection of aligned sequences within this gap revealed high-coverage ($> 10X$) but poorly mapped reads (MAPQ scores < 10), consistent with a camouflage region described by Wang et al³² and refers to genomic regions with high coverage ($>10X$) but poor quality reads (mapping $< 10\%$). We compared the UU_GSD_1.0 reference sequence in this region to well-annotated, contiguous mammalian genomes (e.g., human, GRCh38/hg38; mouse, GRCm39/mm39) using the UCSC LiftOver tool³³ and found minimal similarity and an absence of transcribed sequences.

Extended haplotype homozygosity. We performed cross population extended haplotype homozygosity testing (XP-EHH) for primary hypoadrenocorticism using the GWAS population of 93 dogs. Signals of selection were detected on 4 chromosomes (Fig 2c; Table 1). Three regions on two chromosomes were under putative selection in cases, one of which encompassed the associated locus on chromosome 17 (chr17:47,651,869 – 47,881,710). The SNV with the greatest XP-EHH score (4.99) was also in this region at position 47,781,262 bp. Chromosome 27 contained two additional signals of selection in cases: chr27:1,716,753 – 1,916,753 and chr27:6,394,124 – 6,852,301. The former region contained two genes, *calcium voltage-gated channel subunit alpha1 C (CACNA1C)* and *Mitogen-Activated Protein Kinase 3 (MAPK3)*; the

latter region contained three genes, *Ubiquinone Oxidoreductase Subunit A9* (*NDUFA9*), *Neurotrophin 3* (*NTF3*), and *Anoctamin 2* (*ANO2*).

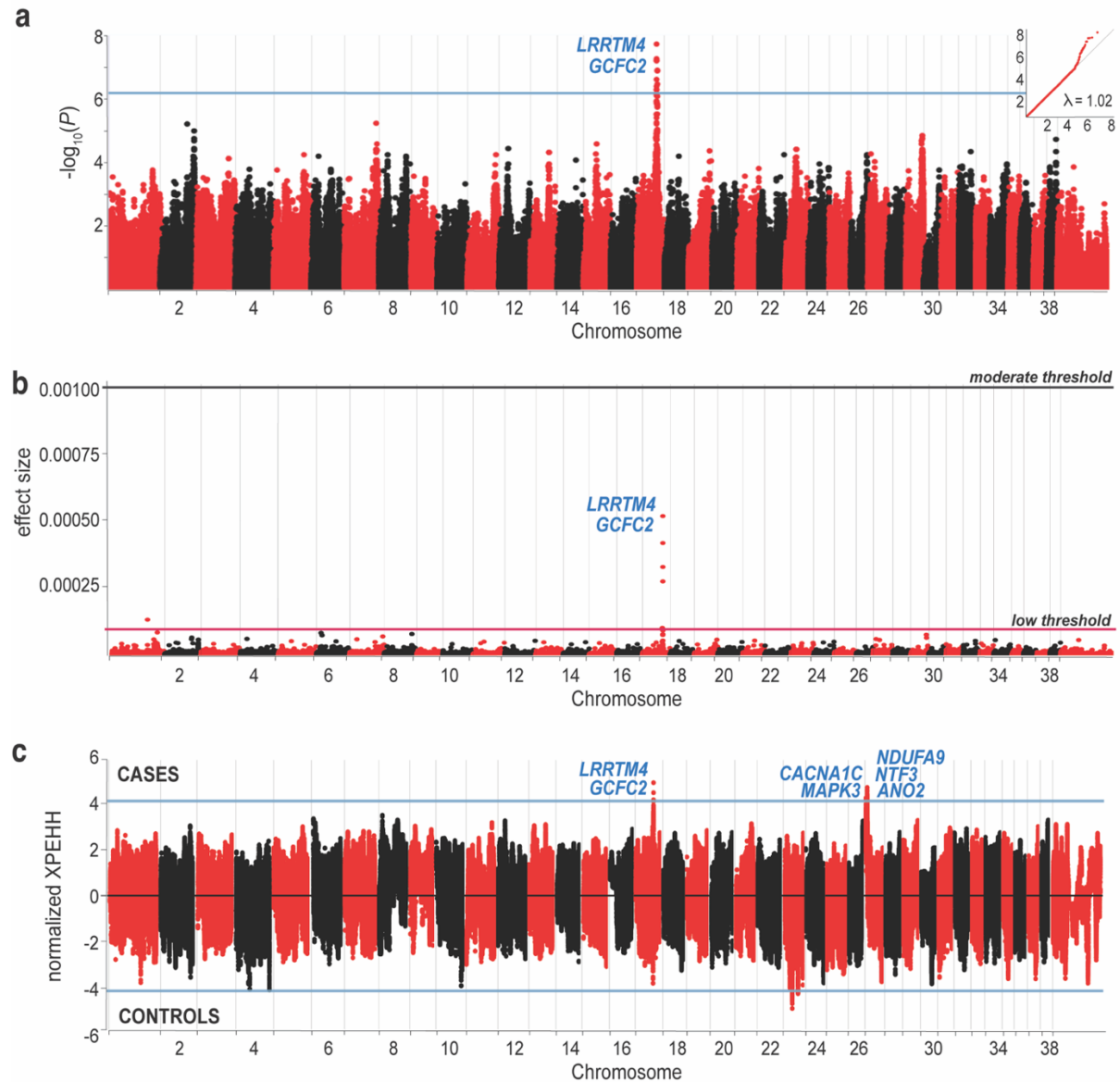


Fig 2. Results of genome-wide analyses for primary hypoadrenocorticism using 56 cases and 37 controls. (a) Manhattan plot of GWAS results shows a single region of association on chromosome 17 (Bonferroni significance = 1×10^{-7} , denoted by blue horizontal line). Inset depicts QQ plot with observed vs expected $-\log_{10}(p)$; genomic inflation factor (λ) is shown. Flanking genes are listed. (b) Manhattan plot of BayesR results shows a low-to-moderate effect size for the association on chromosome 17 (small effect size threshold = 0.0001, red line; moderate effect size = 0.001, black line). (c) Miami plot of normalized XP-EHH scores illustrates selection signatures in cases (top) and controls (bottoms). The blue horizontal lines denote the top 0.5% of SNVs. Genes within the selected regions on chromosome 27 are given; the genes on chromosome 17 flank the selected intergenic region.

Table 1. Genomic regions with signals of selection in Standard Poodles (56 cases vs. 37 controls) for primary hypoadrenocorticism determined via XP-EHH testing.

Selected Population	Chr	Region	Genes
control	4	36,655,104 – 36,855,104	<i>SINHCAF, FAM193B, DOK3, DDX41, PDLIM7, DBN1, GRK6, F12, PFN3, SLC34A1</i>
control	4	87,574,125 – 87,775,049	<i>BASPI</i>
case	17	47,651,869 – 47,881,710	---
control	23	18,244,478 – 18,464,564	<i>OXSM, NGLY1, TOP2B</i>
control	23	23,814,270 – 24,476,457	<i>EFHB, PP2D1, RAB5A, KCNH8</i>
control	23	38,985,271 – 39,213,562	<i>TRPC1, PCOLCE2, PAQR9, U2SURP</i>
case	27	1,716,753 – 1,916,753	<i>CACNA1C, MAPK3</i>
case	27	6,394,124 – 6,852,301	<i>NDUFA9, NTF3, ANO2</i>

Variant Analyses. Within our XP-EHH candidate regions on chromosomes 17 and 27, we did not identify any variants that were in high LD ($r^2 > 0.8$) with the lead SNVs and located within coding regions, splice sites, or untranslated regions (Supplemental Table 2.1). We next filtered for variants in conserved positions (phyloP³⁴ score > 2). There were no conserved SNVs in the window of association on chromosome 17; however, we identified 6 conserved SNVs on chromosome 27, which were also significantly associated with primary hypoadrenocorticism in the 93-dog population ($p \leq 0.01$) and 4 of the SNVs were located within putative enhancer elements³⁵ (Table 2). One of these variants was intronic to *ANO2* and had a highly conserved PhyloP score of 8.415 at position chr27:6,992,728. Further investigation of the SNV revealed it to be located within a distal cis-regulatory element³⁵ and is predicted *in silico* to significantly change the binding affinity of 4 transcription factors: GATA1, EVI1, TBP, and GATA3 (Supplemental Fig 2.2). The alternate allele (ref:G; alt:A) is on the haplotype that is overrepresented in cases and has a low frequency (0.009) across other breeds in the 2,771 WGS dataset. The alternate allele frequency in our GWAS population of 93 Standard Poodles was

0.38. Seventy-nine percent of Standard Poodles that were homozygous for the risk allele were affected.

Table 2. Conserved, intronic variants (phyloP score >2.0) in linkage disequilibrium ($r^2 > 0.6$) with the lead SNVs based on 39 high-coverage Standard Poodles. Minor allele frequencies are provided for 2,771 dogs representing 387 breeds including the 39 Standard Poodles and for 93 low-pass Standard Poodles (56 cases, 37 controls); percent homozygosity is also provided for these Standard Poodles. Variants are significantly associated with primary hypoadrenocorticism in the 93-dog population ($p \leq 0.01$). Enhancer ID and description of gene(s) or location that the enhancer may regulate is provided in the last column.

Position	Variant	MAF		% Homozygosity		Gene	PhyloP Score	Element	
		Dog <i>n</i> = 2771	Poodle <i>n</i> = 39	Cases <i>n</i> = 56	Controls <i>n</i> = 37			Enhancer ID	Target
27:1744491	C > T	0.067	0.44	35.7 %	10.8%	<i>CACNA1C</i>	2.125	GH12J002255	<i>CACNA1C</i> <i>FKBP4</i> <i>TULP3</i> <i>NRIP2</i> <i>DCP1B</i> <i>LRRTM2</i> <i>ITFG2</i>
27:1888920	C > T	0.011	0.40	30.4%	10.8%	<i>CACNA1C</i>	2.443	GH12J002109	<i>CACNA1C</i>
27:6329788	G > A	0.127	0.39	30.4%	5.4%	lncRNA	3.047	GH12J005094	<i>KCNA5</i> <i>NTF3</i>
27:6906806	C > T	0.197	0.41	30.4%	8.1%	<i>ANO2</i>	2.388	---	
27:6928091	C > T	0.175	0.39	49.1%	24.3%	<i>ANO2</i> lncRNA	2.236	---	
27:6992728	G > A	0.015	0.38	30.4%	8.1%	<i>ANO2</i>	8.415	EM10E0835398	Cis-regulatory with distal signature

To search for structural variants, we manually scanned candidate regions in IGV in high-coverage sequences from cases that were homozygous for risk alleles across the haplotypes and from controls homozygous for the alternate haplotypes. On a chromosome 27 risk haplotype, we identified a 1,106 bp deletion intronic to *CACNA1C* (Supplemental Fig 2.3) that was 5 kb from the lead SNV. This deletion was not present in our variant call file. Pairwise LD revealed that the deletion and lead SNV were perfectly correlated in 39 Standard Poodles with high-coverage sequences. Using the lead SNV as a proxy, we estimated the allele frequency of the deletion in the 2,771-dog database to be 0.2. In our GWAS population of 93 dogs, homozygosity was significantly overrepresented in cases, where 72% of dogs homozygous for the risk allele were

affected. Twenty-six SNVs within the deletion had phyloP scores between 4.0 and 8.5. The deletion was also within a 1.9 kb enhancer element that regulates *CACNA1C*, *FKBP4*, and *DCP1B*. Furthermore, the deletion was within two antisense transcripts, exonic to CFRNASEQ_AS_00100781 and intronic to CFRNASEQ_AS_00100780.

DISCUSSION

In this study, we carefully selected a cohort of Standard Poodles to maximize the likelihood of identifying genetic factors contributing to primary hypoadrenocorticism through various genome-wide approaches. In contrast to a previous study¹⁹, our assembled population is minimally related, geographically balanced, and all individuals had undergone gonadectomy, the strongest environmental risk factor known for the development of hypoadrenocorticism^{26–28}. Further, our use of low-pass sequencing followed by genotype imputation allowed us to perform these analyses with a comprehensive set of unbiased variants, thereby increasing statistical power. Through GWAS and XP-EHH, we identified three loci on chromosomes 17 and 27 that distinguish affected from unaffected dogs. Within these loci, we identified genes implicated in brain development and animal domestication. Consistent with our expectation that primary hypoadrenocorticism is a complex genetic trait, high-coverage genomes from affected and unaffected dogs did not reveal coding variants that segregate with affected animals. We did, however, identify several non-coding variants with high PhyloP scores in genes related to synaptic plasticity. Our data suggest that primary hypoadrenocorticism in Standard Poodles may at least, in part, be driven by components of the central nervous system and its interactions with the hypothalamic-pituitary-adrenal (HPA) axis.

The chromosome 17 locus identified in both our GWAS and XP-EHH analyses contains two genes, *LRRTM4* and *GCF2*. LRRTM proteins are well-known mediators of glutamatergic

synapses^{36–46}. Regulation of these synapses is crucial for maintaining normal brain function, developmental processes, and synaptic plasticity. In humans, learning and psychiatric disorders have been traced to dysfunction of glutamatergic synapse activity, and *LRRTM4* specifically is associated with attempted suicide^{47,48}, depression⁴⁹, substance abuse^{50,51}, Tourette syndrome, autism, and ADHD⁵². Consistent with its importance in behavior, *LRRTM4* may be associated with predation across dog breeds⁵³ and fear of fireworks in Standard Poodles⁵⁴. Interestingly, primary hypoadrenocorticism in Bearded Collies maps to another leucine-rich repeat family member involved in synaptic plasticity, *LRRC4C*²⁰. Less is known about *GCFC2*; however, it too is believed to play a role in brain health and has been associated with dyslexia⁵⁵, learning impairment⁵⁶, general cognitive ability⁵⁷, and hippocampal volume⁵⁸.

Candidate variants in genes with roles in synaptic plasticity were found in the chromosome 27 loci, specifically within introns of *CACNA1C*⁵⁹ and *ANO2*^{60–67}. *CACNA1C* encodes a subunit of CaV1.2, a voltage gated-calcium channel important for electrical signaling between neurons⁶⁸. In humans, *CACNA1C* mutations underlie psychiatric disorders including autism^{69,70}, schizophrenia, bipolar disorder, and major depression⁷¹. In canids, *CACNA1C* has been implicated with nonsocial fear⁷² and domestication^{73,74}. *ANO2* encodes a channel responsible for depolarizing calcium-activated chloride currents critical for smell⁷⁵, with expression highly localized to the olfactory system and the hippocampus. *ANO2* has been associated with aggression, anxiety, and memory in mice^{63,64}, while in canids, has been implicated with fear of other dogs and with domestication⁷².

The mechanism by which neural synapse genes might contribute to adrenocortical dysfunction is unclear. One possibility involves dysfunction of sympathetic neurons that terminate in the adrenal cortex. In dogs, sympathetic innervation of the adrenal gland can affect

corticosteroid secretion without influence from the HPA-axis, suggesting that the nervous system may play a role in adrenocortical function^{76,77}. Another mechanism may involve alterations in glutamatergic synapses that modulate the HPA-axis through signaling to the paraventricular nucleus of the hypothalamus⁷⁸. Interestingly, selection for variants in glutamate receptors in dogs may have occurred because of their influence on social behaviors and domestication⁷⁹.

Domesticated animals have a reduced stress response compared to their fearful or aggressive pre-domesticated ancestors that facilitates their interactions with humans. This may entail a blunted adrenal stress response, thereby increasing the risk of primary hypoadrenocorticism in certain groups of animals^{80,81}. Further investigation of the mechanisms by which neural synapse genes could affect the adrenal cortex and contribute to primary hypoadrenocorticism is needed.

In conclusion, a carefully designed GWAS that accounted for the environmental effect of gonadectomy yielded only a single locus of low-to-moderate effect on primary hypoadrenocorticism. A limitation of this study was our inability to consider the age of the dog at the time of gonadectomy or its relationship with the onset of clinical signs. Additionally, we were unable to completely interrogate a window centromeric to the association on chromosome 17, which could potentially harbor deleterious variants. Still, our inability to detect a major risk locus for primary hypoadrenocorticism suggests that breed-defining alleles may underlie the increased disease risk observed in the Standard Poodle breed. Consistent with this idea, we observed increased homozygosity among cases at the associated locus and two additional loci. Finally, it is notable that we did not find any evidence for the involvement of genes that are known to be related to the immune system. Although the disease in humans is primarily immune-mediated, there is limited evidence to date to support a role for the immune system in the etiology of canine primary hypoadrenocorticism.

MATERIALS & METHODS

Study population. Whole blood or buccal swabs were collected with informed owner consent from Standard Poodles across the United States, Canada, and Europe (University of Minnesota IACUC Protocol 2207-40214A). In addition, hundreds of archival Standard Poodles DNA samples from previous studies were available¹⁹. Cases were diagnosed via serum electrolyte levels (sodium:potassium ratio < 27:1) and ACTH stimulation testing (pre- and post-ACTH cortisol levels < 2 µg/dL). Controls were at least 9 years of age and had normal baseline cortisol levels (> 2 µg/dL), no clinical history of autoimmune disease, and no known relatives with primary hypoadrenocorticism. Genomic DNA was isolated using routine methods.

Low-pass whole-genome sequencing. Pedigrees from our study population were evaluated to select a subset of 138 dogs to minimize relatedness. All selected dogs had undergone gonadectomy. PCR-free libraries were constructed and low-pass sequencing targeting 3X coverage was performed on an Illumina NovaSeq 6000 to generate dual-index 150 bp paired-end reads. Low-pass sequence coverage averaged 4.3X (Supplemental Table 2.2). Raw sequencing reads were aligned to the UU_GSD_1.0 reference genome³² concatenated with the Y chromosome contigs from the ROS_Cfam_1.0 reference genome⁸² using the *OneWAG* pipeline⁸³. A target panel was then prepared using *-mpileup* (BCFtools v1.15.1) and filtered to include only high-quality (quality scores ≥ 20), non-missing, biallelic SNVs.

High-coverage whole-genome sequencing. We developed an in-house database of high-coverage (> 10X) whole-genome sequences comprising 1,971 publicly available dogs from the Dog10K project⁸⁴ and 800 private whole-genome sequences from various ongoing collaborative efforts. All sequences were initially processed using the *OneWAG* pipeline⁸³, however the Dog10K sequences began from CRAM files rather than FASTQs. Joint genotyping was conducted with

the *ManyWAGS* pipeline⁸³. Our database of 2,771 WGS dogs includes 21 Standard Poodles with primary hypoadrenocorticism, 18 unaffected Standard Poodles, and 2,732 dogs across 389 additional breeds.

Genotype imputation. We developed an imputation reference panel from a subset of our high-coverage database to impute low-pass sequences from Standard Poodles and 6 other target breeds for separate projects. From the 2,771 dog database, we removed all village dogs, mixed-breed dogs, and dogs with a median coverage less than 18X. We included all available sequences from our 7 target breeds (Standard Poodle, Portuguese Water Dog, German Shepherd Dog, Great Dane, Belgian Tervuren, White Swiss Shepherd, and Belgian Malinois) and sequences from 7 random dogs per breed for other breeds with at least that many individuals available. The final panel included 742 publicly available sequences from 94 breeds (Supplemental Table 2.3). The BCFtools plugins *+fill-tags* and *+fixploidy* were used to populate default tags and enforce diploid states. Next, we filtered for biallelic, non-missing SNVs with allele frequencies $> 1/742$ (~ 0.001348), no more than 1% missing genotypes, and passing variant quality score recalibration (VQSR). We phased these SNVs using Beagle 5.1⁸⁵. Low-coverage data were imputed from this reference panel using Beagle 4.0⁸⁶ in genotype likelihood mode with standard flags and filtered for dosage R-squared ($DR2$) ≥ 0.8 . A containerized version of this pipeline is available via GitHub (<https://github.com/jonahcullen/SLOPIdog>). Imputation accuracy was assessed by comparing non-reference genotype concordance between high and low-coverage whole genome sequencing data from 10 Standard Poodles using the GenotypeConcordance function of Picard Tools (<https://broadinstitute.github.io/picard/>).

Genome Wide Association Studies. From our imputed dataset, we removed SNVs with minor allele frequencies $< 5\%$ and significant deviation from Hardy-Weinberg equilibrium ($p < 0.0004$)

using PLINKv1.9 with *--maf* and *--hwe* flags. A kinship matrix was generated for the filtered, imputed dataset using SNP & Variation Suite v8 (SVS, Golden Helix) and identity-by-state (IBS) distances were plotted to assess relatedness between individuals (Supplemental Fig 2.4). After applying a cutoff of 0.75, we removed 29 dogs from the dataset. A principal component analysis (PCA) plot was generated in SVS after linkage disequilibrium (LD) pruning to a threshold of $r^2 > 0.20$, and 16 dogs in a distant cluster were removed (Supplemental Fig 2.5). This left a population of 93 dogs available for GWAS analyses.

GWASs were performed in SVS using a numeric regression model with genotype likelihood scores from Beagle 4.0 and an LD pruned ($r^2 > 0.99$) dataset. Sex was used as a covariate in the GWAS for primary hypoadrenocorticism. Bonferroni significance threshold was based on independent SNVs ($r^2 > 0.20$). Pairwise LD analysis between the lead variant and unpruned SNVs within 2 Mb was conducted using all control Standard Poodles and plotted via LocusZoom⁸⁷.

A Bayesian mixture model was applied to estimate the effect sizes of all variants simultaneously. Our MAF and HWE-filtered dataset was LD pruned ($r^2 > 0.15$) to target approximately 500,000 SNVs. BayesR was then employed to estimate the genetic architecture, incorporating sex as a covariate. The number of iterations (*--numit*) was increased from 50,000 to 300,000, while all other parameters were left at their default settings. SNVs were categorized based on their effect size, with thresholds of 0.0001, 0.001, 0.01 used to define small, moderate, and large effects, respectively.

Extended haplotype homozygosity. Cross-population extended haplotype homozygosity (XP-EHH) testing was performed using the pruned dataset ($r^2 > 0.99$) containing 93 dogs. XP-EHH scores were generated using the *--xpehh* flag with default settings in selscan⁸⁸ and normalized in

R with the bestNormalize package. Normalized values in the top 0.5% were considered to be under selection.

Variant analyses. Candidate regions were defined as 500 kb flanking the intervals identified through XP-EHH, which encompassed the single associated GWAS region on chromosome 17 (Table 1). We manually scanned the candidate regions in high-coverage genomes using Integrated Genome Viewer⁸⁹ (IGV) and searched for possible causal variants in coding regions, splice sites, and 5' or 3' UTRs. Non-coding variants within associated regions with a phyloP score $> 2.0^{34}$ were evaluated in UCSC Genome Browser for overlap with known regulatory elements using GeneHancer v5.2 track⁹⁰ in human (GRCh38/hg38) and the ENCODE candidate cis-regulatory elements (cCREs) track³⁵ in mouse (GRCm39/mm39). Additionally, we searched for changes in binding motif specificity (≥ 10 -fold P -value difference) using the sTRAP webtool (trap.molgen.mpg.de) and visualized motif sites using JASPAR (jaspar2020.genereg.net).

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AUTHOR CONTRIBUTIONS

S.G.F., L.A.C., and E.A.G. conceptualized the study; S.G.F., E.A.G., F.F.A., J.M.B., and A.M.O. recruited the study cohort; J.N.C. created the reference panel and performed the imputation.

E.A.G., K.E.D., H.K.R.H., S.G.F., and L.A.C. performed data analyses; E.A.G., S.G.F., and L.A.C. wrote the manuscript; E.A.G. prepared the figures; all authors reviewed the manuscript.

DATA AVAILABILITY

High- and low-coverage sequencing data has been deposited in the sequence read archive (SRA) under BioProject Nos PRJNA937381 and PRJNA1170923.

ADDITIONAL INFORMATION

The authors declare no competing interests.

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CHAPTER 3

UNDERSTANDING THE GENETIC BACKGROUNDS OF TWO DOG BREEDS WITH
HIGH RISK FOR PRIMARY HYPOADRENOCORTICISM

ABSTRACT

Primary hypoadrenocorticism is a complex, lifelong illness with increased risk in Portuguese Water Dogs and Standard Poodles, suggesting a genetic predisposition. Here, we investigate the genetic backgrounds of each breed using candidate and genome-wide approaches. We first discover that the major histocompatibility complex class II compositions differ between the breeds and that only Portuguese Water Dogs possess a clear risk haplotype for primary hypoadrenocorticism. Next, we use imputed low-coverage whole genome sequencing data from minimally related dogs to perform selective sweep analyses aimed at identifying breed-defining loci, both shared and distinct. Functional enrichment analysis reveals that only Portuguese Water Dogs have an overrepresentation of genes related to the immune system, specifically to interleukin-1. Finally, we perform filtering analyses for unique coding variants and identify four mutations associated with primary hypoadrenocorticism. These mutations are not shared between Portuguese Water Dogs and Standard Poodles, further supporting previous observations that major contributors driving disease differ between the breeds.

INTRODUCTION

Primary hypoadrenocorticism, commonly known as Addison's disease, is an endocrine disorder of the adrenal glands characterized by deficient aldosterone and cortisol production. The Portuguese Water Dog and Standard Poodle have the highest incidence of the disease compared to any other dog, and the two breeds are closely related^{1,2}. Dogs share similar disease pathophysiology to people; however, subtle clinical presentations can delay diagnosis, increasing the likelihood of fatality in the dog. Expensive and regimented treatment can further make managing a dog's illness particularly challenging. Understanding risk factors of the disease is therefore crucial to preventing future cases.

The most common etiology for primary hypoadrenocorticism in people involves an autoimmune attack against 21-hydroxylase^{3,4}. Testing for 21-hydroxylase antibodies is key for diagnosing autoimmune primary hypoadrenocorticism, but in dogs, only one study investigated 21-hydroxylase and found no evidence of immunoreactivity⁵. The major histocompatibility complex (MHC) class II genes have been associated with the disease in both people⁶⁻⁸ and dogs⁹⁻¹²; however, the effects of these genes in Portuguese Water Dogs and Standard Poodles are unclear^{10,12}. To date, MHC class II genotyping between affected and unaffected individuals has not been performed in Portuguese Water Dogs, despite the breed having the highest incidence of the disease across all dogs¹. A late-onset form of the disease in Portuguese Water Dogs was investigated using microsatellite markers, which identified quantitative trait loci surrounding the MHC region and another immune gene, *CTLA-4*¹³, but further investigation of these loci, which were published in 2006¹³, have not been performed.

Recently, we reported a novel association on chromosome 17 with primary hypoadrenocorticism in Standard Poodles (Greif et al., submitted 2024). Two additional loci were reported with increased haplotype homozygosity across cases, and candidate variants were identified in genes canonically associated with the central nervous system (Greif et al., submitted 2024). Variants at the associated locus on chromosome 17 had high allele frequencies across 387 dog breeds (Greif et al., submitted 2024), and therefore, we suspect additional risk factors are underlying the disease within Standard Poodles.

Here, we investigate the genetic backgrounds of primary hypoadrenocorticism in Portuguese Water Dogs and Standard Poodles by genotyping MHC class II haplotypes and by performing genome-wide analyses for selection signatures. Evidence herein suggests that breed-defining risk factors contribute to primary hypoadrenocorticism predisposition, but shared

contributors are also likely and merits further investigation. Risk factors related to the immune system are identified in Portuguese Water Dogs, while the etiology in Standard Poodles will require additional studies.

MATERIALS & METHODS

Study population. Whole blood or buccal cells were obtained with informed owner consent from purebred Portuguese Water Dogs and Standard Poodles according to protocols approved by IACUC (University of Minnesota IACUC Protocol 2207-40214A). Diagnosis of typical or atypical primary hypoadrenocorticism was determined via serum electrolyte levels (Na/K ratio < 27:1) and ACTH stimulation testing (pre- and post-ACTH cortisol levels < 2µg/dL) by the pet's veterinarian. Control dogs were at least 9 years old, had normal baseline cortisol levels (> 2µg/dL), and had no known autoimmune diseases nor affected relatives. Genomic DNA was extracted using the Gentra Puregene DNA Isolation kit (Qiagen), the QIAamp DNA Blood Mini and Midi kits (Qiagen), or the Nucleospin kit (Machery Nagel).

Sanger sequencing and genotyping of MHC class II genes. We selected cohorts of Portuguese Water Dogs (53 cases, 61 controls) and Standard Poodles (92 cases, 67 controls) for major histocompatibility complex (MHC) class II sequencing. Specifically, we investigated three-locus haplotypes comprising of DRB1, DQA1, and DQB1 genes. For Portuguese Water Dogs, only exon II of DRB1 was amplified because, to date, variability in DQA1 and DQB1 genotypes within three-locus haplotypes in the breed has not been observed. Variability does exist in Standard Poodles, and we therefore amplified exon II of DRB1, DQA1, and DQB1 in their cohort. We utilized primers described in Treeful et al.¹² and confirmed amplicon quality via gel electrophoresis. Products were cleaned using ExoSAP-IT (Thermo Fisher Scientific) and submitted to the University of Minnesota Genomics Center for Sanger sequencing. Genotypes

were assigned using Geneious Prime 2023.2.1 (<https://www.geneious.com>) by aligning sequences to known haplotypes from the Immuno Polymorphism Database (www.ebi.ac.uk/ipd) and three-locus haplotypes were determined for each dog. We compared allele frequencies between the Portuguese Water Dog and Standard Poodle breeds. Between cases and controls within each breed, we calculated two-tailed Fisher exact tests and odds ratios (OR) with 95% confidence intervals using VassarStats (vassarstats.net).

Low-coverage whole genome sequencing. For genomic analyses, we selected 101 minimally related Portuguese Water Dogs for low-coverage whole genome sequencing (low-pass) aimed at 3X coverage. Ninety-three neutered Standard Poodles with minimal relatedness were also selected for low-pass as previously described in Greif et al. (submitted, 2024). Libraries were constructed with the Illumina DNA Prep Kit and sequencing was performed on an Illumina NovaSeq 6000 to generate dual-index 150 bp paired-end reads, averaging 4.51X coverage across both breeds. Raw sequencing reads were aligned to the UU_GSD_1.0 reference genome concatenated with the Y chromosome contigs from the ROS_Cfam_1.0 reference genome using the *OneWAG* pipeline¹⁴ and filtered to include only high-quality (quality scores ≥ 20), non-missing, biallelic SNVs.

High-coverage whole-genome sequencing. High-coverage whole genome sequences from 2,771 publicly available dogs were processed and joint called using the *OneWAG* and *ManyWAGS* pipelines¹⁴ as previously described in Greif et al. (submitted, 2024). Using a subset of these genomes, we created a reference panel designed for the imputation of 7 dog breeds, referred to as target breeds henceforth, which included Portuguese Water Dogs and Standard Poodles. This imputation reference panel was limited to purebred dogs of at least 18X coverage. Additionally, non-target breeds were restricted to 7 randomly selected individuals per breed or were removed

from the panel if less than 7 individuals were available. A final reference panel with 742 dogs aligned to canFam4 comprised of 34 Portuguese Water Dogs, 31 Standard Poodles, and 677 other dogs from 93 breeds.

Genotype Imputation. We prepared the reference panel for genotype imputation by filtering for biallelic, non-missing SNVs with allele frequencies $> 1/742$ (~ 0.001348), $\leq 1\%$ missing genotypes, and passing variant quality score recalibration (VQSR). Haplotypes from the reference panel and partial haplotypes from the low-pass data were phased using Beagle 5.1. Low-pass sequences from Portuguese Water Dogs and Standard Poodles were imputed together up to high-coverage using Beagle 4.0 with standard flags and filtered for quality using dosage R-squared ($DR2 > 0.8$).

Runs of Homozygosity. We performed runs of homozygosity analysis with all markers in SNP & Variation Suite v8 (SVS, Golden Helix) to assess ongoing fixation in the Portuguese Water Dog and Standard Poodle breeds. Each breed was analyzed independently, and runs were generated using the following parameters: $\geq 500\text{kb}$, minimum of 100 SNPs per window, and allowing 1 heterozygous SNV. Autosomal runs were scanned using all dogs in each cohort ($n = 101$ for Portuguese Water Dogs, 93 for Standard Poodles), while runs in the X chromosome were scanned using females only ($n = 60$ for both breeds). We investigated runs found in at least 50% of the population and determined what genes were within 500kb of each region using the UCSC Genome Browser (Supplemental Tables 3.2-3). Runs containing a known gene under selection or consisting of a single gene were labeled on breed-specific Manhattan plots (Figure 2). We scanned high-coverage genomes in Integrated Genome Browser (IGV) to search for candidate variants under selection in coding regions, splice sites, and 5' or 3' UTRs for runs on chromosomes 7, 8, 11, 17, and 22.

Pairwise F_{ST} . We performed F_{ST} analyses to identify genomic regions under artificial selection in Portuguese Water Dogs or Standard Poodles compared to 49 other dog breeds with high coverage whole genome sequences. We filtered out samples with call rate $\leq 99\%$ and removed markers based on $MAF < 0.05$. We calculated pairwise F_{ST} , known as d_i statistic, for all autosomal SNVs (8,447,951) in R as previously described^{15,16}. Locally weighted scatterplot smoothing (LOESS) of the d_i values for each chromosome were used to visualize the data. Regions crossing the top 1% threshold of LOESS-smoothed values were considered as a region under selection (Supplemental Tables 3.4-5).

Variant filtering. We generated a table of unique, coding variants in Portuguese Water Dogs and Standard Poodles based on MAF thresholds in high-coverage datasets. We designated three groups from which MAFs were calculated for all variants: (1) 34 Portuguese Water Dogs, (2) 39 Standard Poodles, and (3) 2,692 dogs from across 384 other breeds that excluded poodle varieties or mixes. A table of unique bi-allelic variants was generated by filtering for variants with $MAF > 0.10$ in groups 1 or 2 and with $MAF < 0.00$ in group 3. Missense mutations were evaluated for conservation and deleterious effects using phyloP scores (>2) and Polyphen-2 predictions, respectively (Tables 1-2, Supplemental Tables 3.6-7).

Gene Ontology. Enrichment analyses were performed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID, <https://david.ncifcrf.gov/tools.jsp>) webtool on genes identified from runs of homozygosity, F_{ST} , and unique variant filtering for each breed. We assessed pathway terms based on P -values (≤ 0.05 after Benjamini correction) and enrichment clustering (scores > 1.3) (Supplemental Tables 3.8-15).

RESULTS

MHC Candidate Gene Study. Three-locus haplotypes comprising of DRB1, DQA1, and DQB1 MHC class II genes were assigned in 114 Portuguese Water Dogs and 159 Standard Poodles (Table 1, Figure 1A). Six haplotypes were identified in Portuguese Water Dogs, with the two most common appearing at roughly equal allele frequencies across the breed (Table 1, Haplotype Nos 1 and 2; 36.0% and 35.1%). Haplotypes 3 and 4 were less frequent (15.8% and 10.5%, respectively), while the final two haplotypes (Nos 5 and 6) were rare and had allele frequencies < 2%. Standard Poodles shared four of the Portuguese Water Dog haplotypes but at different proportions (Figure 1A). The predominant haplotype (No 7) in Standard Poodles did not appear in Portuguese Water Dogs and had an allele frequency of 67.0%. When grouped with two other haplotypes that differed by a single amino acid in DRB1 (Nos 4 and 8, Supplemental Table 3.1), hereinafter referred to as the 150X haplotype, the allele frequency was 82.4%. Seven haplotypes make up the remaining 17.6% of the MHC composition in Standard Poodles.

Table 1. Frequency of DLA-DRB1/-DQA1/-DQB1 haplotypes in Portuguese Water Dogs and Standard Poodles. The number of times each haplotype was observed with frequency for each breed is reported.

Haplotype No	Class II DRB1*/DQA1*/DQB1*	Portuguese Water Dogs (2n=228)			Standard Poodles (2n=318)		
		Total n (%)	Cases n (%)	Controls n (%)	Total n (%)	Cases n (%)	Controls n (%)
1	001:01/001:01/002:01 ^a	82 (36.0)	53 (50.0)	29 (23.8)	2 (0.6)	1 (0.5)	1 (0.7)
2	008:02/003:01/004:01 ^b	80 (35.1)	28 (26.4)	52 (42.6)	0 (0.0)	0 (0.0)	0 (0.0)
3	023:01/003:01/005:01	36 (15.8)	12 (11.3)	24 (19.7)	0 (0.0)	0 (0.0)	0 (0.0)
4	015:02/006:01/023:01	24 (10.5)	10 (9.4)	14 (11.5)	39 (12.3)	23 (12.5)	16 (11.9)
5	009:01/001:01/008:01:1	4 (1.8)	2 (1.9)	2 (1.6)	17 (5.3)	10 (5.4)	7 (5.2)
6	006:01/050:11/007:01	2 (0.9)	1 (0.9)	1 (0.8)	2 (0.6)	1 (0.5)	1 (0.7)
7	015:01/006:01/023:01	0 (0.0)	0 (0.0)	0 (0.0)	213 (67.0)	124 (67.4)	89 (66.4)
8	015:03/006:01/023:01	0 (0.0)	0 (0.0)	0 (0.0)	10 (3.1)	5 (2.7)	5 (3.7)
9	015:01/009:01/001:01	0 (0.0)	0 (0.0)	0 (0.0)	29 (9.1)	18 (9.8)	11 (8.2)
10	020:01/004:01/013:03	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	2 (1.1)	2 (1.5)
11	015:01/006:01/003:01	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0	1 (0.7)
12	015:01/006:01/049:01	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0	1 (0.7)

^a P-value = 0.0000537, OR = 3.21, CI = 1.82 - 5.64 in Portuguese Water Dogs

^b P-value = 0.0123, OR = 0.48, CI = 0.28 - 0.85 in Portuguese Water Dogs

Between cases and controls, we observed significant allele and genotype frequency differences in Portuguese Water Dogs but not in Standard Poodles (Figure 1B-D, Table 1). Haplotype No 1 was highly associated with risk of primary hypoadrenocorticism in Portuguese Water Dogs (P -value = 0.0000537), while haplotype No 2 conferred protection (P -value = 0.0123). In homozygosity, haplotype Nos 1 and 2 equally contributed to risk and protection (P -values = 0.02, Figure 1D). Standard Poodles were largely homogeneous with similar proportions of allele and genotype distributions between cases and controls (Figure 1C-D).

Low-pass dataset. For genome-wide analyses, we selected 101 Portuguese Water Dogs and 93 Standard Poodles with minimal relatedness for low-coverage whole genome sequencing (low-pass). Low-pass data were imputed together using a high-coverage reference panel of 742 purebred dogs, including 34 Portuguese Water Dogs and 31 Standard Poodles. After filtering for quality ($DR2 > 0.8$), the imputed dataset contained 8,864,770 confidently called bi-allelic SNVs.

Runs of homozygosity. To identify regions with selection signatures in each breed, we scanned for runs of homozygosity that were $>500\text{kb}$ across a minimum of 100 SNVs. Four autosomal regions were shared between Portuguese Water Dogs and Standard Poodles, located on chromosomes 8, 10, and 13 (Figure 2A-C, Supplemental Tables 3.2-3). Two additional regions were shared on the X chromosome (Figure 2A-C, Supplemental Tables 3.2-3). The region on chromosome 8 (chr8:75,568,220 – 76,080,185) contained no genes within or flanking 500kb; however, three retrogenes characterized in Batcher et al.¹⁷ were identified. Notably, this shared region is subtelomeric. The next two runs encompassed single genes, *glutamate receptor interacting protein 1* (*GRIPI*) on chromosome 10 (chr10:9,157,623 – 9,175,890) and *oxidation resistance 1* (*OXR1*) on the chromosome 13 (chr13:7,331,634 – 7,592,907). A second run on chromosome 13 (chr13:8,157,682 – 9,124,580) adjacent to *OXR1* contained three genes,

including the gene responsible for the furnishings trait in Portuguese Water Dogs and Standard Poodles, *R-spondin 2* (*RSPO2*). On the X chromosome, two regions encompassed single genes, *eukaryotic translation elongation factor 1 alpha 1* (*EEF1A1*) and *glutamate ionotropic receptor AMPA type subunit 3* (*GRIA3*), respectively (chrX:71,947,343 – 72,520,501 and chrX:94,290,302 – 95,760,830).

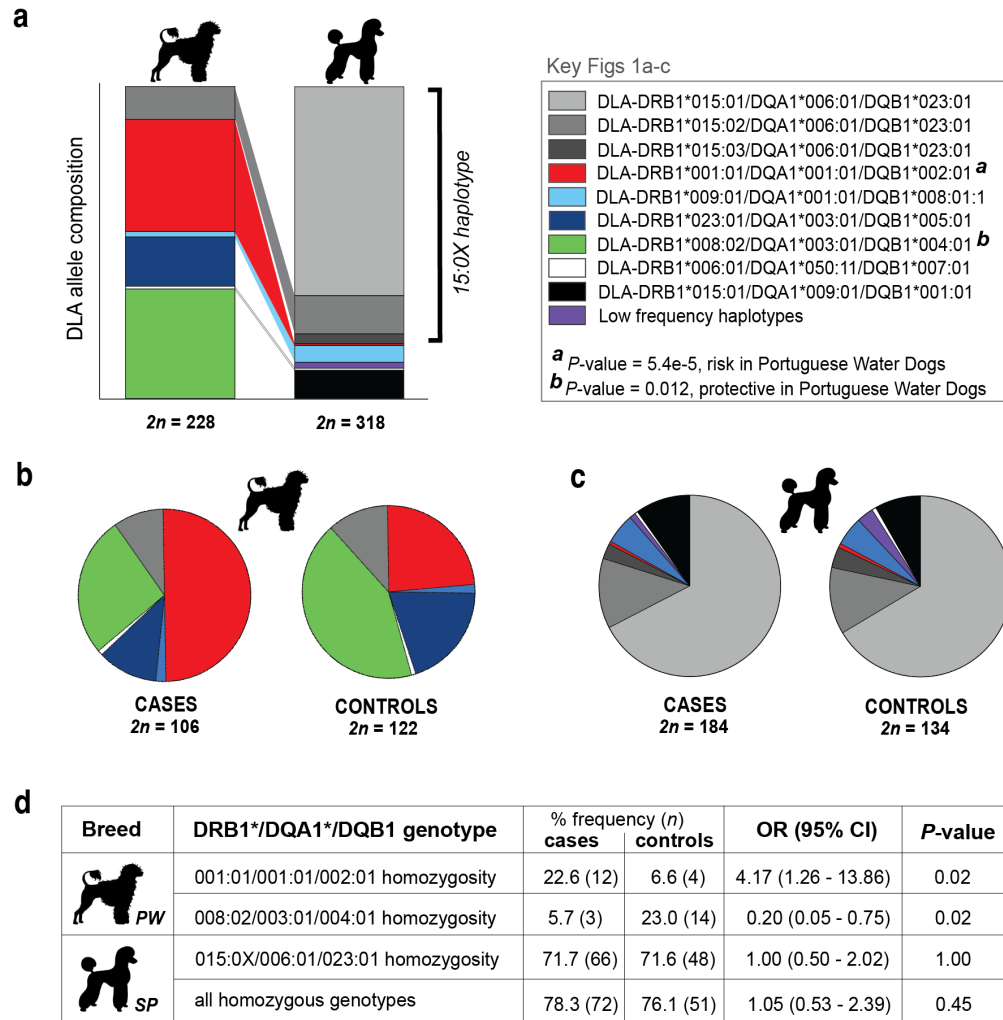


Fig 1. Three-locus MHC class II haplotype allele and genotype distributions in Portuguese Water Dogs and Standard Poodles. Allele frequency compositions are displayed for (a) all Portuguese Water Dogs (left) and Standard Poodles (right), and between cases (left) and controls (right) in (b) Portuguese Water Dogs and (c) Standard Poodles. (d) The number of times each genotype was observed with frequencies are provided in a table for genotypes that are listed in column 2. Listed genotypes were compared with all other genotypes to calculate odds ratios and P-values. Fisher's exact two-tailed t tests were used for P-values reported in the figure key and table. PW = Portuguese Water Dogs, SP = Standard Poodles.

Runs unique to Portuguese Water Dogs were detected on chromosomes 17, 21, and X (Figure 2A, Supplemental Table 3.2). Five genes were within the region on 17 (chr17:36,157,677 – 36,801,125), and upon scanning of high-coverage genomes, a missense mutation in *myeloid-epithelial-reproductive tyrosine kinase* (*MERTK*) was identified on the haplotype in homozygosity at position 36,584,148. The variant is common among dogs, with an allele frequency of 0.54 based on 2,771 dogs from across 389 breeds, but is predicted to impact protein function ($P\text{-del} = 0.5$, possibly damaging). No other coding variants were identified in this run. Only one gene was found in the next region on chromosome 21 (chr21:30,594,057 – 31,310,220), *Zinc finger protein 214* (*ZNF214*), and genes being selected for on the X chromosome could not be narrowed down due to run lengths.

In Standard Poodles, unique runs were detected on chromosomes 3, 11, 16, and X (Figure 2B, Supplemental Table 3.3). Several genes were in the region on chromosomes 3 (chr3:91,680,939 – 92,211,379); however, we deduced that selection likely occurred for *LCORL* because of body size. Runs on chromosome 11 also contained several genes, but with no clear candidates for selection. Single genes were found in regions on chromosomes 16 and X. *Contactin-associated protein 2* (*CNTNAP2*) spanned three runs on 16 (chr16:1,658,514 – 2,240,964, chr16:2,438,779 – 3,128,728, and chr16:3,321,487 – 4,239,385), and the X (chrX:71,947,343 – 72,520,501 and chrX:94,290,302 – 95,760,830) contained *EEF1A1* and *GRIA3*, respectively. A distinct run on chromosome 16 contained several genes, but given our population was largely made up of eumelanic coated poodles (65%), we deduced that selection here was for *β -defensin 103* (*CBD103*)¹⁸.

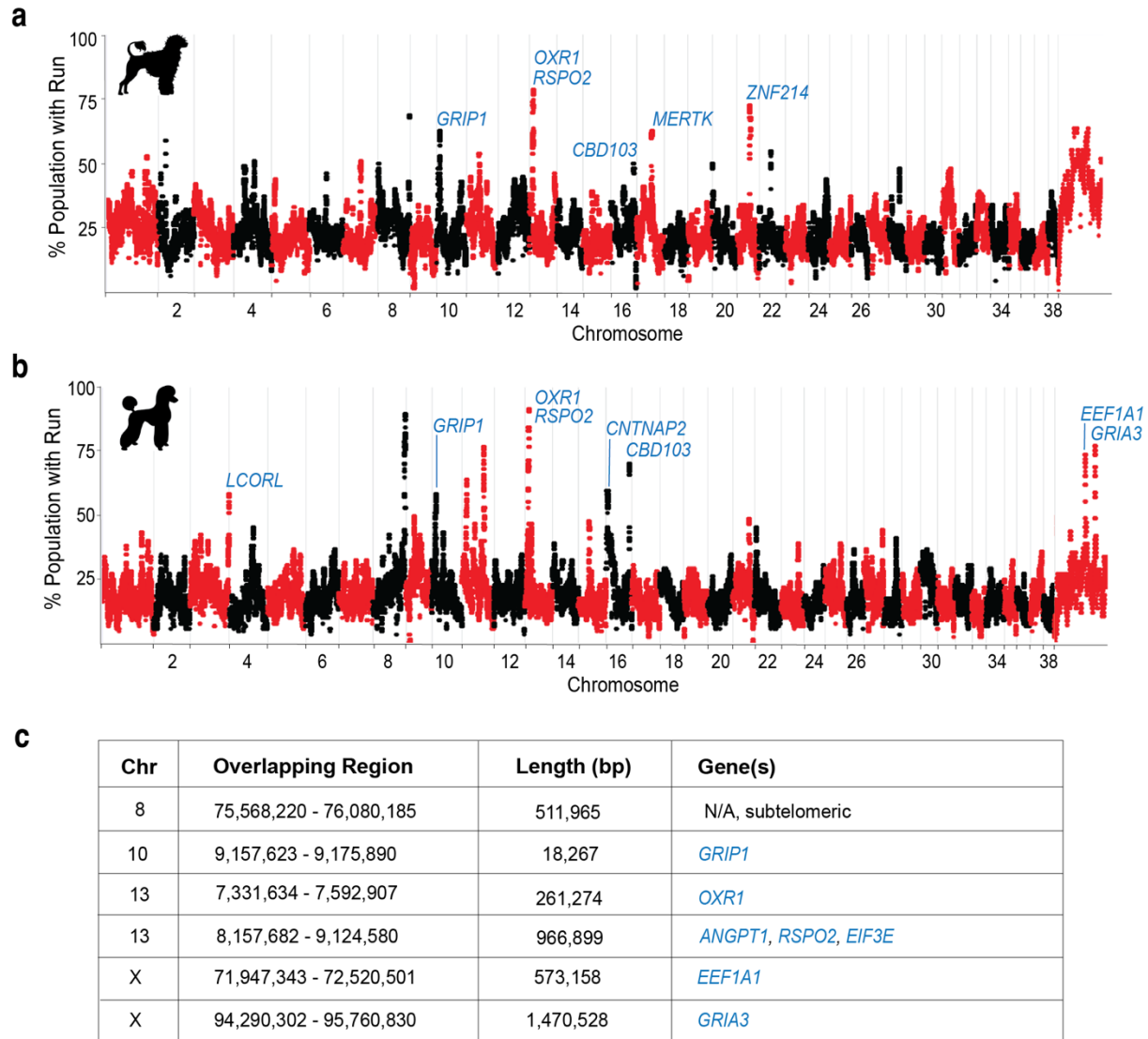


Fig 2. Runs of homozygosity in Portuguese Water Dogs and Standard Poodles. Manhattan plots depict the percent of the population with runs of homozygosity for (a) Portuguese Water Dogs and (b) Standard Poodles. Known genes under selection or runs consisting of a single gene are labeled in blue. (c) Regions that overlap between the two breeds are reported in a table with length of the overlapping region and the encompassed genes.

Pairwise F_{ST} . Breed-defining signatures of selection were compared using d_i statistics between Portuguese Water Dogs or Standard Poodles and 500+ dogs from across 49 breeds, which included poodle varieties. Locus specific deviation was observed on 9 chromosomes in Portuguese Water Dogs, and one region was previously identified from the runs of homozygosity analysis at 9Mb on chromosome 10 (Supplemental Table 3.4). Seven loci were identified in

Standard Poodles, with 2 overlapping regions from runs of homozygosity on chromosomes 3 and 16 (Supplemental Table 3.5). No breed-defining signatures were shared between Portuguese Water Dogs and Standard Poodles when compared to the 49 selected breeds.

Unique Coding Variants. To identify unique variants, MAFs (> 0.10) from 34 Portuguese Water Dog and 39 Standard Poodle high-coverage genomes were filtered against the MAF (< 0.00) from a population of 2,692 high-coverage genomes that excluded poodle mix, poodle variety, and Portuguese Water Dog breeds. Thirty-three conserved, missense variants were found in Portuguese Water Dogs, 19 of which were predicted to be damaging (Supplemental Table 3.6, Table 2). In the low-pass population ($n=101$), a glycine to arginine substitution in *myopalladin* (*MYPN*) was associated with protection (P -value = 0.04) and a threonine to arginine substitution in *activating signal cointegrator 1 complex subunit 3* (*ASCC3*) was associated with risk (P -value = 0.03) of primary hypoadrenocorticism. Additionally, both positions were highly conserved (PhyloP scores, *MYPN* = 8.38 and *ASCC3* = 8.48), and *ASCC3* was also detected in a F_{ST} region aforementioned in Portuguese Water Dogs.

In Standard Poodles, 16 conserved, missense variants were found and 11 were predicted to be damaging (Supplemental Table 3.7, Table 3). Two of these variants were associated with primary hypoadrenocorticism in the low-pass population ($n=93$), with a proline to arginine substitution in *AT-rich interaction domain 5B* (*ARID5B*) being protective (P -value = 0.03) and a valine to methionine substitution in *SET and MYND domain containing 1* (*SMYD1*) conferring risk (P -value = 0.006). Both positions were conserved (PhyloP scores, *ARID5B* = 8.58 and *SMYD1* = 6.73). Shared variants between Portuguese Water Dogs and Standard Poodles were not identified.

Table 2. Unique coding variants predicted to be damaging based on minor allele frequencies in 34 Portuguese Water Dogs (MAF > 0.10) versus 2,692 dogs from breeds excluding poodle mixes, poodle varieties, and Portuguese Water Dogs (MAF < 0.00). Protein predictions were based on Polyphen-2 scores and Fisher's exact two-tailed *P*-values from the low pass cohorts are provided.

Chr	Position	Variant		Portuguese W. D. MAF	Gene	Mutation	PhyloP Score	PolyPhen-2 Score	<i>P</i> -value <i>n</i> = 101
1	108,372,583	G	A	0.12	<i>FAM83E</i>	R231Q	3.90	0.953	0.52
1	111,120,628	G	A	0.41	<i>ZNF296</i>	R231Q	4.01	0.987	0.32
4	20,183,532	G	A	0.34	<i>MYPN</i>	G919R	8.38	1.000	0.04
4	23,211,207	C	T	0.34	<i>ZNF488</i>	M64I	4.58	0.893	0.08
4	35,846,321	G	A	0.38	<i>C4H10</i>	R84H	6.20	0.988	0.66
5	58,758,791	G	A	0.34	<i>SMIM1</i>	G56R	5.96	1.000	0.23
6	40,352,860	G	A	0.18	<i>FBXL16</i>	V284M	8.38	1.000	0.58
7	21,366,864	G	C	0.25	<i>RASAL2</i>	P15R	3.78	0.988	0.74
10	11,201,245	G	A	0.42	<i>TTC7A</i>	A191T	4.62	0.972	0.25
10	45,851,117	C	A	0.22	<i>TMEM131</i>	S1329Y	8.58	0.916	0.13
12	58,963,809	G	C	0.20	<i>ASCC3</i>	T1480R	8.48	0.998	0.03
16	15,856,471	G	A	0.29	<i>FASTK</i>	P133S	2.72	0.957	0.44
17	21,112,928	C	A	0.21	<i>AGBL5</i>	S25R	4.75	0.900	0.86
20	47,167,619	G	A	0.10	<i>WIZ</i>	D756N	8.46	1.000	0.82
21	16,135,599	G	A	0.14	<i>PCF11</i>	S140L	8.47	0.982	0.54
22	60,548,430	C	T	0.12	<i>ATP11A</i>	R473W	6.36	1.000	1.00
24	17,101,758	C	T	0.17	<i>SLC23A2</i>	T29M	8.55	0.810	1.00
24	18,898,611	C	T	0.11	<i>TMEM239</i>	A79T	6.73	0.997	0.12
35	5,600,465	G	C	0.17	<i>PRPF4B</i>	Q1010H	2.62	0.722	1.00

Table 3. Unique coding variants predicted to be damaging based on minor allele frequencies in 39 Standard Poodles (MAF > 0.10) versus 2,692 dogs from breeds excluding poodle mixes, poodle varieties, and Portuguese Water Dogs (MAF < 0.00). Protein predictions were based on Polyphen-2 scores and Fisher's exact two-tailed *P*-values from the low pass cohort are provided.

Chr	Position	Variant		Standard Poodle MAF	Gene	Mutation	PhyloP Score	PolyPhen-2 Score	<i>P</i> -value <i>n</i> = 93
4	14,746,238	C	G	0.16	<i>ARID5B</i>	P232R	8.58	1.000	0.02
4	19,041,136	G	A	0.11	<i>LRRTM3</i>	R194Q	8.48	1.000	1.00
6	42,208,111	C	T	0.14	<i>KCNC4</i>	R582H	8.45	0.981	0.28
9	48,841,393	C	T	0.14	<i>DIPK1B</i>	V41M	6.50	0.951	0.67
9	49,232,150	G	A	0.44	<i>QSOX2</i>	V315M	8.07	1.000	0.13
9	51,273,314	C	T	0.12	<i>PPP1R26</i>	T450I	3.15	0.997	0.36
11	74,086,918	C	A	0.12	<i>CDK5RAP2</i>	S111I	5.66	0.997	0.11
17	38,562,905	C	T	0.11	<i>SMYD1</i>	V176M	6.73	0.999	0.006
20	44,436,096	G	A	0.21	<i>TMEM161A</i>	R44Q	8.23	0.955	0.59
24	47,125,195	G	A	0.44	<i>OSBPL2</i>	V239M	8.06	1.000	0.43
28	1,902,150	T	C	0.24	<i>PARG</i>	R424G	6.12	0.985	0.59

Gene enrichment analyses. We grouped genes identified from ROH, F_{ST} , and unique variant filtering together for each breed and performed functional enrichment analyses using DAVID¹⁹ (Supplemental Tables 3.8-9). Phosphoprotein (KW-0597) and protein binding (GO:0005515) were two terms significantly overrepresented in Portuguese Water Dogs ($P\text{-values}_{\text{benj}} < 0.01$, Supplemental Table 3.10), and two clusters of terms were also enriched (score > 1.3) that involved ribosome structures and lysosomes, respectively (Supplemental Table 3.11). We analyzed the set of genes from ROH alone and identified another enriched cluster pertaining to the interleukin-1 (IL-1) family of proteins (enrichment score = 1.7, Supplemental Table 3.12). Within the cluster, one term (SM00125:IL1) was significantly overrepresented ($P\text{-values}_{\text{benj}} = 0.02$, Supplemental Table 3.12).

Terms related to β -defensin and keratin were significantly overrepresented in Standard Poodles, but we suspected these results were biased because of the large number of β -defensin and keratin genes closely surrounding *CBD103* on chromosome 16 and *KRT71* on chromosome 27 (Supplemental Table 3.13). We therefore re-analyzed functional enrichment after excluding these genes, and found no terms were significantly overrepresented (Supplemental Table 3.14-15). Like in Portuguese Water Dogs, we also analyzed the set of genes from ROH alone, but found no significant enrichment.

DISCUSSION

Here, we performed a comprehensive genetic investigation on two dog breeds with the highest incidence of primary hypoadrenocorticism: the Portuguese Water Dog and the Standard Poodle. We first take a candidate gene approach to determine what effect, if any, the MHC has on disease risk. We find that not only do the two breeds have different MHC class II compositions, but also only Portuguese Water Dogs have a clear risk three-locus haplotype.

Genomic analyses for selection signatures and breed-defining loci further reveal that the two breeds are not enriched for the same annotated gene-sets; however, some loci contributing to phenotypic traits are shared and may still influence primary hypoadrenocorticism predisposition.

In Portuguese Water Dogs, we are the first group to report MHC class II three-locus haplotype associations with the disease. We identify two haplotypes affecting susceptibility, risk haplotype DLA-DRB1*001:01/DQA1*001:01/DQB1*002:01 and protective haplotype DLA-DRB1*008:02/DQA1*003:01/DQB1*004:01. The risk haplotype has been associated in primary hypoadrenocorticism in three other breeds: Labrador Retrievers, Springer Spaniels, and West Highland White Terriers¹⁰. To the best of our knowledge, no disease associations have been reported for the protective haplotype. As the two haplotypes appear at roughly equal frequencies across Portuguese Water Dogs, the protective haplotype may be consequentially associated due to its commonness. MHC molecules are crucial for T-cell differentiation and regulation²⁰. The region encoded by the class II haplotype sequence, in particular, plays an important role in determining peptide-binding avidity for presentation to T cells. Presentation of self-antigens regulates the deletion of autoreactive T cells, which can prevent immune disorders, such as human Addison's disease^{20,21}. This understanding, supported by both human and canine associations, highlights the significance of the MHC in primary hypoadrenocorticism, though the exact mechanism by which specific haplotypes influence disease risk remains unclear.

Interestingly, we do not find any associations of MHC class II haplotypes with primary hypoadrenocorticism in Standard Poodles. The breakdown of their allele composition differs from that in Portuguese Water Dogs; however, Standard Poodles do possess DLA-DRB1*001:01/DQA1*001:01/DQB1*002:01 in low frequency (<1%). The breed instead is largely made up of the 150X-haplotype, which is approaching fixation at an allele frequency of

82%. This sweep may be hindering our ability to detect an association, and the haplotype may withal be contributing to disease risk. Previously, DLA- DRB1*015:01/DQA1*006:01/DQB1*023:01 or DLA-DRB1*015:02/DQA1*006:01/DQB1*023:01 were associated with primary hypoadrenocorticism in Cocker Spaniels¹⁰, Springer Spaniels¹⁰, and Nova Scotia Duck Tolling Retrievers⁹, as well as in Standard Poodles^{10,12}. Notably, the two studies performed in Standard Poodles had reported contradictory findings about DLA-DRB1*015:01/DQA1*006:01/DQB1*023:01 conferring risk or protection, which indicates the associations may have been skewed by the study populations due to its high allele frequency.

Because DLA-DRB1*001:01/DQA1*001:01/DQB1*002:01 and the 150X-haplotypes are common in other dog breeds, we next looked genome-wide to determine if breed-defining loci contained genes overrepresented in functional pathways, such as those related to immune function. In Portuguese Water Dogs, we found significant enrichment of genes involved with IL-1, a family of cytokines most known for their role in inflammation and immunostimulating activity²². IL-1 proteins are expressed ubiquitously across various tissues, including the brain and the adrenal glands. Additionally, they are potent regulators of the hypothalamus-pituitary-adrenal (HPA) axis by stimulating corticotropin releasing hormone (CRH) secretion from the hypothalamus²³. Discerning whether increased IL-1 activity is a clinical sign or a cause of autoimmune reactions can aid in our understanding of disease pathogenesis²². Therefore, revealing enrichment for genes involved with IL-1 function here may indicate that, at least for primary hypoadrenocorticism in Portuguese Water Dogs, increased IL-1 activity is a driver and not a consequence of the disease. In addition to enrichment of IL-1 gene-sets, our cohort of low-pass Portuguese Water Dogs had a unique coding mutation in *ASCC3* associated with increased risk for primary hypoadrenocorticism. *ASCC3* encodes a DNA helicase that has been shown to

inhibit interferon-stimulated gene expression to help control inflammation and prevent damage from an overreactive immune response²⁴. Altogether, our results support that Portuguese Water Dogs may have an increased predisposition for primary hypoadrenocorticism because of their genetic background.

We did not find an overrepresentation of immune-related terms in Standard Poodles, but we did note two unique missense variants that were associated with primary hypoadrenocorticism in our low-pass population ($n=93$). Both mutations were in genes that have been associated with blood phenotypes: *ARID5B* in acute lymphoblastic leukemia²⁵ and *SMYD1* in the AnWj-negative blood group phenotype²⁶. The latter disorder is associated with autoimmune hemolytic anemia, but the connection between *SMYD1* and an autoimmune response is equivocal. Previous GWASs performed in Standard Poodles for primary hypoadrenocorticism had not identified genetic factors related to the immune system²⁷ (Greif et al., submitted 2024), and our group recently implicated the central nervous system in disease etiology (Greif et al., submitted 2024). Similarly, we here identify four selection signatures over *GRIP1*, *OXR1*, *CNTNAP2*, and *GRIA3*, all of which are well-known genes involved in synaptic plasticity or neurodegeneration^{28–35}.

Selection signatures for *GRIP1* and *OXR1* were also shared in Portuguese Water Dogs, along with signatures subtelomeric on chromosome 8, over *RSPO2* on chromosome 13, and over *EEF1A1* and *GRIA3* and the X chromosome. We suspect a retrogene is within the chromosome 8 region that may be important for a shared phenotype found in Portuguese Water Dogs and Standard Poodles. Although *RSPO2* is responsible for furnishings, other R-spondin family members are important for adrenal gland maintenance^{36–38}; therefore, it is plausible that *RSPO2* may be exhibiting pleiotropic effects to also impact adrenal health. The genes identified on the X

chromosome have roles in protein synthesis (*EEF1A1*) and synaptic transmission (*GRIA*), with *GRIA3* interacting directly with another gene under selection, *GRIP1* from chromosome 10.

Whether or not the six shared regions under selection in Portuguese Water Dogs and Standard Poodles influence their increased risk for primary hypoadrenocorticism will require further investigation. We acknowledge that there were limitations in this study regarding population size of gonadectomized Portuguese Water Dogs, but we are actively collecting more dogs to validate and further the investigation.

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CHAPTER 4

CONCLUSIONS

The canine model can help identify novel variants underlying rare, complex diseases. Closed breeding populations create a unique population structure allowing for an increased frequency of rare, disease-causing variants that would otherwise be difficult to identify in heterogeneous human populations. Here, we present a canine model of primary hypoadrenocorticism, a genetically complex disease of the adrenal cortex that occurs naturally in dogs and is relatively rare in humans. We study the two most affected dog breeds, Portuguese Water Dogs and Standard Poodles, which have a 29-fold and 17-fold increased risk, respectively, compared to other dogs¹. Although phylogenetically the two breeds are closely related², we uncover separate risk factors driving disease predisposition. We reveal six shared loci, likely contributing to breed-defining phenotypes like size and coat type, but overall find that Portuguese Water Dogs have distinct gene enrichments and different risk factors compared to Standard Poodles. It is possible that the shared loci are minor contributors to primary hypoadrenocorticism, but the different underlying genetic factors may explain why Portuguese Water Dogs have a ~2-fold greater risk than Standard Poodles. Like in humans, primary hypoadrenocorticism appears to have a complex inheritance pattern in these two breeds, each with their own drivers influencing disease susceptibility.

In the Standard Poodle, we identified multiple loci conferring risk that contain neural synapse genes. First, we performed a GWAS and associated a novel locus on chromosome 17 with primary hypoadrenocorticism. Two genes flanked the associated region, *GCF2* and

LRRTM4. Another leucine rich repeat family member, *LRRC4C*, was previously mapped in a GWAS for primary hypoadrenocorticism in Bearded Collies³, highlighting the gene family's potential importance in adrenal insufficiency. Next, we uncovered two additional risk loci with extended haplotype homozygosity unique to cases. Within the loci, we identified candidate causal variants at conserved positions intronic to *CACNA1C* and *ANO2*. We noted that all the aforementioned genes are canonically involved in the central nervous system. Other candidate variants were identified by filtering high-coverage whole genome sequencing datasets, revealing two missense mutations in *ARID5B* and *SMYD1* associated with the disease. To date, the involvement of neural synapse genes in primary hypoadrenocorticism has not been proposed, but several cases manifesting with neuropsychiatric symptoms are reported⁴. Furthermore, in an original description of the disease in 1855, Thomas Addison states that primary hypoadrenocorticism may present with psychiatric symptoms⁴. To our knowledge, innervation of the adrenal cortex in primary hypoadrenocorticism patients has not been explored, and we hypothesize that innervation in the adrenal cortex of Standard Poodles differs from breeds that are not susceptible to the disease, including in small varieties of poodles. Future research efforts should target adrenal innervation comparisons.

In Portuguese Water Dogs, distinct risk factors underlying primary hypoadrenocorticism were found. First, we identified MHC class II three-locus haplotypes associated with the disease, one with risk and one with protection. Because the haplotypes are common in other dog breeds, we next investigated the genetic background of Portuguese Water Dogs by looking at selection signatures. We performed runs of homozygosity and pairwise F_{ST} analyses, identifying 15 breed-defining loci, collectively. Within the loci, we found functional enrichment for gene-sets related to ribosomes, lysosomes, and most notably, to interleukin-1. Interleukin-1 is a crucial cytokine

for immune regulation, indirectly influencing MHC molecules by enhancing the effectiveness of antigen presenting cells during antigen presentation⁵. Lastly, we identified unique coding mutations in *MYPN* and *ASCC3*, with *ASCC3* being a gene identified in IL-1 regulation.

Overwhelmingly our results point to the immune system as the driving risk factor in this breed.

In summary, two closely related dog breeds with the highest incidence of primary hypoadrenocorticism were found to have different risk factors underlying the disease. We implicate the central nervous system in disease etiology for Standard Poodles, while Portuguese Water Dogs appear to have risk factors linked to the immune system, resembling autoimmune Addison's disease in humans. By accounting for major influencers of disease, other contributors may be identified to further elucidate disease etiology and pathogenesis. Using the canine model, we uncovered a previously overlooked variable—the central nervous system—and gained valuable insights into primary hypoadrenocorticism.

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APPENDIX A

GWAS USING LOW-PASS WHOLE GENOME SEQUENCE REVEALS A NOVEL LOCUS IN CANINE CONGENITAL IDIOPATHIC MEGAESOPHAGUS

ABSTRACT

Congenital idiopathic megaesophagus (CIM) is a gastrointestinal disorder of dogs wherein the esophagus is dilated and swallowing activity is reduced, causing regurgitation of ingesta.

Affected individuals experience weight loss and malnourishment and are at risk for aspiration pneumonia, intussusception, and euthanasia. Great Danes have among the highest incidences of CIM across dog breeds, suggesting a genetic predisposition. We generated low-pass sequencing data for 83 Great Danes and used variant calls to impute missing whole genome single nucleotide variants (SNVs) for each individual based on haplotypes phased from 624 high-coverage dog genomes, including 21 Great Danes. We validated the utility of our imputed data set for genome-wide association studies (GWASs) by mapping loci known to underlie coat phenotypes with simple and complex inheritance patterns. We conducted a GWAS for CIM with 2,010,300 SNVs, identifying a novel locus on canine chromosome 1 ($P\text{-val} = 2.76 \times 10^{-10}$). Associated SNVs are intergenic or intronic and are found in two clusters across a 1.7 Mb region. Inspection of coding regions in high-coverage genomes from affected Great Danes did not reveal candidate causal variants, suggesting that regulatory variants underlie CIM. Further studies are necessary to assess the role of these non-coding variants.

Key words: low-coverage sequence, Great Dane, imputation, gastrointestinal dysmotility,

DOK6, *CDH19*

INTRODUCTION

Dysmotility is a central component of gastrointestinal disease and a comorbidity of disorders of the central nervous system, both of which are major concerns for human and canine health (Clark et al. 2023; Miron and Dumitrascu 2019; Niesler and Rappold 2021; Poirier et al. 2016; Sperber et al. 2021; Whitehead et al. 2016). Congenital idiopathic megaesophagus (CIM)

is a hypomotility disorder of dogs characterized by reduced peristaltic activity and dilation of the esophagus that impede passage of food into the stomach (Richter 2014; Tams 2003). The congenital form of megaesophagus is usually idiopathic and diagnosed shortly after weaning onto solid food. The predominant clinical sign is regurgitation, which may occur only occasionally in mild cases, or several times a day in severe cases (Johnson et al. 2009, Palmer 1968; Tams 2003). Affected dogs suffer from weight loss and malnourishment and are at lifelong risk for aspiration pneumonia and intussusception (Graham et al. 1998; Grimes et al. 2020; Kogan et al. 2008). CIM is diagnosed via radiography, with or without barium contrast (Fig. 1) (Johnson et al. 2009; McBrearty et al. 2011). Although mortality is high in neonates, CIM cases can usually be managed with frequent, high-caloric, liquid meals fed in an elevated position (Guilford 1990).

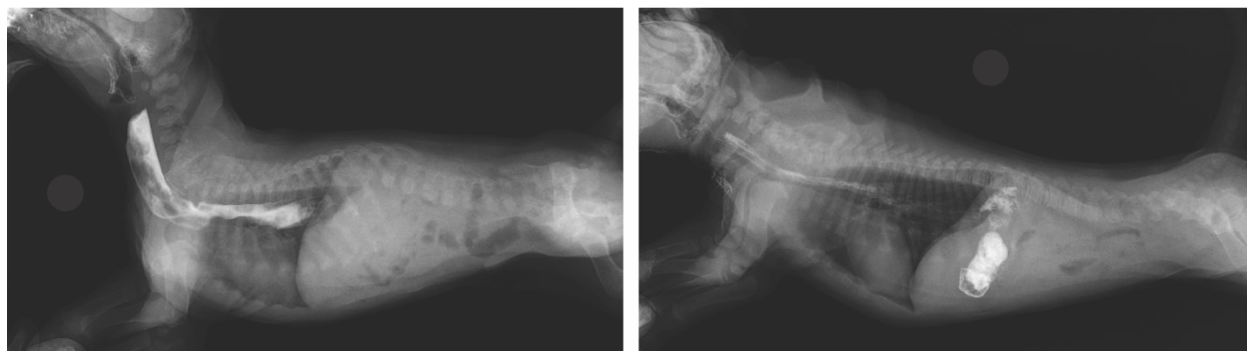


Fig. 1 Barium-contrast radiographs of affected and healthy Great Dane littermates. Radiographs were taken at five weeks of age following a barium meal. Barium is retained in the enlarged esophagus of the CIM-affected individual (left) and passes through to the stomach in the healthy puppy (right).

While CIM has been reported across breeds, German shepherd dogs (GSDs) and Great Danes have among the highest incidences (Cox et al. 1980; Guilford 1990; Haines et al. 2019, Harvey et al. 1974). In GSDs, we previously uncovered a sex bias wherein males are approximately twice as likely to be affected as females (Bell et al. 2022). Using a genome-wide association study (GWAS) and high-coverage whole genome sequence, we detected a major

locus associated with CIM in GSDs and an allele of a variable number tandem repeat (VNTR) that confers risk (Bell et al. 2022).

The study of complex diseases such as CIM may be aided by the emerging method of low-pass whole genome sequencing, which is a cost-effective alternative to SNP arrays for the generation of genome-wide genetic profiles (Martin et al. 2021). Variant calls from low coverage sequence (usually an average of 1X) are used to impute missing whole genome data for each individual based on haplotypes phased from high-coverage genomes (Buckley et al. 2022; Li et al. 2011; Wasik et al. 2021). Unlike commercial arrays where markers were selected for informativeness in limited populations, low-pass whole genome sequencing is an unbiased alternative in which novel variants can be detected in specific populations (Martin et al. 2021). GWASs conducted with complete genome data have allowed for direct identification of the genetic basis for disease (Hayward et al. 2019; Mansour et al. 2018). Further, high-density genotype data may reduce post-GWAS efforts to refine candidate intervals and identify the best regional associations in genetically complex disorders, which are often attributed to non-coding regulatory variants (Hayward et al. 2019; Li et al. 2011; Plassais et al. 2019).

Here, we generated low-pass whole genome sequences for CIM-affected and unaffected dogs, imputed genotypes using a multi-breed reference panel, and conducted a GWAS to identify genomic regions associated with esophageal hypomotility in the Great Dane.

METHODS

Population. Whole blood, buccal cells, or skin tissues were obtained from purebred Great Danes with informed owner consent, and DNA was prepared using the Gentra Puregene DNA Isolation kit (Qiagen). Pedigrees, radiographs, and additional phenotypic data (*e.g.*, coat color/pattern) were collected when available. Cases were diagnosed by a veterinarian via a standard or barium

contrast radiograph, history of clinical signs from puppyhood, and exclusion of secondary causes (e.g., myasthenia gravis, persistent right aortic arch), with the exception of four cases diagnosed based on clinical signs alone. Controls were at least one year old, had no history of clinical signs consistent with CIM, and had no relatives known to be affected by CIM. A subset of 81 dogs with sufficient DNA were genotyped for the VNTR associated with CIM in GSDs, as previously described (Bell et al. 2022). A two-tailed Fisher's exact probability test was performed to evaluate the association of CIM with the VNTR. A one-way chi square test was used to assess sex bias (<http://vassarstats.net/>).

Whole genome sequencing. Dogs were selected for low-pass whole genome sequencing such that known relatives within three generations were excluded, and sex and coat color were roughly balanced between cases and controls. Libraries were constructed for 83 dogs with the Illumina DNA Prep kit and low-pass whole genome sequencing was performed on an Illumina NovaSeq 6000, generating dual-index 150 bp paired-end reads. Total reads generated ranged from 18,453,514 to 157,596,075 per sample. Paired-end reads were aligned to CanFam3.1 using Burrows-Wheeler Aligner (Li and Durbin 2009) and variants were jointly called using BCFtools mpileup function (Li 2011). Variants with a phred-scaled quality score < 20 were removed, and biallelic SNVs were selected using the BCFtools view command. These variants comprised the imputation target panel.

Nine ancestrally diverse Great Danes were selected for high-coverage whole genome sequencing. We generated paired-end 100, 125, or 150 bp sequencing on Illumina HiSeq systems. For each sample, paired-end reads were trimmed and aligned to CanFam3.1.

Imputation reference panel

Publicly available and private high-coverage whole genome sequence data for 624 dogs representing 65 breeds were used to create a custom variant call format (VCF) file to serve as an imputation reference panel. The reference panel includes 21 genetically diverse Great Danes, including 16 private genomes and five public genomes sequenced herein (four controls and one CIM-affected dog). This VCF was created using a previously described bioinformatics pipeline (Friedenberg and Meurs 2016), with the following updates: GATK was updated to version 4.1 and dbSNP was updated to version 151. Variants were subset using BCFtools (Li et al. 2009; Li 2011) to include only bi-allelic SNVs ($n=21,809,094$) called in at least 98% of dogs and phased using Beagle 5.1 (Browning and Browning 2007) on a per chromosome basis with standard options.

Imputation. Prior to imputation, the target panel from low-pass sequencing was compared to the reference panel using conform-gt (Browning and Browning 2007) to exclude target variants without a corresponding reference panel variant and to adjust target variants to match the allele order and chromosome strand in the reference panel. The target panel was imputed to the reference panel on a chromosome-by-chromosome basis with Beagle 4.0 (Browning and Browning 2007) using the genotype likelihood method with the following flags: window=50000, overlap=20000, phase-its=12, burnin-its=12.

Imputation accuracy was assessed using four Great Danes who were not included in the imputation reference panel and from whom both high-coverage and low-pass whole genome sequences were generated. Genotype concordance was calculated by comparing imputed SNV genotypes having $DR^2 > 0.8$ ($n=8,227,616$) with high-coverage genotypes from the same individual.

Genome-wide association studies. Linkage disequilibrium (LD) pruning was performed using SNP & Variation Suite v8 (SVS, Golden Helix) with the following parameters: window size = 50, window increment = 5, CHM r^2 LD threshold = 0.99. All GWASs were performed in SVS using the filtered set of 2,010,300 SNVs. Validation GWASs for dilute and merle pigmentation phenotypes were conducted using a single locus mixed linear model (EMMAX), under recessive and dominant models, respectively. GWAS for CIM was performed using a single locus mixed linear model (EMMAX) under an additive model with sex as a covariate and correction for hemizygous males on the X chromosome. *P*-values were calculated using an additive genetic model.

Variant analyses. A regional genotype association test (additive model) was performed for all (unpruned) chromosome 1 SNVs. The top 20 lead variants were evaluated using Ensembl Genes 100, RefSeq Genes 105 (NCBI), and the UCSC Genome Browser to determine if variants were expressed and/or coding. Genotypes from 1,351 publicly available dog genomes (Bell et al. 2022) were used to determine the major allele for each variant and to identify alleles unique to the Great Dane.

Data Availability. Sample Read Archive accession numbers for 9 high-coverage and 83 low-pass Great Dane genomes are provided in Supplementary Table 1. The VCF, index file, and metadata are available through the Data Repository for University of Minnesota (<https://doi.org/10.13020/GKXV-GT86>).

RESULTS

Population. Among the total number of affected dogs collected (n=69), we observed a slight overrepresentation of males (27 females, 42 males, *P*-val = 0.09). Genotyping of the tri-allelic VNTR, previously associated with CIM in GSDs, in the reference panel and 81 study dogs

(n=102) revealed that allele 2 is the major allele (68%) among Great Danes (Bell et al. 2022).

Great Danes also possess GSD risk allele 1, but allele 3 was not observed herein. The VNTR was not associated with CIM (44 cases vs. 37 controls, P -val = 0.51; Supplementary Table 2).

Whole genome sequence & imputation. High-coverage whole genome sequencing data (13X to 25X coverage) were generated for four CIM-affected and five CIM-unaffected Great Danes.

Low-pass whole genome sequences (1.1X to 9.5X coverage, average coverage = 2.9X) were generated for 83 dogs (45 females, 38 males). These numbers include four dogs for whom we generated both high- and low-coverage sequence data. A single VCF was created from the low-pass data containing variant calls for all 83 dogs, and the data were imputed using a reference panel of 624 high-coverage whole genome sequences, which includes 21 Great Danes from diverse backgrounds. A total of 21,809,094 SNVs were imputed, and among those, only SNVs having $DR^2 > 0.8$ (n=8,227,616) were retained for downstream analysis. Imputation accuracy calculated for four dogs ranged from 96.4 to 98%.

Genome-wide association studies. After LD pruning, 2,010,300 SNVs were used for GWAS. A principal component analysis (PCA) showed minimal underlying population substructure between CIM cases and controls (Supplementary Fig. 1). Genomic differences between coat phenotypes were apparent and consistent with common breeding practices that separate fawn and brindle lines from harlequin, merle, and mantle lines (Fig. 2A).

To validate the utility of this data set for GWAS, we mapped two phenotypes for which the genetic bases are known: dilute coat color and merle coat pattern. Both test GWASs were performed using 69 dogs with owner-reported coat phenotypes (Fig. 2B). The lead SNV (chr25:48138845, P -val = 4.08×10^{-31}) in the GWAS for recessive dilute coat color is located within the second intron of *Melanophilin* (*MLPH*, *D* locus). Dilute fur across breeds, including

the Great Dane, is proposed to be caused by an exon 1 splice variant in *MLPH*, which yielded the second best association (chr25:48121642, $P\text{-val} = 9.71 \times 10^{-22}$; Drögemüller et al. 2007).

Examination of the genotypes for the causal variant revealed that a fawn individual classified as a dilute control was homozygous for the causal allele. This individual was heterozygous at the lead GWAS variant. In a second GWAS that excluded this individual, the causal splice variant is the leading SNV ($P\text{-val} = 1.92 \times 10^{-30}$).

The GWAS for merle coat patterning, a semidominant and incompletely penetrant trait, revealed a primary signal on chromosome 10 (chr10:643797, $P\text{-val} = 4.08 \times 10^{-20}$) and a secondary signal on chromosome 31 (chr31:15722, $P\text{-val} = 6.96 \times 10^{-16}$). The lead variant for merle is located downstream of *Premelanosome Protein* (*PMEL*, *M* locus), 351 kb telomeric to the causal short-interspersed element insertion (Clark et al. 2006; Murphy et al. 2018). The chromosome 31 signal represents a CanFam3.1 genome assembly error; these SNVs are in LD with the *M* locus on chromosome 10. The assembly has been corrected in CanFam4 (Wang et al. 2021), placing these SNVs 340 kb centromeric to *PMEL*. The results of these test GWASs validate the utility of our imputed data set for mapping simple Mendelian and complex traits.

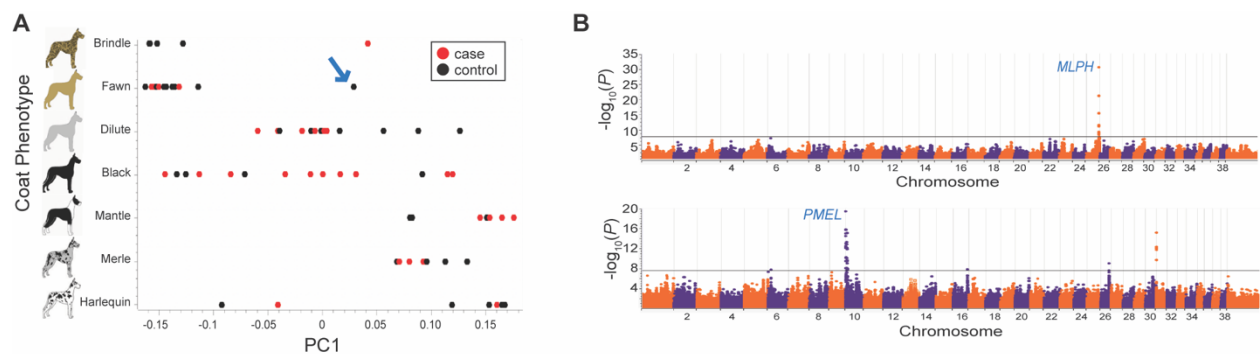


Fig. 2 Principal component analysis and GWAS for coat phenotypes. **A** Principal component 1 (PC1) is plotted against seven common coat color and pattern combinations in Great Danes ($n=69$). A fawn individual homozygous for the dilute causal allele is marked by a blue arrow. **B** Manhattan plots illustrate results of GWASs conducted with 2,010,300 SNVs for dilute coat color (13 cases vs. 56 controls; top) and merle coat pattern (14 cases vs. 55 controls; bottom). Bonferroni significance is denoted by the black horizontal lines.

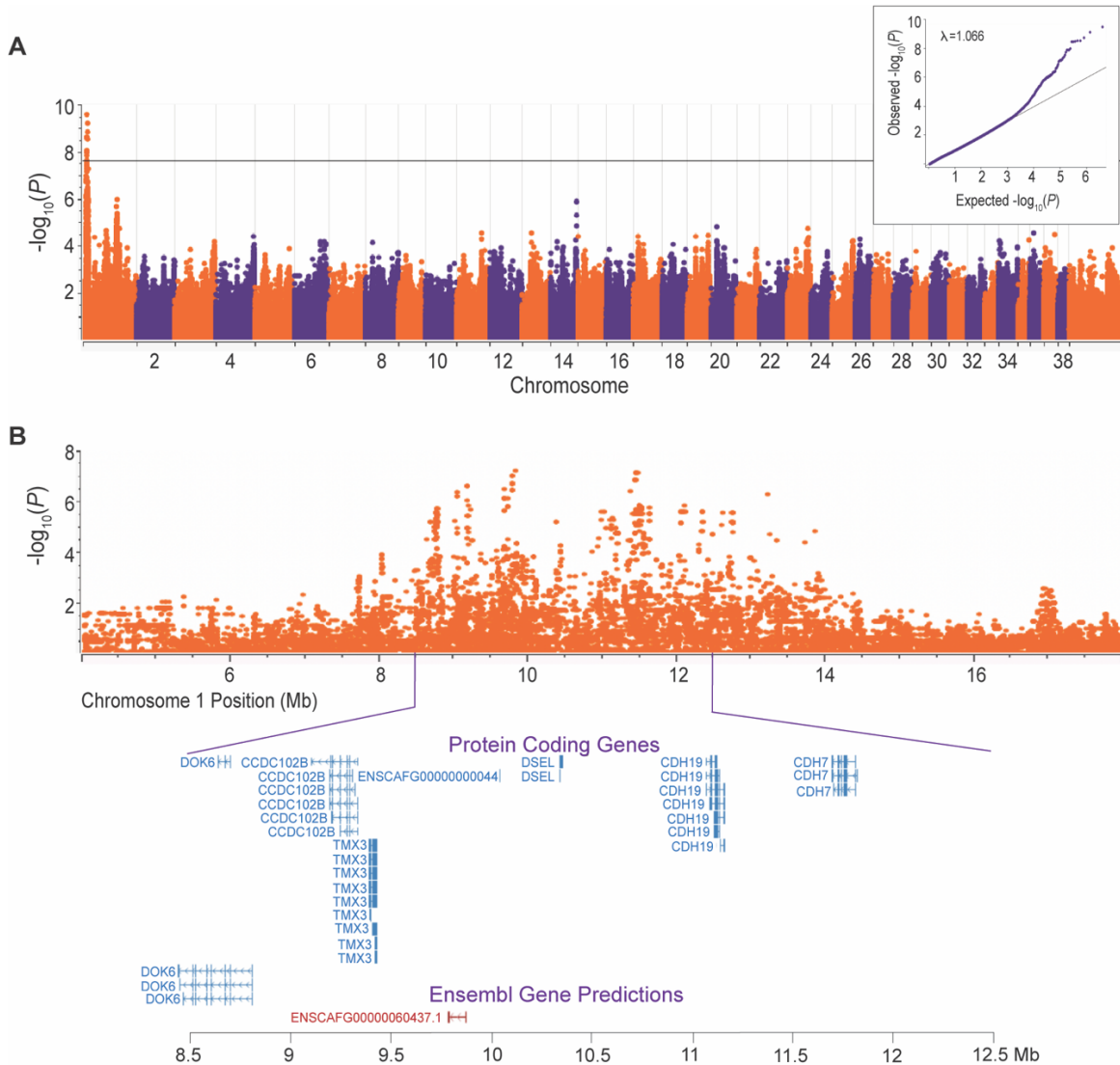


Fig. 3 Manhattan plots illustrating association results for CIM in 45 case and 38 control Great Danes. **A** GWAS conducted with sex as a covariate using 2,010,300 SNVs. Bonferroni significance is denoted by the black horizontal line. A Q-Q plot shows observed vs. expected $-\log_{10}P$ -vals with the genomic inflation factor (λ) (inset). **B** Regional Fisher's exact association tests for 394,308 chromosome 1 SNVs with genes 1Mb centromeric and telomeric to the two lead SNVs shown below (UCSC, CanFam3.1).

We conducted a GWAS for CIM with sex as a covariate, using 45 cases (23 females, 22 males) and 38 controls (22 females, 16 males; Fig. 3A). A 2.3 Mb region of association on chromosome 1 includes 14 SNVs surpassing Bonferroni significance (Supplementary Table 3). Ten SNVs lie within an 800 kb region starting at 9 Mb, and four SNVs lie in a 93 kb window at 11 Mb.

Variant analyses. To identify the best associated variants within the unpruned dataset, Fisher's exact association tests were performed for all 394,308 chromosome 1 SNVs (Fig. 3B). The lead SNV was identical to the GWAS. The top 20 variants were annotated and none were within protein coding or splicing regions (Supplementary Table 4) or unique to the Great Dane breed. The lead variant (chr1:9814231) is intronic to a predicted lncRNA (ENSCAFT00000060437.1), and all other variants are intergenic. Using IGV, we manually scanned four high-coverage genomes (three affected, one unaffected) for exonic variants in the seven positional genes (Fig. 3B) or structural variants. We identified a single nonsynonymous variant in *CCDC102B* that fits the expected pattern of zygosity in the four genomes but is not associated with CIM ($P\text{-val} = 0.25$). No evidence of structural variation was observed.

The top two SNVs (chr1:9814231, $P\text{-val} = 2.76 \times 10^{-10}$; chr1:11437660, $P\text{-val} = 6.41 \times 10^{-10}$) are not in high LD ($r^2 = 0.59$; Fig. 4A). In the intervening region, from approximately 10 to 11 Mb, we observed high levels of homozygosity across both cases and controls (Fig. 4B). Comparisons between canine reference genomes reveals no major rearrangements from 8-13 Mb, but highlights a genome misassembly at ~10.5 Mb in both CanFam3 and CanFam4. Approximately 40 kb of extra sequence has been removed in CanFam5 and CanFam6, corresponding to the region of lowest heterozygosity in Fig. 4B. The leading SNVs occur in regions where the controls have higher frequencies of the dog minor alleles, based on 1,351 dogs representing at least 233 breeds (Fig. 4C). We observed increased homozygosity (29-42%) for the dog minor allele among controls and lower levels in cases (2-4%).

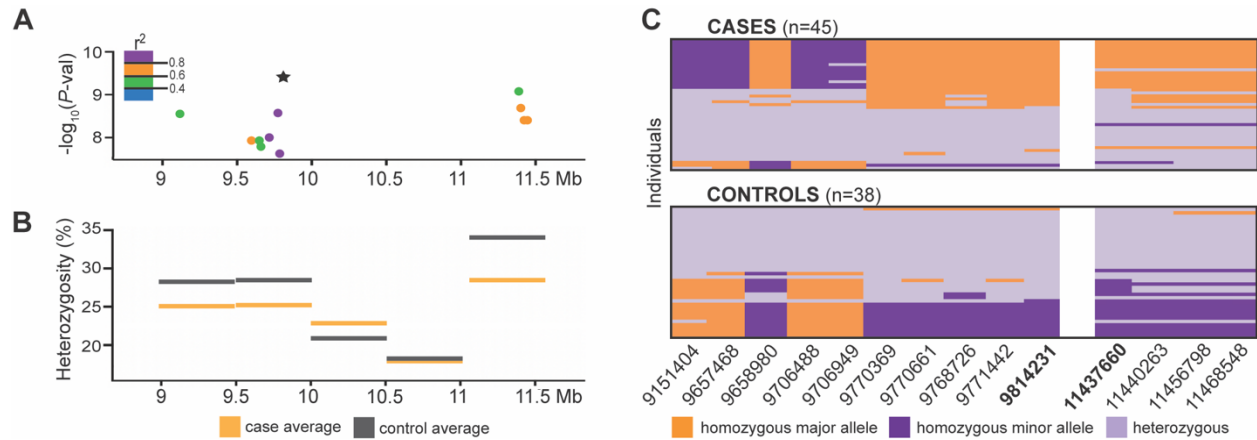


Fig. 4 Analyses of the chromosome 1 CIM locus. **A** Pairwise LD (r^2) for the 14 significant SNVs relative to the lead SNV (star). **B** Average case and control percent heterozygosity in 500 kb windows. **C** Genotypes for the 14 significant SNVs are color-coded relative to the major allele across dogs (based on 1,351 dogs of 233 pure and mixed breeds). Individuals are in rows, SNVs are in columns with chromosome 1 position at the bottom. White bar denotes the large interval with no associated or informative SNVs.

DISCUSSION

We conducted one of the first GWASs in dogs with imputed low-pass whole genome sequence and identified a novel locus associated with a genetically complex gastrointestinal dysmotility in Great Danes (Morrill et al. 2022, Piras et al. 2020). A single region of association with CIM was detected on chromosome 1, tagged by two leading SNVs positioned 1.6 Mb apart and in modest LD. No SNVs in the intervening region reach significance, likely a consequence of the low levels of heterozygosity among both cases and controls. Genomic comparisons with the latest canine reference genomes reveal an assembly error in this region and highlight the need for future studies to understand its structure. All lead SNVs are intergenic or intronic and none were unique to the Great Dane breed, suggesting that the causal variants are regulatory polymorphisms. CIM cases possess the dog major alleles at these loci. The minor dog alleles are predominant among controls, suggesting that the identified locus may confer protection from CIM. Protective haplotypes have been previously identified in complex canine diseases (Bianchi et al. 2020; Karamatic et al. 2022; Tsai et al. 2013). Alternatively, the major alleles could

uniquely confer risk in the Great Dane because of their genetic background (Abrams et al. 2020; Evans et al. 2017; Ivansson et al. 2016). Notably, none of the variants surpassing Bonferroni significance are represented on the Illumina CanineHD BeadChip array (containing 220,853 SNPs), thus our approach allowed us to detect an association that may have been missed using SNP array technology.

The lead SNV is intronic to a lncRNA. While lncRNAs have been implicated in diseases and other traits, the importance of intronic variants is largely unknown (Aznaourova et al. 2020; Plassais et al. 2020). The broad chromosome 1 signal spans seven protein coding genes. *Docking Protein 6 (DOK6)* and *Cadherin-19 (CDH19)* are intriguing candidates because they have both been associated with the gastrointestinal motility disorder, Hirschsprung disease (Gao et al. 2017; Huang et al. 2022; Lan et al. 2021). Also known as congenital aganglionic megacolon, Hirschsprung disease is a developmental disorder of the enteric nervous system characterized by lack of peristalsis in the colon (Diposarosa et al. 2021). DOK6 is an intracellular adapter molecule and a key promoter of neurite outgrowth (Li et al. 2010). *CDH19* lies in the region of low variability between the two leading SNVs. A type II cadherin, *CDH19* is a marker of Schwann cell lineage (originating from neural crest-derived cells) and may play a role in myelin formation (Kameneva et al. 2021; Stratton et al. 2017; Takahashi et al. 2005). Neural crest cell migration is important in the development of the enteric nervous system, which regulates many gastrointestinal activities, including motility (Huang et al. 2022). Our low-pass GWAS resulted in a prioritized list of non-coding variants for future studies to determine their impact on expression of *DOK6*, *CDH19*, and/or other positional genes.

Traditionally, GWASs in dogs are performed using commercial genotyping arrays (Ostrander et al. 2019a). At about 50% of the cost of array technologies in dogs, low-pass

sequencing is emerging as a feasible alternative that yields considerably more data. Whereas only a fraction of SNPs on a genotyping array are informative in a given breed due to ascertainment bias, low-pass sequencing captures intrabreed variation within the study population. The advantage of this approach for complex disease where regulatory variants are involved is a comprehensive list of candidate causal variants as a GWAS outcome. Here, after pruning for markers in perfect LD, we were able to perform a dense GWAS with over 2 million variants informative in the Great Dane breed. For comparison, published GWASs in the Great Dane included about 100,000 SNPs (Metzger et al. 2015; Sarviaho et al. 2020).

Design of the reference panel for imputation presents study limitations. We excluded variants that are difficult to genotype accurately from next generation sequencing data (*e.g.*, insertions, deletions, structural changes, multi-allelic variants), thus causal variants may not have been included in the GWAS. Our imputed data were sufficient to map directly to the causal SNV for dilute coat color (Drögemüller et al. 2007), a simple Mendelian trait. However, we could not directly identify the large insertion causing merle patterning. Inclusion of small insertions and deletions in the reference panel would maximize the utility of this approach, although the latter example would still necessitate post-GWAS analysis of high-coverage genomes.

While imputation accuracy across breeds improves with breed representation (Hayward et al. 2019), accuracy within a given breed requires inclusion of diverse individuals to capture breed-specific haplotypes. This necessity may hinder studies in breeds from whom high-coverage genomes are unavailable or limited. Five Great Danes in a multi-breed reference panel was previously insufficient for highly accurate imputation (86.8% average genotype concordance; Friedenberg and Meurs 2016). Here, genomes from 21 Great Danes were included in a larger multi-breed reference panel, resulting in greater accuracy (97% average genotype

concordance). The number of individuals necessary to capture the haplotypes present within a breed will vary based on population structure, size, *etc.* Still, as more high-coverage genomes become publicly available, through sequencing efforts such Dog10k (Ostrander et al. 2019b), low-pass sequencing and imputation becomes increasingly feasible across dog breeds.

CONTRIBUTIONS

L.A.C., K.L.T., and S.G.F. conceptualized the study; S.M.B. and K.L.T. recruited the study cohort; S.G.F. created the reference panel and performed the imputation, S.M.B., E.A.G., J.M.E., and L.A.C. performed data analysis; L.A.C. and J.M.E. wrote the manuscript; E.A.G. prepared the figures; All authors reviewed the manuscript.

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STATEMENTS AND DECLARATIONS

The authors declare that they have no competing interests.

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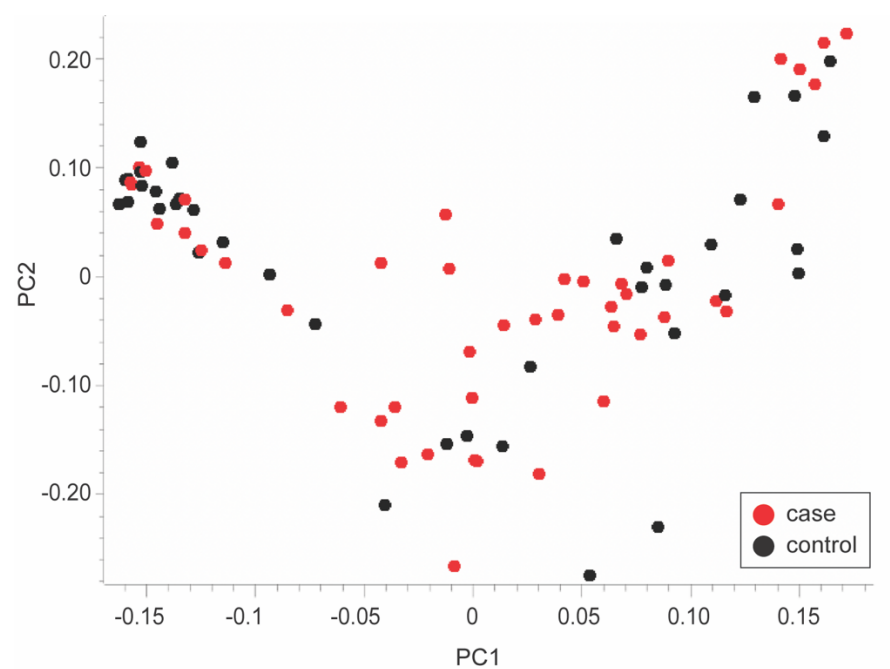
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SUPPLEMENTAL INFORMATION

Supplementary Figure 1 Principal component analysis for the CIM GWAS cohort. Principal components (PC) 1 and 2 are plotted for 83 Great Danes.

Supplemental Table 1 BioSample Objects. Dogs with both high- and low- coverage whole genome sequences are color coded.

[illegible]

Supplemental Table 2 VNTR genotypes in study population.

VNTR Genotype	Males				Females			
	Cases	(n = 22)	Controls	(n = 15)	Cases	(n = 22)	Controls	(n = 22)
1/1	6	[27%]	3	[20%]	3	[14%]	3	[14%]
1/2	8	[36%]	6	[40%]	9	[41%]	7	[31%]
2/2	8	[36%]	6	[40%]	10	[45%]	12	[55%]

Supplemental Table 3 SNVs surpassing Bonferroni significance.

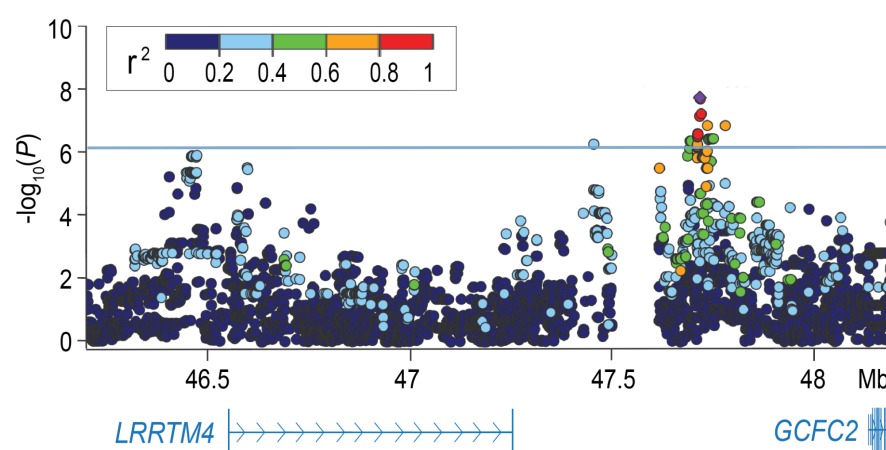
Position	P-value	Minor Allele Frequency (Dogs)		
		Dogs	Controls	Cases
1:9814231	2.76x10 ⁻¹⁰	0.163	0.632	0.244
1:11437660	6.41x10 ⁻¹⁰	0.475	0.711	0.333
1:11440263	1.56x10 ⁻⁹	0.26	0.671	0.278
1:9151404	2.45x10 ⁻⁹	0.355	0.303	0.667
1:9770661	2.48x10 ⁻⁹	0.217	0.645	0.278
1:9770369	2.84x10 ⁻⁹	0.089	0.618	0.244
1:11456798	2.93x10 ⁻⁹	0.188	0.658	0.267
1:11468548	2.93x10 ⁻⁹	0.196	0.658	0.267
1:9768726	8.86x10 ⁻⁹	0.089	0.605	0.233
1:9658980	1.10x10 ⁻⁸	0.493	0.697	0.322
1:9657468	1.12x10 ⁻⁸	0.363	0.276	0.644
1:9706488	1.12x10 ⁻⁸	0.46	0.276	0.644
1:9706949	1.59x10 ⁻⁸	0.34	0.276	0.622
1:9771442	2.39x10 ⁻⁸	0.092	0.605	0.244

Supplemental Table 4 Top 20 SNVs annotated from chr1-wide association study.

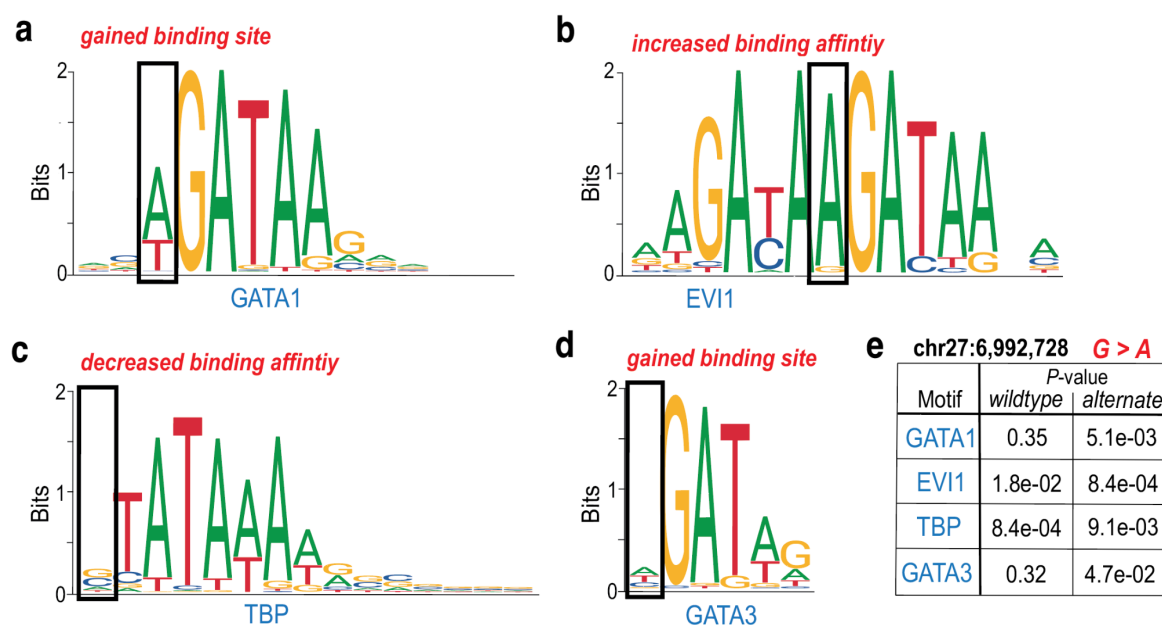
Position	P-value	Region
1:9814231	7.36x10 ⁻⁸	Intron of ENSCAFT00000060437, lncRNA
1:11456798	8.40x10 ⁻⁸	intergenic
1:11468548	8.40x10 ⁻⁸	intergenic
1:11438841	8.43x10 ⁻⁸	intergenic
1:11439616	8.43x10 ⁻⁸	intergenic
1:11439652	8.43x10 ⁻⁸	intergenic
1:11439803	8.43x10 ⁻⁸	intergenic
1:11440263	8.43x10 ⁻⁸	intergenic
1:9769365	1.15x10 ⁻⁷	intergenic
1:9769965	1.15x10 ⁻⁷	intergenic
1:9770369	1.15x10 ⁻⁷	intergenic
1:11433647	1.59x10 ⁻⁷	intergenic
1:11435414	1.59x10 ⁻⁷	intergenic
1:11435872	1.59x10 ⁻⁷	intergenic
1:11436249	1.59x10 ⁻⁷	intergenic
1:11436605	1.59x10 ⁻⁷	intergenic
1:11437605	1.59x10 ⁻⁷	intergenic
1:11437660	1.59x10 ⁻⁷	intergenic
1:9768698	2.29x10 ⁻⁷	intergenic
1:9768726	2.29x10 ⁻⁷	intergenic

APPENDIX B

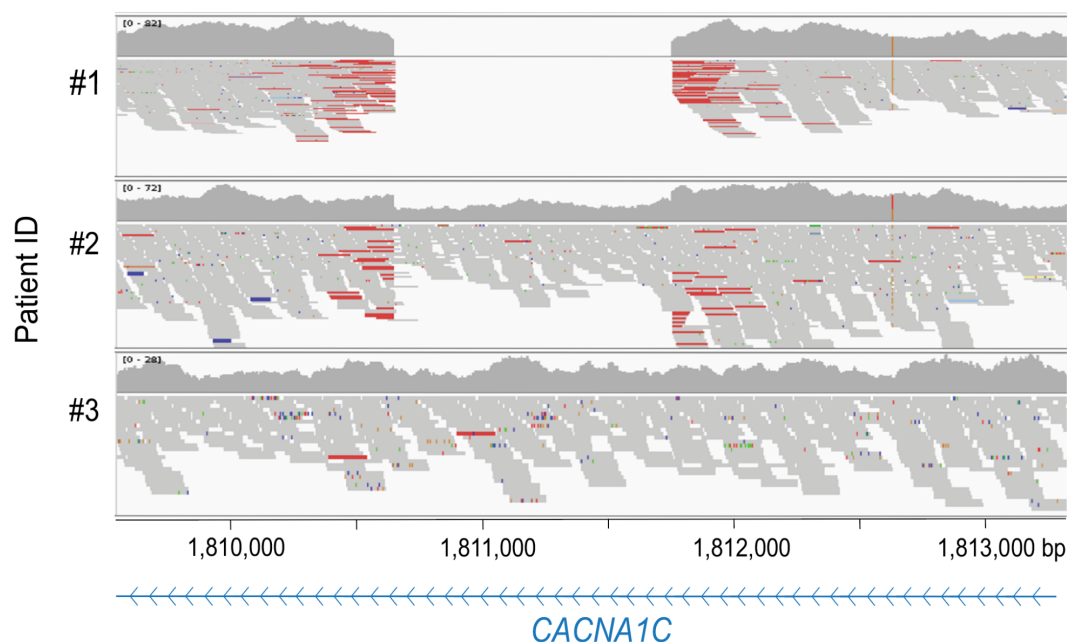
Supplemental information for Chapter 2



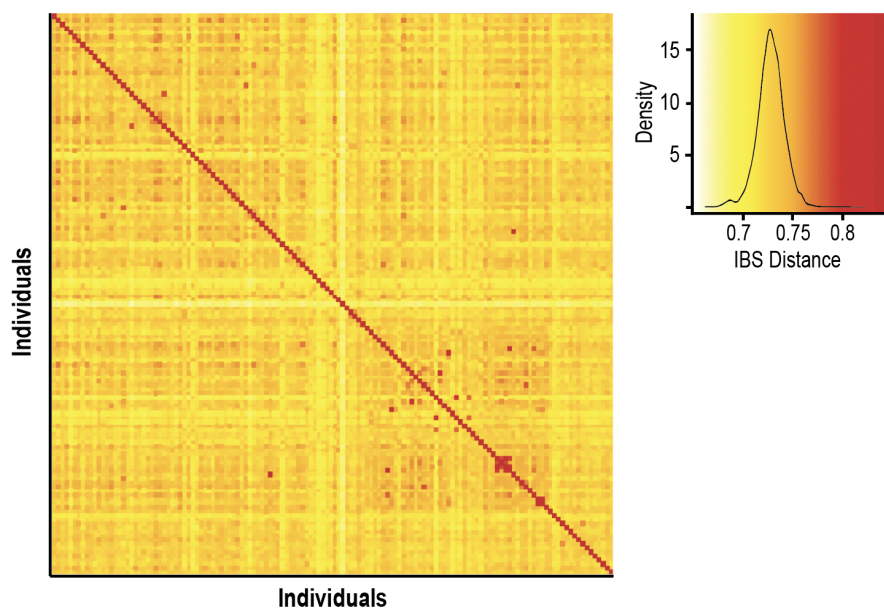
Supplemental Fig 1. A LocusZoom plot using unpruned SNVs depicts color-coded pairwise LD (r^2) with the lead SNV (purple diamond) based on all 37 controls.



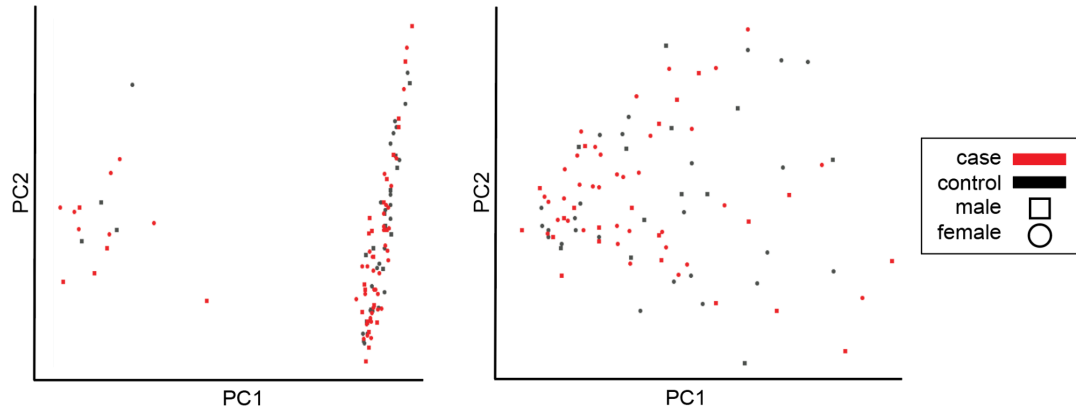
Supplemental Fig 2. Sequence of binding motifs (a) GATA1, (b) EVI1, (c) TBP, and (d) GATA3 with conserved variant (chr27:6,992,728) boxed in black. Red text denotes the predicted effect of the alternate allele in the binding motif. (e) P -values for binding specificity between the wildtype and alternate alleles are compared in each motif.



Supplemental Fig 3. Intronic 1,106 bp deletion in *CACNA1C* segregates with the lead SNV on chromosome 27. IGV shows individuals homozygous (#1) and heterozygous (#2) for the deletion, or individuals without the deletion (#3).



Supplemental Fig 4. Heat map of IBS distance scores in 138 Standard Poodles.



Supplemental Fig 5. PCA plot for (a) 109 Standard Poodles and (b) 93 Standard Poodles after removal of 16-dog outlier cluster.

Supplemental Table 1. Variants located within coding regions, splice sites, or untranslated regions in candidate regions on chromosome 17 and 27.

Chr	Position	Variant	Pairwise LD 37 Controls	Controls AF	Cases AF	2771 Dog AF	Gene	Consequence	PolyPhen-2 Score	PhyloP Score
17	47239182	G > C	0.05	0.80	0.81	0.58	<i>LRRTM4</i>	missense (E > D)	0.00	-4.50
17	47239396	G > C	0.24	0.78	0.49	0.50	<i>LRRTM4</i>	3' UTR		na
17	47240845	A > G	0.00	0.28	0.39	0.47	<i>LRRTM4</i>	3' UTR		-0.46
17	48135065	T > C	0.00	0.24	0.24	0.16	<i>GCFC2</i>	synonymous		-0.88
17	48135261	A > G	0.34	0.15	0.31	0.26	<i>GCFC2</i>	missense (I > V)	unknown	na
17	48149742	A > G	0.12	0.36	0.15	0.24	<i>GCFC2</i>	synonymous		1.46
17	48177214	G > A	0.01	0.26	0.13	0.14	<i>GCFC2</i>	missense (R > H)	1.00	8.31
17	48181932	A > C	0.19	0.20	0.34	0.25	<i>GCFC2</i>	3' UTR		na
17	48182116	T > C	0.12	0.36	0.15	0.25	<i>GCFC2</i>	3' UTR		-1.24
17	48182124	G > A	0.00	0.57	0.49	0.53	<i>GCFC2</i>	3' UTR		na
17	48182298	T > G	0.00	0.57	0.49	0.52	<i>GCFC2</i>	3' UTR		na
27	1215636	G > C	0.79	0.43	0.54	0.27	<i>TMEM121B</i>	synonymous		-0.31
27	1216961	T > C	0.71	0.28	0.50	0.06	<i>TMEM121B</i>	3' UTR		na
27	1217417	T > A	0.68	0.32	0.50	0.17	<i>TMEM121B</i>	3' UTR		-0.5
27	1224921	G > A	0.61	0.27	0.49	0.03	<i>IL1RA</i>	3' UTR		0.10
27	1227218	C > T	0.61	0.27	0.49	0.12	<i>IL1RA</i>	missense (S > N)	0.25	na
27	1294140	G > A	0.49	0.49	0.38	0.48	<i>CACNA1C</i>	synonymous		2.23
27	1322326	T > G	0.58	0.52	0.38	0.59	<i>CACNA1C</i>	synonymous		-0.03
27	2034925	G > A	0.01	0.72	0.83	0.52	<i>CACNA1C</i>	missense (R > Q)	0.66	4.21
27	2364189	G > A	0.67	0.28	0.50	0.08	<i>WNT5B</i>	3' UTR		na
27	2373193	G > C	0.39	0.65	0.68	0.419	<i>WNT5B</i>	synonymous		3.08
27	6773832	A > G	0.63	0.30	0.59	0.23	<i>ANO2</i>	3' UTR		-3.29
27	7090718	A > G	0.48	0.39	0.64	0.61	<i>ANO2</i>	synonymous		-2.05
27	7142810	G > A	0.23	0.51	0.71	0.46	<i>VWF</i>	missense (P > L)	0.00	0.71
27	7151867	A > G	0.35	0.35	0.54	0.33	<i>VWF</i>	synonymous		-2.34
27	7168583	C > A	0.63	0.30	0.56	0.20	<i>VWF</i>	missense (A > S)	0.09	0.41
27	7168932	G > A	0.63	0.30	0.56	0.20	<i>VWF</i>	synonymous		-8.14
27	7254705	T > C	0.21	0.68	0.79	0.61	<i>VWF</i>	missense (I > V)	0.00	3.47
27	7254757	G > A	0.40	0.36	0.54	0.14	<i>VWF</i>	synonymous		2.35

Supplemental Table 2. Low-coverage whole genome sequencing reads meta-report with SRA accession ID.

Accession	Dog_ID	% Reads Identified (PF)	Total Read Bases (bp)	Total Reads	Gb of Data	Estimated Coverage
SAMN44114386	D000058	0.8466	8,587,354,862	56,869,900	8.59	3.43
SAMN44114387	D000059	0.8396	8,516,351,456	56,399,679	8.52	3.41
SAMN44114388	D000060	1.0559	10,710,356,720	70,929,515	10.71	4.28
SAMN44114389	D000082	1.1671	11,838,296,550	78,399,315	11.84	4.74
SAMN44114390	D000083	0.9996	10,139,286,464	67,147,592	10.14	4.06
SAMN44114391	D000097	0.1193	1,210,100,915	8,013,913	1.21	0.48
SAMN44114392	D000098	1.0222	10,368,526,034	68,665,735	10.37	4.15
SAMN44114393	D000100	0.717	7,272,777,506	48,164,089	7.27	2.91
SAMN44114394	D000103	0.8468	8,589,383,531	56,883,335	8.59	3.44
SAMN44114395	D000111	0.7932	8,045,700,303	53,282,783	8.05	3.22
SAMN44114396	D000116	0.872	8,844,995,795	58,576,131	8.84	3.54
SAMN44114397	D000118	0.5436	5,513,921,690	36,516,038	5.51	2.21
SAMN44114398	D000121	0.9232	9,364,334,997	62,015,464	9.36	3.75
SAMN44114399	D000122	0.921	9,342,019,641	61,867,680	9.34	3.74
SAMN44114400	D000128	0.9522	9,658,491,968	63,963,523	9.66	3.86
SAMN44114401	D000130	0.6569	6,663,162,543	44,126,904	6.66	2.67
SAMN44114402	D000133	1.6308	16,541,765,071	109,548,113	16.54	6.62
SAMN44114403	D000135	1.0043	10,186,960,180	67,463,312	10.19	4.07
SAMN44114404	D000144	4.3696	44,322,355,074	293,525,530	44.32	17.73
SAMN44114405	D000155	0.8775	8,900,784,186	58,945,591	8.90	3.56
SAMN44114406	D000156	0.7028	7,128,742,024	47,210,212	7.13	2.85
SAMN44114407	D000172	0.9552	9,688,921,999	64,165,046	9.69	3.88
SAMN44114408	D000215	1.0088	10,232,605,227	67,765,598	10.23	4.09
SAMN44114409	D000285	0.9995	10,138,272,129	67,140,875	10.14	4.06
SAMN44114410	D000373	0.8249	8,367,244,302	55,412,214	8.37	3.35
SAMN44114411	D000377	0.9317	9,450,553,420	62,586,446	9.45	3.78
SAMN44114412	D000378	0.979	9,930,333,581	65,763,799	9.93	3.97
SAMN44114413	D000385	0.9363	9,497,212,801	62,895,449	9.50	3.80
SAMN44114414	D000399	0.8734	8,859,196,476	58,670,175	8.86	3.54
SAMN44114415	D000477	0.9976	10,118,999,776	67,013,244	10.12	4.05
SAMN44114416	D000525	0.9555	9,691,965,002	64,185,199	9.69	3.88
SAMN44114417	D000530	3.1858	32,314,664,682	214,004,402	32.31	12.93
SAMN44114418	D000671	0.9921	10,063,211,385	66,643,784	10.06	4.03
SAMN44114419	D000672	0.8985	9,113,794,405	60,356,254	9.11	3.65
SAMN44114420	D000684	0.9706	9,845,129,494	65,199,533	9.85	3.94
SAMN44114421	D000954	1.0071	10,215,361,542	67,651,401	10.22	4.09
SAMN44114422	D001028	0.9612	9,749,782,062	64,568,093	9.75	3.90
SAMN44114423	D001031	0.9291	9,424,180,726	62,411,793	9.42	3.77
SAMN44114424	D001079	0.9956	10,098,713,089	66,878,895	10.10	4.04
SAMN44114425	D001080	1.009	10,234,633,895	67,779,032	10.23	4.09
SAMN44114426	D001108	0.9818	9,958,734,944	65,951,887	9.96	3.98
SAMN44114427	D001169	1.0039	10,182,902,842	67,436,443	10.18	4.07
SAMN44114428	D001237	1.0308	10,455,758,790	69,243,436	10.46	4.18
SAMN44114429	D001287	0.9064	9,193,926,821	60,886,933	9.19	3.68
SAMN44114430	D001610	0.934	9,473,883,110	62,740,948	9.47	3.79
SAMN44114431	D001618	0.9675	9,813,685,128	64,991,292	9.81	3.93
SAMN44114432	D002075	2.2448	22,769,778,165	150,793,233	22.77	9.11
SAMN44114433	D002097	3.0647	31,086,305,748	205,869,574	31.09	12.43
SAMN44114434	D002385	0.9865	10,006,408,660	66,267,607	10.01	4.00
SAMN44114435	D002406	0.8141	8,257,696,189	54,686,730	8.26	3.30
SAMN44114436	D002414	3.7518	38,055,797,274	252,025,148	38.06	15.22
SAMN44114437	D002437	0.9411	9,545,900,851	63,217,886	9.55	3.82
SAMN44114438	D002513	1.0031	10,174,788,167	67,382,703	10.17	4.07
SAMN44114439	D002524	0.8305	8,424,047,027	55,788,391	8.42	3.37
SAMN44114440	D002943	0.9561	9,698,051,008	64,225,503	9.70	3.88
SAMN44114441	D003308	1.01	10,244,777,239	67,846,207	10.24	4.10
SAMN44114442	D003460	0.8795	8,921,070,873	59,079,940	8.92	3.57
SAMN44114443	D003684	1.1046	11,204,337,563	74,200,911	11.20	4.48
SAMN44114444	D004417	0.9241	9,373,464,007	62,075,921	9.37	3.75
SAMN44114445	D004604	0.9038	9,167,554,128	60,712,279	9.17	3.67
SAMN44114446	D005821	0.9046	9,175,668,803	60,766,019	9.18	3.67
SAMN44114447	D006011	0.9506	9,642,262,617	63,856,044	9.64	3.86
SAMN44114448	D006376	0.7906	8,019,327,609	53,108,130	8.02	3.21
SAMN44114449	D006624	1.2573	12,753,226,161	84,458,451	12.75	5.10
SAMN44114450	D006625	0.8525	8,647,200,591	57,266,229	8.65	3.46

SAMN44114451	D006629	0.9444	9,579,373,886	63,439,562	9.58	3.83
SAMN44114452	D006654	0.8631	8,754,720,035	57,978,278	8.75	3.50
SAMN44114453	D006671	0.9554	9,690,950,668	64,178,481	9.69	3.88
SAMN44114454	D006735	1.0485	10,635,295,976	70,432,424	10.64	4.25
SAMN44114455	D006761	1.002	10,163,630,489	67,308,811	10.16	4.07
SAMN44114456	D006865	1.0782	10,936,553,287	72,427,505	10.94	4.37
SAMN44114457	D006878	1.0701	10,854,392,202	71,883,392	10.85	4.34
SAMN44114458	D006899	1.0213	10,147,333,718	67,200,886	10.15	4.06
SAMN44114459	D006900	0.7315	7,267,966,919	48,132,231	7.27	2.91
SAMN44114460	D006901	0.7565	7,516,359,500	49,777,215	7.52	3.01
SAMN44114461	D007922	0.0044	43,651,840	289,085	0.04	0.02
SAMN44114462	D008167	0.9389	9,314,707,470	61,686,804	9.31	3.73
SAMN44114463	D008168	1.0617	10,532,990,650	69,754,905	10.53	4.21
SAMN44114464	D008169	1.1751	11,658,017,625	77,205,415	11.66	4.66
SAMN44114465	D008170	1.088	10,793,909,605	71,482,845	10.79	4.32
SAMN44114466	D008171	1.1745	11,652,065,102	77,165,994	11.65	4.66
SAMN44114467	D008172	1.1518	11,426,861,289	75,674,578	11.43	4.57
SAMN44114468	D008173	1.0095	10,015,121,090	66,325,305	10.02	4.01
SAMN44114469	D008174	1.1957	11,862,387,605	78,558,858	11.86	4.74
SAMN44114470	D008175	1.0093	10,013,136,915	66,312,165	10.01	4.01
SAMN44114471	D008176	0.9936	9,857,379,212	65,280,657	9.86	3.94
SAMN44114472	D008177	1.2143	12,046,915,839	79,780,900	12.05	4.82
SAMN44114473	D008178	0.9362	9,287,921,114	61,509,411	9.29	3.72
SAMN44114474	D008179	1.0914	10,827,640,572	71,706,229	10.83	4.33
SAMN44114475	D008180	1.1346	11,256,222,277	74,544,518	11.26	4.50
SAMN44114476	D008181	1.0234	10,153,021,222	67,238,551	10.15	4.06
SAMN44114477	D008182	0.8021	7,957,532,072	52,698,888	7.96	3.18
SAMN44114478	D008183	1.2041	11,945,722,937	79,110,748	11.95	4.78
SAMN44114479	D008184	0.7012	6,956,516,006	46,069,642	6.96	2.78
SAMN44114480	D008185	0.8486	8,418,852,657	55,753,991	8.42	3.37
SAMN44114481	D008186	1.152	11,445,930,132	75,800,862	11.45	4.58
SAMN44114482	D008187	1.1348	11,275,036,036	74,669,113	11.28	4.51
SAMN44114483	D008188	1.3555	13,467,845,741	89,191,031	13.47	5.39
SAMN44114484	D008189	1.2252	12,173,223,609	80,617,375	12.17	4.87
SAMN44114485	D008190	1.4499	14,405,776,127	95,402,491	14.41	5.76
SAMN44114486	D008191	0.8816	8,746,241,459	57,922,129	8.75	3.50
SAMN44114487	D008192	1.0519	10,435,766,097	69,111,034	10.44	4.17
SAMN44114488	D008193	1.0583	10,499,259,683	69,531,521	10.50	4.20
SAMN44114489	D008194	0.8564	8,496,235,465	56,266,460	8.50	3.40
SAMN44114490	D008195	0.9698	9,621,262,440	63,716,970	9.62	3.85
SAMN44114491	D008196	0.9405	9,330,580,867	61,791,926	9.33	3.73
SAMN44114492	D008197	0.869	8,621,238,462	57,094,294	8.62	3.45
SAMN44114493	D008198	0.9911	9,832,577,030	65,116,404	9.83	3.93
SAMN44114494	D008199	1.0284	10,202,625,586	67,567,057	10.20	4.08
SAMN44114495	D008200	0.9203	9,130,179,236	60,464,763	9.13	3.65
SAMN44114496	D008201	1.4378	14,264,230,909	94,465,105	14.26	5.71
SAMN44114497	D008202	1.0877	10,790,933,343	71,463,135	10.79	4.32
SAMN44114498	D008203	0.9422	9,347,446,351	61,903,618	9.35	3.74
SAMN44114499	D008204	1.0218	10,137,147,825	67,133,429	10.14	4.05
SAMN44114500	D008205	0.8059	7,995,231,388	52,948,552	8.00	3.20
SAMN44114501	D008206	1.0638	10,553,824,483	69,892,877	10.55	4.22
SAMN44114502	D008207	0.9088	9,016,089,199	59,709,200	9.02	3.61
SAMN44114503	D008209	1.143	11,339,557,609	75,096,408	11.34	4.54
SAMN44114504	D008210	1.1386	11,295,905,768	74,807,323	11.30	4.52
SAMN44114505	D008211	1.0432	10,349,454,503	68,539,434	10.35	4.14
SAMN44114506	D008212	1.1168	11,079,630,741	73,375,038	11.08	4.43
SAMN44114507	D008213	1.3264	13,159,045,680	87,145,998	13.16	5.26
SAMN44114508	D008288	1.0361	10,279,016,306	68,072,956	10.28	4.11
SAMN44114509	D008289	1.1199	11,110,385,447	73,578,712	11.11	4.44
SAMN44114510	D008290	1.0649	10,564,737,443	69,965,149	10.56	4.23
SAMN44114511	D008291	1.1391	11,300,866,205	74,840,174	11.30	4.52
SAMN44114512	D008292	1.2387	12,288,985,135	81,384,008	12.29	4.92
SAMN44114513	D008293	1.1048	10,960,580,268	72,586,624	10.96	4.38
SAMN44114514	D008294	0.9278	9,204,585,782	60,957,522	9.20	3.68
SAMN44114515	D008295	1.1016	10,928,833,475	72,376,381	10.93	4.37
SAMN44114516	D008296	0.9543	9,467,488,911	62,698,602	9.47	3.79
SAMN44114517	D008297	1.0039	9,959,564,202	65,957,379	9.96	3.98
SAMN44114518	D008298	1.1888	11,793,933,583	78,105,520	11.79	4.72
SAMN44114519	D008299	0.9261	9,187,720,299	60,845,830	9.19	3.68
SAMN44114520	D008300	1.2567	12,467,560,846	82,566,628	12.47	4.99
SAMN44114521	D008301	1.1352	11,262,174,801	74,583,939	11.26	4.50
SAMN44114522	D008302	1.3085	13,000,867,688	86,098,462	13.00	5.20
SAMN44114523	D008441	1.3234	13,148,909,667	87,078,872	13.15	5.26

Supplemental Table 3. Dogs used in imputation reference panel with SRA accession ID.

Accession	Coverage Type	Sample Name	Organism	Tax ID	Breed	Sex
SRR23628687	high coverage WGS	aria	Canis lupus familiaris	9615	collie	Female
SRR29476553	high coverage WGS	BELS0100 JE	Canis lupus familiaris	9615	belgian sheepdog	Female
SRR29476555	high coverage WGS	BELS0102 JE	Canis lupus familiaris	9615	belgian sheepdog	Female
SRR29476557	high coverage WGS	BOX4015 JE	Canis lupus familiaris	9615	boxer	Male
SRR8163600	high coverage WGS	D00270	Canis lupus familiaris	9615	standard poodle	Male
SRR8163597	high coverage WGS	D00271	Canis lupus familiaris	9615	standard poodle	Male
SRR29744201	high coverage WGS	D00276	Canis lupus familiaris	9615	doberman pinscher	Male
SRR8163598	high coverage WGS	D00285	Canis lupus familiaris	9615	standard poodle	Female
SRR29759791	high coverage WGS	D00315	Canis lupus familiaris	9615	standard poodle	Female
SRR29744200	high coverage WGS	D00340	Canis lupus familiaris	9615	doberman pinscher	Male
SRR8163595	high coverage WGS	D00353	Canis lupus familiaris	9615	standard poodle	Male
SRR8163596	high coverage WGS	D00354	Canis lupus familiaris	9615	standard poodle	Female
SRR8163593	high coverage WGS	D00373	Canis lupus familiaris	9615	standard poodle	Female
SRR29476572	high coverage WGS	D00377	Canis lupus familiaris	9615	standard poodle	Female
SRR8163594	high coverage WGS	D00382	Canis lupus familiaris	9615	standard poodle	Female
SRR8163601	high coverage WGS	D00392	Canis lupus familiaris	9615	standard poodle	Female
SRR8163602	high coverage WGS	D00397	Canis lupus familiaris	9615	standard poodle	Female
SRR29476571	high coverage WGS	D00399	Canis lupus familiaris	9615	standard poodle	Female
SRR29699929	high coverage WGS	D00426	Canis lupus familiaris	9615	miniature poodle	Female
SRR29744199	high coverage WGS	D00465	Canis lupus familiaris	9615	doberman pinscher	Female
SRR28876542	high coverage WGS	D00469	Canis lupus familiaris	9615	standard poodle	Male
SRR8163591	high coverage WGS	D00477	Canis lupus familiaris	9615	standard poodle	Male
SRR8163592	high coverage WGS	D00530	Canis lupus familiaris	9615	standard poodle	Male
SRR29699928	high coverage WGS	D00574	Canis lupus familiaris	9615	sheltie	Female
SRR29749730	high coverage WGS	D00587	Canis lupus familiaris	9615	boxer	Male
SRR29699917	high coverage WGS	D00607	Canis lupus familiaris	9615	sheltie	Male
SRR29699906	high coverage WGS	D00662	Canis lupus familiaris	9615	great dane	Male
SRR29699895	high coverage WGS	D00724	Canis lupus familiaris	9615	sheltie	Female
SRR29699884	high coverage WGS	D00769	Canis lupus familiaris	9615	great dane	Female
SRR29699873	high coverage WGS	D00808	Canis lupus familiaris	9615	sheltie	Female
Already public - Bern dog	high coverage WGS	D008304	Canis lupus familiaris	9615	leonberger	Male
Already public - Bern dog	high coverage WGS	D008307	Canis lupus familiaris	9615	leonberger	Male
Already public - Bern dog	high coverage WGS	D008312	Canis lupus familiaris	9615	leonberger	Male
Already public - Bern dog	high coverage WGS	D008314	Canis lupus familiaris	9615	leonberger	Male
Already public - Bern dog	high coverage WGS	D008317	Canis lupus familiaris	9615	great pyrenees	Male
Already public - Bern dog	high coverage WGS	D008318	Canis lupus familiaris	9615	newfoundland	Male
SRR29699865	high coverage WGS	D00856	Canis lupus familiaris	9615	miniature poodle	Male
SRR8163590	high coverage WGS	D00868	Canis lupus familiaris	9615	standard poodle	Male
SRR29759790	high coverage WGS	D00870	Canis lupus familiaris	9615	standard poodle	Male
SRR29759789	high coverage WGS	D00871	Canis lupus familiaris	9615	standard poodle	Female
SRR29802380	high coverage WGS	D00891	Canis lupus familiaris	9615	scottish deerhound	Female
SRR29802384	high coverage WGS	D00892	Canis lupus familiaris	9615	scottish deerhound	Male
SRR29744202	high coverage WGS	D00912	Canis lupus familiaris	9615	collie	Male
SRR29830227	high coverage WGS	D00915	Canis lupus familiaris	9615	sheltie	Male
SRR29749719	high coverage WGS	D00916	Canis lupus familiaris	9615	german shepherd	Female
SRR29759788	high coverage WGS	D00917	Canis lupus familiaris	9615	standard poodle	Female
SRR29759787	high coverage WGS	D00920	Canis lupus familiaris	9615	standard poodle	Male
SRR29699864	high coverage WGS	D00960	Canis lupus familiaris	9615	cavalier king charles spaniel	Male
SRR29699863	high coverage WGS	D00983	Canis lupus familiaris	9615	portuguese water dog	Male
SRR29009670	high coverage WGS	D01027	Canis lupus familiaris	9615	standard poodle	Male
SRR29009669	high coverage WGS	D01176	Canis lupus familiaris	9615	standard poodle	Female
SRR29699927	high coverage WGS	D01312	Canis lupus familiaris	9615	cavalier king charles spaniel	Female
SRR29699926	high coverage WGS	D01367	Canis lupus familiaris	9615	great dane	Female
SRR29699925	high coverage WGS	D01368	Canis lupus familiaris	9615	scottish deerhound	Male
SRR29476570	high coverage WGS	D01618	Canis lupus familiaris	9615	standard poodle	Female
SRR29009668	high coverage WGS	D01684	Canis lupus familiaris	9615	boxer	Male
SRR29699924	high coverage WGS	D01878	Canis lupus familiaris	9615	cavalier king charles spaniel	Female
SRR23628681	high coverage WGS	D01886	Canis lupus familiaris	9615	boxer	Female
SRR29699923	high coverage WGS	D01953	Canis lupus familiaris	9615	cavalier king charles spaniel	Male
SRR29699922	high coverage WGS	D01970	Canis lupus familiaris	9615	sheltie	Male
SRR29699921	high coverage WGS	D01972	Canis lupus familiaris	9615	great dane	Male
SRR6376929	high coverage WGS	D01991	Canis lupus familiaris	9615	american staffordshire terrier	Male
SRR29699920	high coverage WGS	D02038	Canis lupus familiaris	9615	great dane	Male
SRR29699919	high coverage WGS	D02043	Canis lupus familiaris	9615	yorkshire terrier	Male
SRR29699918	high coverage WGS	D02063	Canis lupus familiaris	9615	great dane	Male
SRR29699916	high coverage WGS	D02064	Canis lupus familiaris	9615	great dane	Male
SRR29699915	high coverage WGS	D02116	Canis lupus familiaris	9615	scottish deerhound	Male
SRR23628678	high coverage WGS	D02133	Canis lupus familiaris	9615	standard poodle	Male
SRR29699914	high coverage WGS	D02331	Canis lupus familiaris	9615	yorkshire terrier	Female
SRR29476569	high coverage WGS	D02406	Canis lupus familiaris	9615	standard poodle	Male
SRR23628674	high coverage WGS	D02462	Canis lupus familiaris	9615	standard poodle	Female
SRR29009667	high coverage WGS	D02474	Canis lupus familiaris	9615	boxer	Male
SRR29009666	high coverage WGS	D02478	Canis lupus familiaris	9615	portuguese water dog	Female

SRR29699913	high coverage WGS	D02479	Canis lupus familiaris	9615	portuguese water dog	Male
SRR29699912	high coverage WGS	D02480	Canis lupus familiaris	9615	rottweiler	Male
SRR29699911	high coverage WGS	D02495	Canis lupus familiaris	9615	labrador retriever	Male
SRR29009665	high coverage WGS	D02510	Canis lupus familiaris	9615	border collie	Male
SRR9738666	high coverage WGS	D02532	Canis lupus familiaris	9615	boykin spaniel	Male
SRR29699910	high coverage WGS	D02601	Canis lupus familiaris	9615	miniature poodle	Female
SRR29699909	high coverage WGS	D02626	Canis lupus familiaris	9615	labrador retriever	Male
SRR29009664	high coverage WGS	D02667	Canis lupus familiaris	9615	standard poodle	Female
SRR29699908	high coverage WGS	D02702	Canis lupus familiaris	9615	cairn terrier	Male
SRR29744203	high coverage WGS	D02704	Canis lupus familiaris	9615	cairn terrier	Male
SRR29749722	high coverage WGS	D02705	Canis lupus familiaris	9615	golden retriever	Male
SRR23628671	high coverage WGS	D02726	Canis lupus familiaris	9615	miniature poodle	Female
SRR29009663	high coverage WGS	D02841	Canis lupus familiaris	9615	boxer	Male
SRR29699907	high coverage WGS	D02888	Canis lupus familiaris	9615	scottish deerhound	Female
SRR29009662	high coverage WGS	D02908	Canis lupus familiaris	9615	standard poodle	Female
SRR29699905	high coverage WGS	D02945	Canis lupus familiaris	9615	great dane	Male
SRR29699904	high coverage WGS	D02946	Canis lupus familiaris	9615	great dane	Female
SRR29699903	high coverage WGS	D02947	Canis lupus familiaris	9615	great dane	Female
SRR29699902	high coverage WGS	D02965	Canis lupus familiaris	9615	sheltie	Female
SRR29699901	high coverage WGS	D03022	Canis lupus familiaris	9615	miniature poodle	Male
SRR29398863	high coverage WGS	D03036	Canis lupus familiaris	9615	boxer	Male
SRR29699900	high coverage WGS	D03136	Canis lupus familiaris	9615	great dane	Male
SRR29699899	high coverage WGS	D03260	Canis lupus familiaris	9615	welsh springer spaniel	Female
SRR29699898	high coverage WGS	D03261	Canis lupus familiaris	9615	welsh springer spaniel	Female
SRR29699897	high coverage WGS	D03262	Canis lupus familiaris	9615	welsh springer spaniel	Female
SRR29699896	high coverage WGS	D03263	Canis lupus familiaris	9615	welsh springer spaniel	Male
SRR29398862	high coverage WGS	D03294	Canis lupus familiaris	9615	border collie	Male
SRR29398851	high coverage WGS	D03295	Canis lupus familiaris	9615	border collie	Male
SRR29398840	high coverage WGS	D03296	Canis lupus familiaris	9615	border collie	Female
SRR23628669	high coverage WGS	D03297	Canis lupus familiaris	9615	border collie	Male
SRR29699894	high coverage WGS	D03404	Canis lupus familiaris	9615	great dane	Female
SRR29699893	high coverage WGS	D03580	Canis lupus familiaris	9615	miniature schnauzer	Male
SRR29699892	high coverage WGS	D03621	Canis lupus familiaris	9615	corgi	Female
SRR29398829	high coverage WGS	D03645	Canis lupus familiaris	9615	standard poodle	Male
SRR29476568	high coverage WGS	D03684	Canis lupus familiaris	9615	standard poodle	Female
SRR29699891	high coverage WGS	D03742	Canis lupus familiaris	9615	corgi	Female
SRR29699890	high coverage WGS	D03744	Canis lupus familiaris	9615	corgi	Female
SRR29699889	high coverage WGS	D03745	Canis lupus familiaris	9615	corgi	Female
SRR29699888	high coverage WGS	D03746	Canis lupus familiaris	9615	corgi	Female
SRR29699887	high coverage WGS	D03763	Canis lupus familiaris	9615	corgi	Female
SRR29699886	high coverage WGS	D03764	Canis lupus familiaris	9615	corgi	Male
SRR29398828	high coverage WGS	D03887	Canis lupus familiaris	9615	pomeranian	Male
SRR29398827	high coverage WGS	D03957	Canis lupus familiaris	9615	portuguese water dog	Male
SRR29699885	high coverage WGS	D04482	Canis lupus familiaris	9615	yorkshire terrier	Male
SRR29699883	high coverage WGS	D04487	Canis lupus familiaris	9615	yorkshire terrier	Male
SRR29699882	high coverage WGS	D04495	Canis lupus familiaris	9615	lhasa apso	Male
SRR29699881	high coverage WGS	D04496	Canis lupus familiaris	9615	lhasa apso	Male
SRR29699880	high coverage WGS	D04498	Canis lupus familiaris	9615	bichon frise	Male
SRR29699879	high coverage WGS	D04500	Canis lupus familiaris	9615	bichon frise	Female
SRR29699878	high coverage WGS	D04502	Canis lupus familiaris	9615	pomeranian	Male
SRR29398826	high coverage WGS	D04513	Canis lupus familiaris	9615	australian shepherd	Female
SRR29398825	high coverage WGS	D04521	Canis lupus familiaris	9615	portuguese water dog	Male
SRR29398824	high coverage WGS	D04796	Canis lupus familiaris	9615	great dane	Female
SRR29398861	high coverage WGS	D04797	Canis lupus familiaris	9615	great dane	Female
SRR29398860	high coverage WGS	D04819	Canis lupus familiaris	9615	pomeranian	Male
SRR29398859	high coverage WGS	D04858	Canis lupus familiaris	9615	great dane	Female
SRR29398858	high coverage WGS	D04894	Canis lupus familiaris	9615	portuguese water dog	Male
SRR29398857	high coverage WGS	D04898	Canis lupus familiaris	9615	great dane	Female
SRR29699877	high coverage WGS	D05030	Canis lupus familiaris	9615	great pyrenees	Male
SRR29699876	high coverage WGS	D05155	Canis lupus familiaris	9615	yorkshire terrier	Male
SRR29398856	high coverage WGS	D05355	Canis lupus familiaris	9615	miniature schnauzer	Female
SRR9962250	high coverage WGS	D05531	Canis lupus familiaris	9615	labrador retriever	Male
SRR23628643	high coverage WGS	D05542	Canis lupus familiaris	9615	border collie	Male
SRR29699875	high coverage WGS	D05584	Canis lupus familiaris	9615	siberian husky	Male
SRR29699874	high coverage WGS	D05585	Canis lupus familiaris	9615	siberian husky	Female
SRR29699872	high coverage WGS	D05586	Canis lupus familiaris	9615	siberian husky	Male
SRR29699871	high coverage WGS	D05587	Canis lupus familiaris	9615	siberian husky	Male
SRR29699870	high coverage WGS	D05589	Canis lupus familiaris	9615	siberian husky	Female
SRR29699869	high coverage WGS	D05590	Canis lupus familiaris	9615	siberian husky	Male
SRR29699868	high coverage WGS	D05937	Canis lupus familiaris	9615	golden retriever	unknown
SRR29398855	high coverage WGS	D05944	Canis lupus familiaris	9615	american foxhound	Male
SRR29699867	high coverage WGS	D05945	Canis lupus familiaris	9615	boston terrier	Male
SRR29699866	high coverage WGS	D05949	Canis lupus familiaris	9615	german shepherd	Male
SRR29398854	high coverage WGS	D05953	Canis lupus familiaris	9615	portuguese water dog	Female
SRR29398853	high coverage WGS	D05957	Canis lupus familiaris	9615	labrador retriever	Male

SRR29749724	high coverage WGS	D06106	Canis lupus familiaris	9615	french_bulldog	Male
SRR29749723	high coverage WGS	D06114	Canis lupus familiaris	9615	french_bulldog	Male
SRR29749721	high coverage WGS	D06115	Canis lupus familiaris	9615	french_bulldog	Female
SRR29749720	high coverage WGS	D06122	Canis lupus familiaris	9615	french_bulldog	Female
SRR29744198	high coverage WGS	D06129	Canis lupus familiaris	9615	english_bulldog	Male
SRR23628632	high coverage WGS	D06131	Canis lupus familiaris	9615	english_bulldog	Male
SRR29744197	high coverage WGS	D06133	Canis lupus familiaris	9615	english_bulldog	Female
SRR23628630	high coverage WGS	D06139	Canis lupus familiaris	9615	english_bulldog	Female
SRR29744196	high coverage WGS	D06147	Canis lupus familiaris	9615	english_bulldog	Male
SRR29759799	high coverage WGS	D06155	Canis lupus familiaris	9615	irish_wolfhound	Female
SRR23628657	high coverage WGS	D06159	Canis lupus familiaris	9615	irish_wolfhound	Female
SRR29759798	high coverage WGS	D06161	Canis lupus familiaris	9615	irish_wolfhound	Female
SRR29759797	high coverage WGS	D06162	Canis lupus familiaris	9615	irish_wolfhound	Female
SRR29759796	high coverage WGS	D06164	Canis lupus familiaris	9615	irish_wolfhound	Female
SRR23628655	high coverage WGS	D06167	Canis lupus familiaris	9615	irish_wolfhound	Female
SRR29759794	high coverage WGS	D06169	Canis lupus familiaris	9615	irish_wolfhound	Male
SRR29749728	high coverage WGS	D06174	Canis lupus familiaris	9615	bullmastiff	Female
SRR29749727	high coverage WGS	D06178	Canis lupus familiaris	9615	bullmastiff	Female
SRR29749726	high coverage WGS	D06183	Canis lupus familiaris	9615	bullmastiff	Female
SRR29749725	high coverage WGS	D06187	Canis lupus familiaris	9615	bullmastiff	Male
SRR29759795	high coverage WGS	D06208	Canis lupus familiaris	9615	newfoundland	Female
SRR29759793	high coverage WGS	D06209	Canis lupus familiaris	9615	newfoundland	Female
SRR29759792	high coverage WGS	D06213	Canis lupus familiaris	9615	newfoundland	Female
SRR29802386	high coverage WGS	D06214	Canis lupus familiaris	9615	rottweiler	Female
SRR29802385	high coverage WGS	D06217	Canis lupus familiaris	9615	rottweiler	Female
SRR29802379	high coverage WGS	D06219	Canis lupus familiaris	9615	rottweiler	Female
SRR29802383	high coverage WGS	D06220	Canis lupus familiaris	9615	rottweiler	Female
SRR29802382	high coverage WGS	D06226	Canis lupus familiaris	9615	rottweiler	Male
SRR29802381	high coverage WGS	D06228	Canis lupus familiaris	9615	rottweiler	Female
SRR29749733	high coverage WGS	D06229	Canis lupus familiaris	9615	bouvier	Female
SRR29749732	high coverage WGS	D06231	Canis lupus familiaris	9615	bouvier	Male
SRR29749731	high coverage WGS	D06232	Canis lupus familiaris	9615	bouvier	Male
SRR23628647	high coverage WGS	D06235	Canis lupus familiaris	9615	bouvier	Female
SRR29749729	high coverage WGS	D06236	Canis lupus familiaris	9615	bouvier	Male
SRR23628629	high coverage WGS	D06240	Canis lupus familiaris	9615	whippet	Female
SRR29759786	high coverage WGS	D06244	Canis lupus familiaris	9615	whippet	Male
SRR29759785	high coverage WGS	D06250	Canis lupus familiaris	9615	whippet	Female
SRR29759784	high coverage WGS	D06251	Canis lupus familiaris	9615	whippet	Female
SRR29759783	high coverage WGS	D06253	Canis lupus familiaris	9615	whippet	Female
SRR23628627	high coverage WGS	D06254	Canis lupus familiaris	9615	whippet	Male
SRR29749718	high coverage WGS	D06258	Canis lupus familiaris	9615	golden_retriever	Female
SRR29749717	high coverage WGS	D06276	Canis lupus familiaris	9615	golden_retriever	Female
SRR23628628	high coverage WGS	D06279	Canis lupus familiaris	9615	golden_retriever	Female
SRR29749716	high coverage WGS	D06285	Canis lupus familiaris	9615	golden_retriever	Male
SRR29398852	high coverage WGS	D06536	Canis lupus familiaris	9615	pomeranian	Male
SRR29476567	high coverage WGS	D06654	Canis lupus familiaris	9615	standard_poodle	Male
SRR29398850	high coverage WGS	D06665	Canis lupus familiaris	9615	cavalier_king_charles_spaniel	Male
SRR29398849	high coverage WGS	D06741	Canis lupus familiaris	9615	dachshund	Male
SRR29398848	high coverage WGS	D06774	Canis lupus familiaris	9615	labrador_retriever	Female
SRR29398847	high coverage WGS	D06779	Canis lupus familiaris	9615	english_bulldog	Male
SRR29398846	high coverage WGS	D06790	Canis lupus familiaris	9615	miniature_schnauzer	Male
SRR29398845	high coverage WGS	D06794	Canis lupus familiaris	9615	yorkshire_terrier	Male
SRR29398844	high coverage WGS	D06797	Canis lupus familiaris	9615	yorkshire_terrier	Male
SRR23628618	high coverage WGS	D06812	Canis lupus familiaris	9615	siberian_husky	Male
SRR29398843	high coverage WGS	D06819	Canis lupus familiaris	9615	shiloh_shepherd	Female
SRR29398842	high coverage WGS	D06820	Canis lupus familiaris	9615	shiloh_shepherd	Male
SRR29398841	high coverage WGS	D06821	Canis lupus familiaris	9615	shiloh_shepherd	Female
SRR29398839	high coverage WGS	D06822	Canis lupus familiaris	9615	shiloh_shepherd	Male
SRR29398838	high coverage WGS	D06823	Canis lupus familiaris	9615	shiloh_shepherd	Female
SRR29398837	high coverage WGS	D06824	Canis lupus familiaris	9615	brittany_spaniel	Female
SRR23628614	high coverage WGS	D06838	Canis lupus familiaris	9615	boston_terrier	Male
SRR23628613	high coverage WGS	D06946	Canis lupus familiaris	9615	shiloh_shepherd	Male
SRR29398836	high coverage WGS	D06948	Canis lupus familiaris	9615	shiloh_shepherd	Male
SRR29398835	high coverage WGS	D06949	Canis lupus familiaris	9615	shiloh_shepherd	Female
SRR29398834	high coverage WGS	D06950	Canis lupus familiaris	9615	shiloh_shepherd	Female
SRR29398833	high coverage WGS	D06968	Canis lupus familiaris	9615	labrador_retriever	Male
SRR23628612	high coverage WGS	D06969	Canis lupus familiaris	9615	labrador_retriever	Male
SRR29398832	high coverage WGS	D06999	Canis lupus familiaris	9615	boston_terrier	Female
SRR29398831	high coverage WGS	D07001	Canis lupus familiaris	9615	boston_terrier	Female
SRR7120196	high coverage WGS	D07202	Canis lupus familiaris	9615	portuguese_water_dog	unknown
SRR7120197	high coverage WGS	D07203	Canis lupus familiaris	9615	portuguese_water_dog	unknown
SRR7120199	high coverage WGS	D07205	Canis lupus familiaris	9615	portuguese_water_dog	unknown
SRR7120200	high coverage WGS	D07206	Canis lupus familiaris	9615	portuguese_water_dog	unknown
SRR7120201	high coverage WGS	D07207	Canis lupus familiaris	9615	portuguese_water_dog	unknown
SRR7120203	high coverage WGS	D07209	Canis lupus familiaris	9615	portuguese_water_dog	unknown

SRR12330158	high coverage WGS	BASS000002	Canis lupus familiaris	9615	basset hound	Male
SRR12330147	high coverage WGS	BASS000003	Canis lupus familiaris	9615	basset hound	Female
SRR15734701	high coverage WGS	BASS000004	Canis lupus familiaris	9615	basset hound	Male
SRR15100196	high coverage WGS	BASS000005	Canis lupus familiaris	9615	basset hound	Male
SRR15100195	high coverage WGS	BASS000006	Canis lupus familiaris	9615	basset hound	Male
SRR14750386	high coverage WGS	BASS000007	Canis lupus familiaris	9615	basset hound	Female
SRR15734710	high coverage WGS	BBL0000001	Canis lupus familiaris	9615	white swiss shepherd dog	Female
SRR15734708	high coverage WGS	BBL0000002	Canis lupus familiaris	9615	white swiss shepherd dog	Male
SRR15734707	high coverage WGS	BBL0000003	Canis lupus familiaris	9615	white swiss shepherd dog	Female
SRR12330136	high coverage WGS	BEAU0000001	Canis lupus familiaris	9615	beauceron	Female
SRR12330125	high coverage WGS	BEAU0000002	Canis lupus familiaris	9615	belgian terverein	Male
SRR15734706	high coverage WGS	BEAU0000003	Canis lupus familiaris	9615	beauceron	Male
SRR15100204	high coverage WGS	BEAU0000004	Canis lupus familiaris	9615	beauceron	Female
SRR14750387	high coverage WGS	BEAU0000005	Canis lupus familiaris	9615	german shepherd mix	Male
SRR14750388	high coverage WGS	BEAU0000006	Canis lupus familiaris	9615	beauceron	Female
SRR14750509	high coverage WGS	BEAU0000007	Canis lupus familiaris	9615	german shepherd mix	Male
SRR12330114	high coverage WGS	BEDT0000001	Canis lupus familiaris	9615	bedlington terrier	Male
SRR12330093	high coverage WGS	BEDT0000003	Canis lupus familiaris	9615	bedlington terrier	Male
SRR12330085	high coverage WGS	BEDT0000004	Canis lupus familiaris	9615	bedlington terrier	Male
SRR12330083	high coverage WGS	BEDT0000005	Canis lupus familiaris	9615	bedlington terrier	Male
SRR15100153	high coverage WGS	BEDT0000006	Canis lupus familiaris	9615	bedlington terrier	Male
SRR15100152	high coverage WGS	BEDT0000007	Canis lupus familiaris	9615	bedlington terrier	Male
SRR15100151	high coverage WGS	BEDT0000008	Canis lupus familiaris	9615	bedlington terrier	Male
SRR12330082	high coverage WGS	BELS0000001	Canis lupus familiaris	9615	belgian sheepdog	Male
SRR12330081	high coverage WGS	BELS0000002	Canis lupus familiaris	9615	belgian sheepdog	Female
SRR15100182	high coverage WGS	BELS0000003	Canis lupus familiaris	9615	belgian sheepdog	Male
SRR12330080	high coverage WGS	BICH0000001	Canis lupus familiaris	9615	bichon frise	Female
SRR15100194	high coverage WGS	BICH0000004	Canis lupus familiaris	9615	bichon frise	Male
SRR12330077	high coverage WGS	BMAL0000001	Canis lupus familiaris	9615	belgian malinois	Female
SRR12330076	high coverage WGS	BMAL0000002	Canis lupus familiaris	9615	belgian malinois	Male
SRR15734648	high coverage WGS	BMAL0000003	Canis lupus familiaris	9615	belgian malinois	Male
SRR15100179	high coverage WGS	BMAL0000004	Canis lupus familiaris	9615	belgian malinois	Female
SRR16048597	high coverage WGS	BOPD0000001	Canis lupus familiaris	9615	bourbonnais pointing dog	Female
SRR16048558	high coverage WGS	BOPD0000002	Canis lupus familiaris	9615	bourbonnais pointing dog	Male
SRR16048546	high coverage WGS	BOPD0000003	Canis lupus familiaris	9615	bourbonnais pointing dog	Female
SRR16048535	high coverage WGS	BOPD0000004	Canis lupus familiaris	9615	bourbonnais pointing dog	Female
SRR14750524	high coverage WGS	BOPD0000006	Canis lupus familiaris	9615	bourbonnais pointing dog	Female
SRR14750525	high coverage WGS	BOPD0000007	Canis lupus familiaris	9615	bourbonnais pointing dog	Male
SRR14750526	high coverage WGS	BOPD0000008	Canis lupus familiaris	9615	bourbonnais pointing dog	Female
SRR15734684	high coverage WGS	BOST0000001	Canis lupus familiaris	9615	boston terrier	Female
SRR15100186	high coverage WGS	BOST0000002	Canis lupus familiaris	9615	boston terrier	Male
SRR15100185	high coverage WGS	BOST0000003	Canis lupus familiaris	9615	boston terrier	Male
SRR12330068	high coverage WGS	BOYK0000001	Canis lupus familiaris	9615	boykin spaniel	Male
SRR12330067	high coverage WGS	BOYK0000002	Canis lupus familiaris	9615	boykin spaniel	Male
SRR12330066	high coverage WGS	BOYK0000003	Canis lupus familiaris	9615	boykin spaniel	Male
SRR12330065	high coverage WGS	BOYK0000004	Canis lupus familiaris	9615	boykin spaniel	Female
SRR12330064	high coverage WGS	BOYK0000005	Canis lupus familiaris	9615	boykin spaniel	Male
SRR12330058	high coverage WGS	BRIT0000002	Canis lupus familiaris	9615	brittany	Male
SRR15100173	high coverage WGS	BRIT0000004	Canis lupus familiaris	9615	brittany	Male
SRR15100172	high coverage WGS	BRIT0000005	Canis lupus familiaris	9615	brittany	Female
SRR14750539	high coverage WGS	BRIT0000006	Canis lupus familiaris	9615	brittany	Female
SRR14750389	high coverage WGS	BRIT0000008	Canis lupus familiaris	9615	brittany	Male
SRR12330057	high coverage WGS	BRMD0000001	Canis lupus familiaris	9615	bernese mountain dog	Female
SRR12330056	high coverage WGS	BRMD0000002	Canis lupus familiaris	9615	bernese mountain dog	Female
SRR15734682	high coverage WGS	BRMD0000003	Canis lupus familiaris	9615	bernese mountain dog	Female
SRR16289019	high coverage WGS	BRMD0000005	Canis lupus familiaris	9615	bernese mountain dog	Male
SRR16289017	high coverage WGS	BRMD0000007	Canis lupus familiaris	9615	bernese mountain dog	Female
SRR16289016	high coverage WGS	BRMD0000008	Canis lupus familiaris	9615	bernese mountain dog	Female
SRR16289020	high coverage WGS	BRMD0000010	Canis lupus familiaris	9615	bernese mountain dog	Female
SRR12330055	high coverage WGS	BRUS0000001	Canis lupus familiaris	9615	brussels griffon	Male
SRR12330054	high coverage WGS	BRUS0000002	Canis lupus familiaris	9615	brussels griffon	Female
SRR12330053	high coverage WGS	BRUS0000003	Canis lupus familiaris	9615	brussels griffon	Female
SRR12330052	high coverage WGS	BRUS0000004	Canis lupus familiaris	9615	brussels griffon	Female
SRR12330050	high coverage WGS	BRUS0000005	Canis lupus familiaris	9615	brussels griffon	Female
SRR12330049	high coverage WGS	BRUS0000006	Canis lupus familiaris	9615	brussels griffon	Male
SRR16048882	high coverage WGS	BRUS0000007	Canis lupus familiaris	9615	brussels griffon	Female
SRR15100238	high coverage WGS	BULD0000003	Canis lupus familiaris	9615	english bulldog	Female
SRR15734680	high coverage WGS	BULM0000003	Canis lupus familiaris	9615	bullmastiff	Male
SRR15734679	high coverage WGS	BULM0000004	Canis lupus familiaris	9615	bullmastiff	Female
SRR15100188	high coverage WGS	BULM0000006	Canis lupus familiaris	9615	bullmastiff	Female
SRR12330038	high coverage WGS	CAIR0000001	Canis lupus familiaris	9615	cairn terrier	Male
SRR15734668	high coverage WGS	CAIR0000002	Canis lupus familiaris	9615	cairn terrier	Male
SRR15734667	high coverage WGS	CAIR0000003	Canis lupus familiaris	9615	cairn terrier	Female
SRR15100261	high coverage WGS	CAIR0000004	Canis lupus familiaris	9615	cairn terrier	Male
SRR15100260	high coverage WGS	CAIR0000005	Canis lupus familiaris	9615	cairn terrier	Female

SRR29398830	high coverage WGS	D07210	Canis lupus familiaris	9615	great dane	Female
SRR23363274	high coverage WGS	D07211	Canis lupus familiaris	9615	great dane	Male
SRR15446414	high coverage WGS	D07212	Canis lupus familiaris	9615	german shepherd	Female
SRR15446416	high coverage WGS	D07214	Canis lupus familiaris	9615	german shepherd	Female
SRR29476573	high coverage WGS	D07215	Canis lupus familiaris	9615	collie	Male
SRR10077554	high coverage WGS	D07228	Canis lupus familiaris	9615	german shepherd	unknown
SRR10752632	high coverage WGS	D07229	Canis lupus familiaris	9615	german shepherd	unknown
SRR12331647	high coverage WGS	D07234	Canis lupus familiaris	9615	german shepherd	unknown
SRR7772003	high coverage WGS	D07236	Canis lupus familiaris	9615	german shepherd	unknown
SRR7772004	high coverage WGS	D07237	Canis lupus familiaris	9615	german shepherd	unknown
SRR8614058	high coverage WGS	D07239	Canis lupus familiaris	9615	german shepherd	unknown
SRR29476562	high coverage WGS	D07372	Canis lupus familiaris	9615	portuguese water dog	Male
SRR29476551	high coverage WGS	D07407	Canis lupus familiaris	9615	portuguese water dog	Female
SRR29476546	high coverage WGS	D07408	Canis lupus familiaris	9615	portuguese water dog	Female
SRR29476535	high coverage WGS	D07412	Canis lupus familiaris	9615	portuguese water dog	Male
SRR29476534	high coverage WGS	D07414	Canis lupus familiaris	9615	portuguese water dog	Female
SRR29476533	high coverage WGS	D07415	Canis lupus familiaris	9615	portuguese water dog	Male
SRR29476532	high coverage WGS	D07487	Canis lupus familiaris	9615	portuguese water dog	Female
SRR29476583	high coverage WGS	D07489	Canis lupus familiaris	9615	spinone italiano	Female
SRR29476582	high coverage WGS	D07505	Canis lupus familiaris	9615	boykin spaniel	Male
SRR15505576	high coverage WGS	D07513	Canis lupus familiaris	9615	american staffordshire ter	Female
SRR23628611	high coverage WGS	D07546	Canis lupus familiaris	9615	portuguese water dog	Male
SRR23628610	high coverage WGS	D07558	Canis lupus familiaris	9615	portuguese water dog	Male
SRR29476581	high coverage WGS	D07729	Canis lupus familiaris	9615	german shepherd	Female
SRR23628607	high coverage WGS	D07887	Canis lupus familiaris	9615	german shepherd	Male
SRR29476580	high coverage WGS	D07888	Canis lupus familiaris	9615	german shepherd	Male
SRR23628606	high coverage WGS	D07889	Canis lupus familiaris	9615	german shepherd	Male
SRR29476579	high coverage WGS	D07890	Canis lupus familiaris	9615	german shepherd	Male
SRR29476578	high coverage WGS	D07891	Canis lupus familiaris	9615	german shepherd	unknown
SRR29476575	high coverage WGS	D07906	Canis lupus familiaris	9615	miniature poodle	Female
SRR29476577	high coverage WGS	D07937	Canis lupus familiaris	9615	border collie	Female
SRR29476576	high coverage WGS	D07939	Canis lupus familiaris	9615	collie	Female
SRR29476574	high coverage WGS	D08027	Canis lupus familiaris	9615	german shepherd	Female
SRR24017568	high coverage WGS	D08114	Canis lupus familiaris	9615	american staffordshire ter	Female
SRR24899250	high coverage WGS	D08115	Canis lupus familiaris	9615	brittany spaniel	Male
SRR23363278	high coverage WGS	D08128	Canis lupus familiaris	9615	great dane	Male
SRR23363279	high coverage WGS	D08129	Canis lupus familiaris	9615	great dane	Female
SRR23363277	high coverage WGS	D08130	Canis lupus familiaris	9615	great dane	Male
SRR12330380	high coverage WGS	AFOX000001	Canis lupus familiaris	9615	american foxhound	Male
SRR16048740	high coverage WGS	AFOX000002	Canis lupus familiaris	9615	american foxhound	Male
SRR16048739	high coverage WGS	AFOX000003	Canis lupus familiaris	9615	american foxhound	Female
SRR16048460	high coverage WGS	AFOX000004	Canis lupus familiaris	9615	american foxhound	Male
SRR16048547	high coverage WGS	AFOX000006	Canis lupus familiaris	9615	american foxhound	Male
SRR16048879	high coverage WGS	AFOX000007	Canis lupus familiaris	9615	american foxhound	Male
SRR15100209	high coverage WGS	AKIT000002	Canis lupus familiaris	9615	japanese akita	Male
SRR15100198	high coverage WGS	AKIT000003	Canis lupus familiaris	9615	japanese akita	Female
SRR15100154	high coverage WGS	AKIT000005	Canis lupus familiaris	9615	american akita	Male
SRR15100143	high coverage WGS	AKIT000006	Canis lupus familiaris	9615	american akita	Male
SRR15100280	high coverage WGS	AKIT000007	Canis lupus familiaris	9615	american akita	Male
SRR15100269	high coverage WGS	AKIT000008	Canis lupus familiaris	9615	american akita	Female
SRR15734676	high coverage WGS	AKIT000009	Canis lupus familiaris	9615	american akita	Female
SRR15734805	high coverage WGS	ALDB000001	Canis lupus familiaris	9615	alpine dachsbracke	Male
SRR15734709	high coverage WGS	ALDB000002	Canis lupus familiaris	9615	alpine dachsbracke	Male
SRR15734698	high coverage WGS	ALDB000003	Canis lupus familiaris	9615	alpine dachsbracke	Female
SRR15734687	high coverage WGS	ALDB000004	Canis lupus familiaris	9615	alpine dachsbracke	Female
SRR16048868	high coverage WGS	ALDB000005	Canis lupus familiaris	9615	alpine dachsbracke	Female
SRR16048857	high coverage WGS	ALDB000006	Canis lupus familiaris	9615	alpine dachsbracke	Male
SRR16048818	high coverage WGS	ALDB000007	Canis lupus familiaris	9615	alpine dachsbracke	Female
SRR12330303	high coverage WGS	AMST000002	Canis lupus familiaris	9615	american staffordshire ter	Male
SRR12330291	high coverage WGS	AMST000003	Canis lupus familiaris	9615	american staffordshire ter	Male
SRR15734757	high coverage WGS	AMST000005	Canis lupus familiaris	9615	american staffordshire ter	Male
SRR15100223	high coverage WGS	AMST000006	Canis lupus familiaris	9615	american staffordshire ter	Male
SRR15734793	high coverage WGS	APPZ000002	Canis lupus familiaris	9615	appenzeller sennenhund	Male
SRR15734782	high coverage WGS	APPZ000003	Canis lupus familiaris	9615	appenzeller sennenhund	Female
SRR15100236	high coverage WGS	APPZ000005	Canis lupus familiaris	9615	appenzeller sennenhund	Male
SRR15100225	high coverage WGS	APPZ000006	Canis lupus familiaris	9615	appenzeller sennenhund	Female
SRR14750315	high coverage WGS	APPZ000007	Canis lupus familiaris	9615	appenzeller sennenhund	Male
SRR16289012	high coverage WGS	APPZ000011	Canis lupus familiaris	9615	appenzeller sennenhund	Male
SRR16289001	high coverage WGS	APPZ000012	Canis lupus familiaris	9615	appenzeller sennenhund	Female
SRR16048482	high coverage WGS	ASKT000001	Canis lupus familiaris	9615	silky terrier	Male
SRR16048471	high coverage WGS	ASKT000002	Canis lupus familiaris	9615	silky terrier	Male
SRR16048459	high coverage WGS	ASKT000003	Canis lupus familiaris	9615	silky terrier	Female
SRR12330203	high coverage WGS	AUSS000001	Canis lupus familiaris	9615	australian shepherd	Male
SRR15100258	high coverage WGS	AUSS000003	Canis lupus familiaris	9615	australian shepherd	Male
SRR12330169	high coverage WGS	BASS000001	Canis lupus familiaris	9615	basset hound	Female

SRR12330400	high coverage WGS	CKCS000001	Canis lupus familiaris	9615	cavalier king charles spaniel	Female
SRR15100146	high coverage WGS	CKCS000005	Canis lupus familiaris	9615	cavalier king charles spaniel	Female
SRR15100268	high coverage WGS	COLL000005	Canis lupus familiaris	9615	collie	Male
SRR15100133	high coverage WGS	COLL000009	Canis lupus familiaris	9615	collie	Male
SRR15100279	high coverage WGS	COLL000010	Canis lupus familiaris	9615	collie	Male
SRR21121000	high coverage WGS	CRTR000001	Canis lupus familiaris	9615	cretan tracer	Male
SRR21120999	high coverage WGS	CRTR000002	Canis lupus familiaris	9615	cretan tracer	Female
SRR13376337	high coverage WGS	CRTR000003	Canis lupus familiaris	9615	cretan tracer	Female
SRR13376372	high coverage WGS	CRTR000005	Canis lupus familiaris	9615	cretan tracer	Male
SRR13376370	high coverage WGS	CRTR000007	Canis lupus familiaris	9615	cretan tracer	Female
SRR13376356	high coverage WGS	CRTR000008	Canis lupus familiaris	9615	hellenic hound	Male
SRR13376354	high coverage WGS	CRTR000010	Canis lupus familiaris	9615	hellenic hound	Male
SRR12330373	high coverage WGS	DACH000001	Canis lupus familiaris	9615	dachshund	Female
SRR16048856	high coverage WGS	DACH000003	Canis lupus familiaris	9615	dachshund	Female
SRR16048855	high coverage WGS	DACH000004	Canis lupus familiaris	9615	dachshund	Male
SRR16048850	high coverage WGS	DACH000009	Canis lupus familiaris	9615	dachshund	Male
SRR14750416	high coverage WGS	DACH000013	Canis lupus familiaris	9615	dachshund	Male
SRR14750418	high coverage WGS	DACH000015	Canis lupus familiaris	9615	dachshund	Female
SRR15734796	high coverage WGS	DEER000001	Canis lupus familiaris	9615	scottish deerhound	Female
SRR16048819	high coverage WGS	DEER000003	Canis lupus familiaris	9615	scottish deerhound	Male
SRR15734885	high coverage WGS	DOBP000001	Canis lupus familiaris	9615	doberman pinscher	Female
SRR16289014	high coverage WGS	DOBP000002	Canis lupus familiaris	9615	doberman pinscher	Male
SRR16289013	high coverage WGS	DOBP000003	Canis lupus familiaris	9615	doberman pinscher	Female
SRR16289011	high coverage WGS	DOBP000004	Canis lupus familiaris	9615	doberman pinscher	Female
SRR16048805	high coverage WGS	EGTT000007	Canis lupus familiaris	9615	english toy terrier	Female
SRR16048803	high coverage WGS	EGTT000009	Canis lupus familiaris	9615	english toy terrier	Female
SRR16048801	high coverage WGS	EGTT000011	Canis lupus familiaris	9615	english toy terrier	Male
SRR16048800	high coverage WGS	EGTT000012	Canis lupus familiaris	9615	english toy terrier	Male
SRR16048799	high coverage WGS	EGTT000013	Canis lupus familiaris	9615	english toy terrier	Female
SRR16048798	high coverage WGS	EGTT000014	Canis lupus familiaris	9615	english toy terrier	Male
SRR16048736	high coverage WGS	EGTT000016	Canis lupus familiaris	9615	english toy terrier	Male
SRR12330355	high coverage WGS	ENTB000001	Canis lupus familiaris	9615	entlebucher mountain dog	Female
SRR12330354	high coverage WGS	ENTB000002	Canis lupus familiaris	9615	entlebucher mountain dog	Male
SRR16289004	high coverage WGS	ENTB000004	Canis lupus familiaris	9615	entlebucher mountain dog	Female
SRR16289003	high coverage WGS	ENTB000005	Canis lupus familiaris	9615	entlebucher mountain dog	Female
SRR16289002	high coverage WGS	ENTB000006	Canis lupus familiaris	9615	entlebucher mountain dog	Male
SRR16289007	high coverage WGS	ENTB000007	Canis lupus familiaris	9615	entlebucher mountain dog	Female
SRR16289005	high coverage WGS	ENTB000009	Canis lupus familiaris	9615	entlebucher mountain dog	Male
SRR12330352	high coverage WGS	EPNT000002	Canis lupus familiaris	9615	english pointer	Male
SRR12330351	high coverage WGS	EPNT000003	Canis lupus familiaris	9615	english pointer	Female
SRR12330092	high coverage WGS	EPNT000004	Canis lupus familiaris	9615	english pointer	Female
SRR12330091	high coverage WGS	EPNT000005	Canis lupus familiaris	9615	english pointer	Male
SRR12330350	high coverage WGS	EPNT000006	Canis lupus familiaris	9615	english pointer	Female
SRR16048651	high coverage WGS	EPNT000007	Canis lupus familiaris	9615	english pointer	Male
SRR16048650	high coverage WGS	EPNT000008	Canis lupus familiaris	9615	english pointer	Female
SRR16048649	high coverage WGS	FBUL000006	Canis lupus familiaris	9615	french bulldog	Female
SRR14750431	high coverage WGS	FLCD000005	Canis lupus familiaris	9615	bouvier des flandres	Male
SRR14750433	high coverage WGS	FLCD000007	Canis lupus familiaris	9615	bouvier des flandres	Male
SRR16288999	high coverage WGS	GOLD000003	Canis lupus familiaris	9615	golden retriever	Female
SRR15734836	high coverage WGS	GPYR000001	Canis lupus familiaris	9615	great pyrenees	Female
SRR15734834	high coverage WGS	GPYR000002	Canis lupus familiaris	9615	great pyrenees	Male
SRR16048585	high coverage WGS	GPYR000003	Canis lupus familiaris	9615	great pyrenees	Male
SRR16048584	high coverage WGS	GPYR000004	Canis lupus familiaris	9615	great pyrenees	Female
SRR14750316	high coverage WGS	GPYR000006	Canis lupus familiaris	9615	great pyrenees	Female
SRR15734650	high coverage WGS	GRND000001	Canis lupus familiaris	9615	groenendael	Male
SRR14750317	high coverage WGS	GRND000002	Canis lupus familiaris	9615	groenendael	Male
SRR14750318	high coverage WGS	GRND000003	Canis lupus familiaris	9615	groenendael	Male
SRR12330319	high coverage WGS	GRSD000002	Canis lupus familiaris	9615	german shepherd	Female
SRR12330318	high coverage WGS	GRSD000003	Canis lupus familiaris	9615	german shepherd	Male
SRR12330315	high coverage WGS	GSMD000001	Canis lupus familiaris	9615	greater swiss mountain dog	Male
SRR15734792	high coverage WGS	GSMD000002	Canis lupus familiaris	9615	greater swiss mountain dog	Female
SRR15734791	high coverage WGS	GSMD000003	Canis lupus familiaris	9615	greater swiss mountain dog	Female
SRR14750448	high coverage WGS	GSMD000004	Canis lupus familiaris	9615	greater swiss mountain dog	Male
SRR16288954	high coverage WGS	GSMD000006	Canis lupus familiaris	9615	greater swiss mountain dog	Male
SRR16288953	high coverage WGS	GSMD000007	Canis lupus familiaris	9615	greater swiss mountain dog	Female
SRR16288952	high coverage WGS	GSMD000008	Canis lupus familiaris	9615	greater swiss mountain dog	Male
SRR15734653	high coverage WGS	GSPK000003	Canis lupus familiaris	9615	german spitz klein	Female
SRR16048579	high coverage WGS	GSPK000005	Canis lupus familiaris	9615	german spitz klein	Male
SRR16048578	high coverage WGS	GSPK000006	Canis lupus familiaris	9615	german spitz klein	Male
SRR16288981	high coverage WGS	GSPK000007	Canis lupus familiaris	9615	german spitz klein	Female
SRR16288980	high coverage WGS	GSPK000008	Canis lupus familiaris	9615	german spitz klein	Female
SRR16288977	high coverage WGS	GSPK000010	Canis lupus familiaris	9615	german spitz klein	Female
SRR16288976	high coverage WGS	GSPK000011	Canis lupus familiaris	9615	german spitz klein	Female
SRR16288995	high coverage WGS	GSZG000001	Canis lupus familiaris	9615	german giant spitz	Male
SRR16288994	high coverage WGS	GSZG000002	Canis lupus familiaris	9615	german giant spitz	Female

SRR16288993	high coverage WGS	GSZG000003	Canis lupus familiaris	9615	german giant spitz	Female
SRR16288992	high coverage WGS	GSZG000004	Canis lupus familiaris	9615	german giant spitz	Male
SRR16288991	high coverage WGS	GSZG000005	Canis lupus familiaris	9615	german giant spitz	Male
SRR16288989	high coverage WGS	GSZG000006	Canis lupus familiaris	9615	german giant spitz	Male
SRR16288982	high coverage WGS	GSZG000007	Canis lupus familiaris	9615	pomeranian	Female
SRR15734871	high coverage WGS	GSZM000001	Canis lupus familiaris	9615	german spitz mittel	Female
SRR16048577	high coverage WGS	GSZM000005	Canis lupus familiaris	9615	german spitz mittel	Female
SRR16288967	high coverage WGS	GSZM000007	Canis lupus familiaris	9615	german spitz mittel	Female
SRR16288966	high coverage WGS	GSZM000008	Canis lupus familiaris	9615	german spitz mittel	Female
SRR16288965	high coverage WGS	GSZM000009	Canis lupus familiaris	9615	german spitz mittel	Female
SRR16288964	high coverage WGS	GSZM000010	Canis lupus familiaris	9615	german spitz mittel	Female
SRR16288963	high coverage WGS	GSZM000011	Canis lupus familiaris	9615	german spitz mittel	Male
SRR16048508	high coverage WGS	HTSV000001	Canis lupus familiaris	9615	hamiltonstovare	Female
SRR16048507	high coverage WGS	HTSV000002	Canis lupus familiaris	9615	hamiltonstovare	Female
SRR16048506	high coverage WGS	HTSV000003	Canis lupus familiaris	9615	hamiltonstovare	Male
SRR16048505	high coverage WGS	HTSV000004	Canis lupus familiaris	9615	hamiltonstovare	Female
SRR16048503	high coverage WGS	HTSV000005	Canis lupus familiaris	9615	hamiltonstovare	Female
SRR16048502	high coverage WGS	HTSV000006	Canis lupus familiaris	9615	hamiltonstovare	Male
SRR16048501	high coverage WGS	HTSV000007	Canis lupus familiaris	9615	hamiltonstovare	Female
SRR12330309	high coverage WGS	IBIZ000001	Canis lupus familiaris	9615	ibizan hound	Male
SRR12330308	high coverage WGS	IBIZ000002	Canis lupus familiaris	9615	ibizan hound	Female
SRR12330307	high coverage WGS	IBIZ000003	Canis lupus familiaris	9615	ibizan hound	Female
SRR12330305	high coverage WGS	IBIZ000005	Canis lupus familiaris	9615	ibizan hound	Female
SRR12330304	high coverage WGS	IBIZ000006	Canis lupus familiaris	9615	ibizan hound	Female
SRR16048497	high coverage WGS	IBIZ000010	Canis lupus familiaris	9615	ibizan hound	Female
SRR16048496	high coverage WGS	IBIZ000011	Canis lupus familiaris	9615	ibizan hound	Male
SRR15734719	high coverage WGS	JSPZ000001	Canis lupus familiaris	9615	japanese spitz	Male
SRR15734718	high coverage WGS	JSPZ000002	Canis lupus familiaris	9615	japanese spitz	Male
SRR16048485	high coverage WGS	JSPZ000005	Canis lupus familiaris	9615	japanese spitz	Male
SRR16288988	high coverage WGS	JSPZ000007	Canis lupus familiaris	9615	japanese spitz	Female
SRR16288985	high coverage WGS	JSPZ000010	Canis lupus familiaris	9615	japanese spitz	Female
SRR16288984	high coverage WGS	JSPZ000011	Canis lupus familiaris	9615	japanese spitz	Male
SRR16288983	high coverage WGS	JSPZ000012	Canis lupus familiaris	9615	japanese spitz	Male
SRR12330107	high coverage WGS	KEES000002	Canis lupus familiaris	9615	keeshond	Male
SRR15734744	high coverage WGS	KEES000004	Canis lupus familiaris	9615	keeshond	Female
SRR16048476	high coverage WGS	KEES000006	Canis lupus familiaris	9615	keeshond	Female
SRR16288934	high coverage WGS	KEES000007	Canis lupus familiaris	9615	keeshond	Female
SRR16288933	high coverage WGS	KEES000008	Canis lupus familiaris	9615	keeshond	Male
SRR16288932	high coverage WGS	KEES000009	Canis lupus familiaris	9615	keeshond	Male
SRR16288930	high coverage WGS	KEES000011	Canis lupus familiaris	9615	keeshond	Female
SRR12330293	high coverage WGS	KMUM000001	Canis lupus familiaris	9615	small munsterlander	Female
SRR12330290	high coverage WGS	KMUM000002	Canis lupus familiaris	9615	small munsterlander	Male
SRR15734658	high coverage WGS	KMUM000003	Canis lupus familiaris	9615	small munsterlander	Female
SRR14750458	high coverage WGS	KMUM000006	Canis lupus familiaris	9615	small munsterlander	Male
SRR16048470	high coverage WGS	KMUM000007	Canis lupus familiaris	9615	small munsterlander	Female
SRR16048467	high coverage WGS	KMUM000010	Canis lupus familiaris	9615	small munsterlander	Male
SRR16048466	high coverage WGS	KMUM000011	Canis lupus familiaris	9615	small munsterlander	Female
SRR15734661	high coverage WGS	KROM000001	Canis lupus familiaris	9615	kromfohrlander	Male
SRR15734660	high coverage WGS	KROM000002	Canis lupus familiaris	9615	kromfohrlander	Female
SRR15734659	high coverage WGS	KROM000003	Canis lupus familiaris	9615	kromfohrlander	Female
SRR16048465	high coverage WGS	KROM000004	Canis lupus familiaris	9615	kromfohrlander	Female
SRR16048464	high coverage WGS	KROM000005	Canis lupus familiaris	9615	kromfohrlander	Female
SRR16048463	high coverage WGS	KROM000006	Canis lupus familiaris	9615	kromfohrlander	Female
SRR16048462	high coverage WGS	KROM000007	Canis lupus familiaris	9615	kromfohrlander	Male
SRR12330106	high coverage WGS	KUVZ000001	Canis lupus familiaris	9615	kuvasz	Male
SRR12330103	high coverage WGS	KUVZ000003	Canis lupus familiaris	9615	kuvasz	Female
SRR16048461	high coverage WGS	KUVZ000004	Canis lupus familiaris	9615	kuvasz	Female
SRR16048458	high coverage WGS	KUVZ000005	Canis lupus familiaris	9615	kuvasz	Male
SRR16048457	high coverage WGS	KUVZ000006	Canis lupus familiaris	9615	kuvasz	Female
SRR16048456	high coverage WGS	KUVZ000007	Canis lupus familiaris	9615	kuvasz	Male
SRR17176028	high coverage WGS	KUVZ000008	Canis lupus familiaris	9615	kuvasz	Female
SRR12330289	high coverage WGS	LAEK000001	Canis lupus familiaris	9615	belgian laekenois	Female
SRR15734645	high coverage WGS	LAEK000002	Canis lupus familiaris	9615	belgian laekenois	Female
SRR15734647	high coverage WGS	LAEK000003	Canis lupus familiaris	9615	belgian laekenois	Female
SRR15100181	high coverage WGS	LAEK000004	Canis lupus familiaris	9615	belgian laekenois	Female
SRR15100180	high coverage WGS	LAEK000005	Canis lupus familiaris	9615	belgian laekenois	Female
SRR16048835	high coverage WGS	LEON000008	Canis lupus familiaris	9615	leonberger	Female
SRR14750462	high coverage WGS	LEON000011	Canis lupus familiaris	9615	leonberger	Male
SRR15734715	high coverage WGS	LEON000013	Canis lupus familiaris	9615	leonberger	Male
SRR12330282	high coverage WGS	LEOP000002	Canis lupus familiaris	9615	catahoula leopard dog	Female
SRR12330281	high coverage WGS	LEOP000003	Canis lupus familiaris	9615	catahoula leopard dog	Male
SRR12330279	high coverage WGS	LEOP000004	Canis lupus familiaris	9615	catahoula leopard dog	Female
SRR12330278	high coverage WGS	LEOP000005	Canis lupus familiaris	9615	catahoula leopard dog	Female
SRR12330276	high coverage WGS	LEOP000008	Canis lupus familiaris	9615	catahoula leopard dog	Female
SRR12330275	high coverage WGS	LEOP000009	Canis lupus familiaris	9615	catahoula leopard dog	Male

SRR12330274	high coverage WGS	LEOP000010	Canis lupus familiaris	9615	catahoula leopard dog	Male
SRR12330272	high coverage WGS	LHSA000002	Canis lupus familiaris	9615	lhasa apso	Male
SRR12330271	high coverage WGS	LHSA000003	Canis lupus familiaris	9615	lhasa apso	Female
SRR16048831	high coverage WGS	LHSA000005	Canis lupus familiaris	9615	lhasa apso	Male
SRR16048830	high coverage WGS	LHSA000006	Canis lupus familiaris	9615	lhasa apso	Female
SRR16048827	high coverage WGS	LHSA000008	Canis lupus familiaris	9615	lhasa apso	Male
SRR12330268	high coverage WGS	MANT000001	Canis lupus familiaris	9615	manchester terrier standa	Female
SRR12330267	high coverage WGS	MANT000002	Canis lupus familiaris	9615	manchester terrier standa	Male
SRR12330266	high coverage WGS	MANT000003	Canis lupus familiaris	9615	manchester terrier standa	Female
SRR12330089	high coverage WGS	MANT000004	Canis lupus familiaris	9615	manchester terrier standa	Female
SRR12330087	high coverage WGS	MANT000006	Canis lupus familiaris	9615	manchester terrier standa	Female
SRR16048790	high coverage WGS	MANT000008	Canis lupus familiaris	9615	manchester terrier standa	Female
SRR17179517	high coverage WGS	MANT000009	Canis lupus familiaris	9615	manchester terrier standa	Female
SRR15734827	high coverage WGS	MPOO000001	Canis lupus familiaris	9615	miniature poodle	Male
SRR16048779	high coverage WGS	MSNZ000003	Canis lupus familiaris	9615	miniature schnauzer	Female
SRR12330250	high coverage WGS	NELK000001	Canis lupus familiaris	9615	norwegian elkhound	Male
SRR12330249	high coverage WGS	NELK000002	Canis lupus familiaris	9615	norwegian elkhound	Female
SRR12330248	high coverage WGS	NELK000003	Canis lupus familiaris	9615	norwegian elkhound	Male
SRR12330246	high coverage WGS	NELK000004	Canis lupus familiaris	9615	norwegian elkhound	Male
SRR16048770	high coverage WGS	NELK000005	Canis lupus familiaris	9615	norwegian elkhound	Male
SRR16048769	high coverage WGS	NELK000006	Canis lupus familiaris	9615	norwegian elkhound	Male
SRR16048768	high coverage WGS	NELK000007	Canis lupus familiaris	9615	norwegian elkhound	Male
SRR12330245	high coverage WGS	NEWF000002	Canis lupus familiaris	9615	newfoundland	Male
SRR15734856	high coverage WGS	NEWF000004	Canis lupus familiaris	9615	newfoundland	Female
SRR14750474	high coverage WGS	NEWF000006	Canis lupus familiaris	9615	newfoundland	Male
SRR12330241	high coverage WGS	NORF000001	Canis lupus familiaris	9615	norfolk terrier	Female
SRR12330240	high coverage WGS	NORF000002	Canis lupus familiaris	9615	norfolk terrier	Male
SRR15734855	high coverage WGS	NORF000003	Canis lupus familiaris	9615	norfolk terrier	Female
SRR15734854	high coverage WGS	NORF000004	Canis lupus familiaris	9615	norfolk terrier	Male
SRR15734853	high coverage WGS	NORF000005	Canis lupus familiaris	9615	norfolk terrier	Male
SRR16048758	high coverage WGS	NORF000006	Canis lupus familiaris	9615	norfolk terrier	Female
SRR16048757	high coverage WGS	NORF000007	Canis lupus familiaris	9615	norfolk terrier	Female
SRR12330237	high coverage WGS	OLES000001	Canis lupus familiaris	9615	old english sheepdog	Female
SRR12330235	high coverage WGS	OLES000002	Canis lupus familiaris	9615	old english sheepdog	Male
SRR12330234	high coverage WGS	OLES000003	Canis lupus familiaris	9615	old english sheepdog	Female
SRR15734840	high coverage WGS	OLES000004	Canis lupus familiaris	9615	old english sheepdog	Female
SRR15734839	high coverage WGS	OLES000005	Canis lupus familiaris	9615	old english sheepdog	Female
SRR16048749	high coverage WGS	OLES000006	Canis lupus familiaris	9615	old english sheepdog	Female
SRR14750475	high coverage WGS	OLES000007	Canis lupus familiaris	9615	old english sheepdog	Male
SRR15734887	high coverage WGS	OLGS000001	Canis lupus familiaris	9615	old german shepherd	Female
SRR15734876	high coverage WGS	OLGS000002	Canis lupus familiaris	9615	old german shepherd	Female
SRR15734766	high coverage WGS	OLGS000003	Canis lupus familiaris	9615	old german shepherd	Female
SRR15734731	high coverage WGS	OLGS000004	Canis lupus familiaris	9615	old german shepherd	Male
SRR15734657	high coverage WGS	OLGS000005	Canis lupus familiaris	9615	old german shepherd	Male
SRR15734720	high coverage WGS	OLGS000006	Canis lupus familiaris	9615	old german shepherd	Male
SRR12330233	high coverage WGS	OTTR000001	Canis lupus familiaris	9615	otterhound	Female
SRR12330232	high coverage WGS	OTTR000002	Canis lupus familiaris	9615	otterhound	Male
SRR12330231	high coverage WGS	OTTR000003	Canis lupus familiaris	9615	otterhound	Female
SRR16048748	high coverage WGS	OTTR000004	Canis lupus familiaris	9615	otterhound	Female
SRR16048747	high coverage WGS	OTTR000005	Canis lupus familiaris	9615	otterhound	Female
SRR16048746	high coverage WGS	OTTR000006	Canis lupus familiaris	9615	otterhound	Male
SRR16048745	high coverage WGS	OTTR000007	Canis lupus familiaris	9615	otterhound	Female
SRR12330228	high coverage WGS	PBGV000001	Canis lupus familiaris	9615	petit basset griffon vende	Female
SRR15100202	high coverage WGS	PBGV000005	Canis lupus familiaris	9615	petit basset griffon vende	Female
SRR15100200	high coverage WGS	PBGV000006	Canis lupus familiaris	9615	petit basset griffon vende	Male
SRR15100199	high coverage WGS	PBGV000007	Canis lupus familiaris	9615	petit basset griffon vende	Male
SRR15100197	high coverage WGS	PBGV000008	Canis lupus familiaris	9615	petit basset griffon vende	Female
SRR12330086	high coverage WGS	PBGV000009	Canis lupus familiaris	9615	petit basset griffon vende	Male
SRR14750332	high coverage WGS	PBGV000012	Canis lupus familiaris	9615	petit basset griffon vende	Female
SRR16048708	high coverage WGS	POLG000001	Canis lupus familiaris	9615	polish greyhound	Female
SRR16048707	high coverage WGS	POLG000002	Canis lupus familiaris	9615	polish greyhound	Male
SRR16048706	high coverage WGS	POLG000003	Canis lupus familiaris	9615	polish greyhound	Male
SRR16048705	high coverage WGS	POLG000004	Canis lupus familiaris	9615	polish greyhound	Male
SRR16048704	high coverage WGS	POLG000005	Canis lupus familiaris	9615	polish greyhound	Male
SRR16048703	high coverage WGS	POLG000006	Canis lupus familiaris	9615	polish greyhound	Male
SRR16048701	high coverage WGS	POLG000007	Canis lupus familiaris	9615	polish greyhound	Female
SRR16288928	high coverage WGS	POMR000003	Canis lupus familiaris	9615	pomeranian	Male
SRR16288925	high coverage WGS	POMR000006	Canis lupus familiaris	9615	pomeranian	Female
SRR16289022	high coverage WGS	POMR000008	Canis lupus familiaris	9615	pomeranian	Female
SRR12330219	high coverage WGS	PTWD000001	Canis lupus familiaris	9615	portuguese water dog	Female
SRR12330218	high coverage WGS	PTWD000002	Canis lupus familiaris	9615	portuguese water dog	Male
SRR12330217	high coverage WGS	PTWD000003	Canis lupus familiaris	9615	portuguese water dog	Male
SRR15734811	high coverage WGS	PTWD000004	Canis lupus familiaris	9615	portuguese water dog	Female
SRR15734810	high coverage WGS	PTWD000005	Canis lupus familiaris	9615	portuguese water dog	Male
SRR15734809	high coverage WGS	PTWD000006	Canis lupus familiaris	9615	portuguese water dog	Male

SRR16048678	high coverage WGS	PTWD000007	Canis lupus familiaris	9615	portuguese water dog	Male
SRR16048677	high coverage WGS	PTWD000008	Canis lupus familiaris	9615	portuguese water dog	Female
SRR15734678	high coverage WGS	PYSH000001	Canis lupus familiaris	9615	pyrenean shepherd	Male
SRR16048660	high coverage WGS	PYSH000003	Canis lupus familiaris	9615	pyrenean shepherd	Male
SRR14750356	high coverage WGS	PYSH000005	Canis lupus familiaris	9615	pyrenean shepherd	Female
SRR14750479	high coverage WGS	PYSH000008	Canis lupus familiaris	9615	pyrenean shepherd	Female
SRR14750480	high coverage WGS	PYSH000009	Canis lupus familiaris	9615	pyrenean shepherd	Male
SRR14750482	high coverage WGS	PYSH000010	Canis lupus familiaris	9615	pyrenean shepherd	Male
SRR14750483	high coverage WGS	PYSH000011	Canis lupus familiaris	9615	pyrenean shepherd	Female
SRR12330202	high coverage WGS	SEAL000003	Canis lupus familiaris	9615	scalyham terrier	Male
SRR12330200	high coverage WGS	SEAL000005	Canis lupus familiaris	9615	scalyham terrier	Male
SRR12330199	high coverage WGS	SEAL000006	Canis lupus familiaris	9615	scalyham terrier	Female
SRR12330198	high coverage WGS	SEAL000007	Canis lupus familiaris	9615	scalyham terrier	Male
SRR12330197	high coverage WGS	SEAL000008	Canis lupus familiaris	9615	scalyham terrier	Female
SRR12330196	high coverage WGS	SEAL000009	Canis lupus familiaris	9615	scalyham terrier	Female
SRR12330195	high coverage WGS	SEAL000010	Canis lupus familiaris	9615	scalyham terrier	Male
SRR12330193	high coverage WGS	SHAR000002	Canis lupus familiaris	9615	chinese shar pei	Female
SRR20326332	high coverage WGS	SHIL000001	Canis lupus familiaris	9615	shiloh shepherd	Female
SRR12330187	high coverage WGS	SILK000001	Canis lupus familiaris	9615	silky terrier	Female
SRR12330186	high coverage WGS	SILK000002	Canis lupus familiaris	9615	silky terrier	Male
SRR12330185	high coverage WGS	SILK000003	Canis lupus familiaris	9615	silky terrier	Male
SRR12330183	high coverage WGS	SILK000005	Canis lupus familiaris	9615	skye terrier	Male
SRR16048566	high coverage WGS	SLCU000001	Canis lupus familiaris	9615	slovak cuvac	Female
SRR16048565	high coverage WGS	SLCU000002	Canis lupus familiaris	9615	slovak cuvac	Female
SRR16048564	high coverage WGS	SLCU000003	Canis lupus familiaris	9615	slovak cuvac	Male
SRR16048563	high coverage WGS	SLCU000004	Canis lupus familiaris	9615	slovak cuvac	Female
SRR16048562	high coverage WGS	SLCU000005	Canis lupus familiaris	9615	slovak cuvac	Male
SRR16048561	high coverage WGS	SLCU000006	Canis lupus familiaris	9615	slovak cuvac	Female
SRR16048560	high coverage WGS	SLCU000007	Canis lupus familiaris	9615	slovak cuvac	Male
SRR16288942	high coverage WGS	SMSH000001	Canis lupus familiaris	9615	small swiss hound	Female
SRR16288941	high coverage WGS	SMSH000002	Canis lupus familiaris	9615	small swiss hound	Male
SRR16288939	high coverage WGS	SMSH000004	Canis lupus familiaris	9615	small swiss hound	Female
SRR15734779	high coverage WGS	SMSH000007	Canis lupus familiaris	9615	small swiss hound	Female
SRR15734777	high coverage WGS	SMSH000009	Canis lupus familiaris	9615	small swiss hound	Male
SRR15734776	high coverage WGS	SMSH000010	Canis lupus familiaris	9615	small swiss hound	Female
SRR15734774	high coverage WGS	SMSH000012	Canis lupus familiaris	9615	small swiss hound	Female
SRR15734772	high coverage WGS	SPEI000001	Canis lupus familiaris	9615	chinese shar pei	Male
SRR15734770	high coverage WGS	SPEI000002	Canis lupus familiaris	9615	chinese shar pei	Female
SRR15734769	high coverage WGS	SPEI000003	Canis lupus familiaris	9615	chinese shar pei	Male
SRR16048555	high coverage WGS	SPEI000004	Canis lupus familiaris	9615	chinese shar pei	Female
SRR14750490	high coverage WGS	SPEI000005	Canis lupus familiaris	9615	chinese shar pei	Male
SRR14750491	high coverage WGS	SPEI000006	Canis lupus familiaris	9615	chinese shar pei	Male
SRR12330171	high coverage WGS	SPIN000002	Canis lupus familiaris	9615	spinone italiano	Female
SRR12330168	high coverage WGS	SPIN000004	Canis lupus familiaris	9615	spinone italiano	Male
SRR12330167	high coverage WGS	SPIN000005	Canis lupus familiaris	9615	spinone italiano	Male
SRR12330166	high coverage WGS	SPIN000006	Canis lupus familiaris	9615	spinone italiano	Male
SRR16048554	high coverage WGS	SPIN000007	Canis lupus familiaris	9615	spinone italiano	Female
SRR16048553	high coverage WGS	SPIN000008	Canis lupus familiaris	9615	spinone italiano	Male
SRR12330160	high coverage WGS	STBD000001	Canis lupus familiaris	9615	saint bernard	Male
SRR15734798	high coverage WGS	STBD000005	Canis lupus familiaris	9615	saint bernard	Male
SRR15734797	high coverage WGS	STBD000006	Canis lupus familiaris	9615	saint bernard	Male
SRR16288962	high coverage WGS	STBD000008	Canis lupus familiaris	9615	saint bernard	Female
SRR16288959	high coverage WGS	STBD000011	Canis lupus familiaris	9615	saint bernard	Female
SRR16288958	high coverage WGS	STBD000012	Canis lupus familiaris	9615	saint bernard	Female
SRR15734784	high coverage WGS	SWHN000004	Canis lupus familiaris	9615	swiss hound	Male
SRR15734783	high coverage WGS	SWHN000005	Canis lupus familiaris	9615	swiss hound	Female
SRR15734781	high coverage WGS	SWHN000006	Canis lupus familiaris	9615	swiss hound	Male
SRR16288947	high coverage WGS	SWHN000009	Canis lupus familiaris	9615	swiss hound	Female
SRR16288945	high coverage WGS	SWHN000010	Canis lupus familiaris	9615	swiss hound	Female
SRR16288944	high coverage WGS	SWHN000011	Canis lupus familiaris	9615	swiss hound	Male
SRR16288943	high coverage WGS	SWHN000012	Canis lupus familiaris	9615	swiss hound	Female
SRR16048527	high coverage WGS	SWWE000001	Canis lupus familiaris	9615	swedish white elkhound	Male
SRR16048526	high coverage WGS	SWWE000002	Canis lupus familiaris	9615	swedish white elkhound	Female
SRR16048523	high coverage WGS	SWWE000004	Canis lupus familiaris	9615	swedish white elkhound	Male
SRR16048522	high coverage WGS	SWWE000005	Canis lupus familiaris	9615	swedish white elkhound	Male
SRR16048521	high coverage WGS	SWWE000006	Canis lupus familiaris	9615	swedish white elkhound	Female
SRR16048520	high coverage WGS	SWWE000007	Canis lupus familiaris	9615	swedish white elkhound	Male
SRR16048519	high coverage WGS	SWWE000008	Canis lupus familiaris	9615	swedish white elkhound	Male
SRR12330141	high coverage WGS	TERV000001	Canis lupus familiaris	9615	cardigan welsh corgi	Female
SRR12330140	high coverage WGS	TERV000002	Canis lupus familiaris	9615	belgian terverein	Male
SRR15734649	high coverage WGS	TERV000003	Canis lupus familiaris	9615	belgian terverein	Female
SRR15100178	high coverage WGS	TERV000004	Canis lupus familiaris	9615	belgian terverein	Male
SRR15100177	high coverage WGS	TERV000005	Canis lupus familiaris	9615	belgian terverein	Male
SRR14750498	high coverage WGS	TERV000006	Canis lupus familiaris	9615	belgian terverein	Male
SRR15734754	high coverage WGS	THAI000002	Canis lupus familiaris	9615	thai ridgeback	Male

SRR16048518	high coverage WGS	THAI000004	Canis lupus familiaris	9615	thai ridgeback	Female
SRR16048517	high coverage WGS	THAI000005	Canis lupus familiaris	9615	thai ridgeback	Female
SRR16048516	high coverage WGS	THAI000006	Canis lupus familiaris	9615	thai ridgeback	Female
SRR16048515	high coverage WGS	THAI000007	Canis lupus familiaris	9615	thai ridgeback	Female
SRR16048514	high coverage WGS	THAI000008	Canis lupus familiaris	9615	thai ridgeback	Female
SRR16048512	high coverage WGS	THAI000009	Canis lupus familiaris	9615	thai ridgeback	Female
SRR12330137	high coverage WGS	TYFX000001	Canis lupus familiaris	9615	toy fox terrier	Female
SRR12330135	high coverage WGS	TYFX000002	Canis lupus familiaris	9615	toy fox terrier	Male
SRR12330134	high coverage WGS	TYFX000003	Canis lupus familiaris	9615	toy fox terrier	Male
SRR12330133	high coverage WGS	TYFX000004	Canis lupus familiaris	9615	toy fox terrier	Female
SRR12330131	high coverage WGS	TYFX000006	Canis lupus familiaris	9615	toy fox terrier	Female
SRR12330130	high coverage WGS	TYFX000007	Canis lupus familiaris	9615	toy fox terrier	Female
SRR16048450	high coverage WGS	TYFX000009	Canis lupus familiaris	9615	toy fox terrier	Male
SRR16048893	high coverage WGS	WHIP000004	Canis lupus familiaris	9615	whippet	Male
SRR12330119	high coverage WGS	WHPG000001	Canis lupus familiaris	9615	wirehaired pointing griffon	Female
SRR12330118	high coverage WGS	WHPG000002	Canis lupus familiaris	9615	wirehaired pointing griffon	Female
SRR12330117	high coverage WGS	WHPG000003	Canis lupus familiaris	9615	wirehaired pointing griffon	Male
SRR14750506	high coverage WGS	WHPG000004	Canis lupus familiaris	9615	wirehaired pointing griffon	Male
SRR14750507	high coverage WGS	WHPG000005	Canis lupus familiaris	9615	wirehaired pointing griffon	Male
SRR14750508	high coverage WGS	WHPG000006	Canis lupus familiaris	9615	wirehaired pointing griffon	Male
SRR16048891	high coverage WGS	WSSD000003	Canis lupus familiaris	9615	white swiss shepherd dog	Male
SRR16048890	high coverage WGS	WSSD000004	Canis lupus familiaris	9615	white swiss shepherd dog	Female
SRR16288968	high coverage WGS	WSSD000005	Canis lupus familiaris	9615	white swiss shepherd dog	Male
SRR16288957	high coverage WGS	WSSD000006	Canis lupus familiaris	9615	white swiss shepherd dog	Female
SRR16288946	high coverage WGS	WSSD000007	Canis lupus familiaris	9615	white swiss shepherd dog	Male
SRR16288935	high coverage WGS	WSSD000008	Canis lupus familiaris	9615	white swiss shepherd dog	Female
SRR16288922	high coverage WGS	WSSD000009	Canis lupus familiaris	9615	white swiss shepherd dog	Female
SRR16289021	high coverage WGS	WSSD000010	Canis lupus familiaris	9615	white swiss shepherd dog	Male
SRR12330112	high coverage WGS	WSSP000002	Canis lupus familiaris	9615	welsh springer spaniel	Male
SRR16048888	high coverage WGS	WSSP000003	Canis lupus familiaris	9615	welsh springer spaniel	Female
SRR16048887	high coverage WGS	WSSP000004	Canis lupus familiaris	9615	welsh springer spaniel	Female
SRR14750357	high coverage WGS	WSSP000005	Canis lupus familiaris	9615	welsh springer spaniel	Female
SRR20326520	high coverage WGS	ZAGR000001	Canis lupus familiaris	9615	zagar	Male
SRR20326519	high coverage WGS	ZAGR000002	Canis lupus familiaris	9615	zagar	Female
SRR20326518	high coverage WGS	ZAGR000003	Canis lupus familiaris	9615	zagar	Male
SRR20326516	high coverage WGS	ZAGR000004	Canis lupus familiaris	9615	zagar	Female
SRR20326515	high coverage WGS	ZAGR000005	Canis lupus familiaris	9615	zagar	Female
SRR20326514	high coverage WGS	ZAGR000006	Canis lupus familiaris	9615	zagar	Female
SRR20326513	high coverage WGS	ZAGR000007	Canis lupus familiaris	9615	zagar	Male
SRR29476547	high coverage WGS	D08324	Canis lupus familiaris	9615	bichon frise	Female
SRR29476545	high coverage WGS	D08326	Canis lupus familiaris	9615	miniature schnauzer	Male
SRR29476544	high coverage WGS	D08336	Canis lupus familiaris	9615	miniature schnauzer	Male
SRR29476543	high coverage WGS	D08338	Canis lupus familiaris	9615	miniature schnauzer	Male
SRR29476542	high coverage WGS	D08343	Canis lupus familiaris	9615	bichon frise	Male
SRR29476541	high coverage WGS	D08345	Canis lupus familiaris	9615	bichon frise	Male
SRR29476540	high coverage WGS	D08350	Canis lupus familiaris	9615	french bulldog	Male
SRR29476539	high coverage WGS	D08352	Canis lupus familiaris	9615	french bulldog	Male
SRR29476538	high coverage WGS	D08357	Canis lupus familiaris	9615	australian shepherd	Male
SRR29476537	high coverage WGS	D08358	Canis lupus familiaris	9615	wirehaired pointing griffon	Male
SRR29476536	high coverage WGS	D08365	Canis lupus familiaris	9615	portuguese water dog	Male
SRR29795100	high coverage WGS	D08448	Canis lupus familiaris	9615	german shepherd	Female
SRR29795099	high coverage WGS	D08449	Canis lupus familiaris	9615	german shepherd	Female
SRR29476566	high coverage WGS	D08450	Canis lupus familiaris	9615	german shepherd	Male
SRR29476565	high coverage WGS	D08452	Canis lupus familiaris	9615	australian shepherd	Female
SRR29476564	high coverage WGS	D08454	Canis lupus familiaris	9615	australian shepherd	Female
SRR29476563	high coverage WGS	D08456	Canis lupus familiaris	9615	australian shepherd	Female
SRR29476558	high coverage WGS	GSD0100 JE	Canis lupus familiaris	9615	german shepherd	Male
SRR29476561	high coverage WGS	GSD0101 JE	Canis lupus familiaris	9615	german shepherd	Male
SRR29476559	high coverage WGS	GSD0102 JE	Canis lupus familiaris	9615	german shepherd	Male
SRR29476556	high coverage WGS	GSD0103 JE	Canis lupus familiaris	9615	german shepherd	Female
SRR29476548	high coverage WGS	GSD0105 JE	Canis lupus familiaris	9615	german shepherd	Female
SRR23363275	high coverage WGS	kramer	Canis lupus familiaris	9615	great dane	Male
SRR29476550	high coverage WGS	LBKLN101 JE	Canis lupus familiaris	9615	white swiss shepherd dog	Male
SRR29476554	high coverage WGS	LBKLN44 JE	Canis lupus familiaris	9615	white swiss shepherd dog	Female
SRR23363273	high coverage WGS	mariah	Canis lupus familiaris	9615	great dane	Female
SRR29476549	high coverage WGS	SAINT0100 JE	Canis lupus familiaris	9615	saint bernard	Male
SRR29476560	high coverage WGS	TERV0100 JE	Canis lupus familiaris	9615	belgian tervuren	Male
SRR29476552	high coverage WGS	TERV0102 JE	Canis lupus familiaris	9615	belgian tervuren	Female
SRR23363272	high coverage WGS	vanna	Canis lupus familiaris	9615	great dane	Female

APPENDIX C

Supplemental information for Chapter 3

Supplemental Table 1. Protein sequences for DLA-DRB*1*015:01, -DRB*1*015:02, and -DRB*1*015:03 alleles. Amino acid differences are observed at position 78 and 90.

Allele	Protein Sequence	Position
DLA-DRB1*015:01	H F E M V K F E C H F T N G T E R V R L L V R D I Y N R E E H V R F D S D V G E Y R A V T E L G R P D A E Y W N G K E L L E Q R R A E V D T V C R H N Y G V I E S F T V Q R R	10 20 30 40 50 60 70 80 90
DLA-DRB1*015:02	H F E M V K F E C H F T N G T E R V R L L V R D I Y N R E E H V R F D S D V G E Y R A V T E L G R P D A E Y W N G K E L L E Q R R A E V D T V C R H N Y G V I E S F A V Q R R	10 20 30 40 50 60 70 80 90
DLA-DRB1*015:03	H F E M V K F E C H F T N G T E R V R L L V R D I Y N R E E H V R F D S D V G E Y R A V T E L G R P D A E Y W N G K E L L E Q R R A E V D T V C R H N Y G V I E S F T V Q R R	10 20 30 40 50 60 70 80 90

Supplemental Table 2. Runs of homozygosity identified in more than 50% of the Portuguese Water Dog cohort. Genes listed in blue are within region; in black, within 500kb of region.

Chr	Region	Length (bp)	Genes*
8	75,568,220 – 76,080,185	511,965	no genes (end of chromosome)
10	8,524,455 – 9,175,890	651,435	WIF1, LEMD3, HMG2, CLO31, LLP1, TM6IM4, IRAK3, HELB, GRIP1
13	7,012,053 – 7,592,907	580,854	ZFPM2, RPL7, OXR1, ABRA, SF3A3
13	8,157,682 – 9,977,322	1,819,640	OXR1, ABRA, SF3A3, ANGPT1, RSPO2, EIF3E, GAPDH, EMC2, TMEM74, RPL7, TRHR, NUDCD1, ENY2, PKHD1L1, EBAG9, SYBU
17	36,157,677 – 36,801,125	643,448	ACOXL, BCL2L11, ANAPC1, MERTK, TMEM87B, FBLN7, ZC3H8, VCL, TTL, POLR1B, CHCHD5, SLC20A1, CKAP2L, IL37, IL1A, IL1B
21	30,594,057 – 31,310,220	716,163	CCKBR, CAVIN3, TPK1, SMPD1, APBB1, HPX, TRIM3, ARFIP2, DNHD1, RRP8, ILK, TAF10, TPP1, DCHS, MRPL17, CCNB1, ZNF214, NLRP14, SYT9, OLFML1, PPFBP2
X	38,229,111 – 83,725,483	45,496,372	too many genes to list
X	118,526,619 – 119,925,826	1,399,207	AFF2, IDS, HSF3, PSMA2, MAGEA8, TMEM185A, MAMLD1, MTM1, MTMR1, CD99L2,

*genes colored blue are found inside the ROH (column 2); genes in black are within 500kb from the region.

Supplemental Table 3. Runs of homozygosity identified in more than 50% of the Standard Poodle cohort. Genes listed in blue are within region; in black, within 500kb of region.

Chr	Region	Length (bp)	Genes*
3	91,680,939 – 92,211,379	530,379	<i>LCORL</i> , <i>GN3414</i> , <i>ANAPC13</i> , <i>NCAPG</i> , <i>DCAF16</i> , <i>CTBP1</i> , <i>SPON2</i> , <i>TMED11</i> , <i>RNF212</i> , <i>FGFR1</i> , <i>IDUA</i> , <i>SLC26A1</i> , <i>DGKQ</i> , <i>TMEM175</i> , <i>GAK</i> , <i>CPLX1</i> , <i>PCGF3</i> , <i>SLC49A3</i> , <i>MYL5</i> , <i>MLR8</i> , <i>MYL2</i> , <i>ATP5ME</i> , <i>PDE8B</i> , <i>TMEM271</i> , <i>PIGG</i> , <i>USP6NL</i> (end of chromosome)
8	73,652,687 – 76,367,451	2,714,764	<i>MTA1</i> , <i>CRIP2</i> , <i>CRIP1</i> , <i>TEDC1</i> , <i>TMEM121</i> , <i>IGHV4</i> , <i>IGHF</i> , <i>HVM63</i> , <i>RPS24</i> , <i>IGHDM</i> , <i>IGHM</i> (end of chromosome)
10	9,157,623 – 9,752,153	594,530	<i>HMG42</i> , <i>CL031</i> , <i>LLPH</i> , <i>TMBIM4</i> , <i>IRAK3</i> , <i>HELB</i> , <i>GRIP1</i> , <i>CAND1</i>
11	10,551,175 – 11,296,040	744,865	<i>PRR16</i>
11	51,240,220 – 52,700,673	1,460,453	<i>AQP3</i> , <i>NOL6</i> , <i>UBE2R2</i> , <i>UBAP2</i> , <i>DCAF12</i> , <i>UBAP1</i> , <i>KIF24</i> , <i>NUDT2</i> , <i>MYORG</i> , <i>C11H80t124</i> , <i>DNAI1</i> , <i>FAM219A</i> , <i>ENHO</i> , <i>CNTFR</i> , <i>RPP25L</i> , <i>DCTN3</i> , <i>ARID3C</i> , <i>SIGMAR1</i> , <i>GALT</i> , <i>IL11RA</i> , <i>CCL27</i> , <i>CCL13</i> , <i>FAM205A</i> , <i>PHF24</i> , <i>DNAJB5</i> , <i>C11H80t131</i> , <i>VCP</i> , <i>FANCG</i> , <i>PICO</i> , <i>STOML2</i> , <i>FAM214B</i> , <i>UNC13B</i> , <i>RUSC2</i> , <i>FAM166B</i> , <i>TESK1</i> , <i>CD72</i> , <i>SIT1</i> , <i>CDC107</i> , <i>ARHGEF39</i> , <i>CAS</i> , <i>TPM2</i> , <i>TNLI</i> , <i>CREB3</i> , <i>GBA2</i> , <i>RGP1</i> , <i>MSMP</i> , <i>NPR2</i> , <i>SPAG8</i> , <i>HINT2</i> , <i>FAM221B</i> , <i>TMEM8B</i> , <i>HRC11</i> , <i>OR13E1</i> , <i>OR13I1</i> , <i>SPAAR</i> , <i>OR13C11C</i> , <i>OR13C11B</i> , <i>OR13C7F</i> , <i>OR13C7H</i> , <i>OR13C7G</i> , <i>OR13C7I</i> , <i>RECK</i> , <i>GLIPR2</i> , <i>CLTA</i> , <i>CCIN</i> , <i>GNE</i> , <i>RNF38</i>
13	7,331,634 – 9,124,580	1,792,946	<i>ZFPM2</i> , <i>RPL7</i> , <i>OXR1</i> , <i>ABRA</i> , <i>ANGPT1</i> , <i>RSPO2</i> , <i>EIF3E</i> , <i>SF3A3</i> , <i>OXR1</i> , <i>ABRA</i> , <i>GAPDH</i> , <i>EMC2</i> , <i>HSP90AB1</i>
16	1,658,514 – 2,240,964	582,450	<i>TRIM24</i> , <i>PDIA4</i> , <i>FAM183BP</i> , <i>EZH2</i> , <i>CUL1</i> , <i>CNTNAP2</i> , <i>NMT</i>
16	2,438,779 – 3,128,728	689,949	<i>CNTNAP2</i> , <i>NMT</i>
16	3,321,487 – 4,239,385	917,898	<i>CNTNAP2</i>
16	4,422,881 – 5,820,222	1,397,341	<i>CNTNAP2</i> , <i>TPK1</i> , <i>NOBOX</i> , <i>OLFR13</i> , <i>ARHGEF5</i> , <i>OR2A9B</i> , <i>OR2A9</i> , <i>OR2A7</i> , <i>OR2A58</i> , <i>ORA13</i> , <i>OR2A37</i> , <i>OR2A14</i> , <i>OR2A12</i> , <i>OR2A25</i> , <i>OR2A5</i> , <i>OR8B1</i> , <i>OR2Q1</i> , <i>OR2Q2</i> , <i>OR2F1D</i> , <i>OR2F1</i> , <i>OR2F2</i> , <i>TCAF1</i> , <i>TCAF2</i> , <i>EPHA1</i> , <i>ZYX</i> , <i>FAM131B</i> , <i>CLCN1</i> , <i>CASP2</i> , <i>KEL</i> , <i>TMEM139</i> , <i>GSTK1</i> , <i>PIP</i>
16	54,952,906 – 55,475,595	522,689	<i>WDR17</i> , <i>GPMB6A</i> , <i>SMAP</i> , <i>DEFB109B</i> , <i>CBD108</i> , <i>CBD107</i> , <i>DEFB105A</i> , <i>CBD104</i> , <i>SPAG11B</i> , <i>SPAG11E</i> , <i>CBD103</i> , <i>DEFB4A</i> , <i>ZNF705A</i> , <i>PSMA6</i> , <i>CXXC1</i> , <i>RALGDS</i> , <i>DEFB103A</i> , <i>CBD139</i> , <i>DEFB1</i> , <i>XKR5</i> , <i>AGPAT5</i> , <i>MCPH1</i> , <i>ANGPT2</i>
X	71,947,343 – 72,520,501	573,158	<i>RPS24</i> , <i>EEF1A1</i> , <i>TM2D1</i>
X	94,290,302 – 95,760,830	1,470,528	<i>GRIA3</i> , <i>THOC2</i> , <i>XMAP</i> , <i>GPHN</i> , <i>TENM1</i> , <i>STAG2</i> , <i>STAG1</i>

*genes colored blue are found inside the ROH (column 2); genes in black are within 500kb from the region.

Supplemental Table 4. Regions under selection in the Portuguese Water Dog that differ from 49 other dog breeds based on F_{ST} . Regions crossing the top 1% threshold of LOESS-smoothed values were considered as a region under selection

Chr	Region	Length (bp)	Genes*
4	23,574,989 – 26,054,375	2,479,376	SPOCK2, ASCC1, ANAPC16, DDIT4, DNAJB12, MICU1, MCU, OIT3, PLA2G12B, P4HA1, AMN1, NUDT13, ECD, FAM149B1, RPL23A, CFAP70, ANXA7, MSS51, PPP3CB, USP54, MYOZ1, SYNPO2L, RPS21, SEC24C, FUT11, CHCHD1, ZSWIM8, CAMK2G, NDST2, PLAU, VCL, AP3M1, ADK, KAT6B, DUPD1
5	5,444,068 – 8,036,182	2,592,114	ARHGAP32, KONJ5, FLI1, ETS1, KIRREL3
10	3,685,808 – 10,111,559	6,425,751	SLC16A7, TAF42, USP15, CCT6, STMP1, MON2, PPM1H, AVPR1A, RXYLT1, SRGAP1, XPOT, TBK1, QTS, RASSF3, GNS, WIF1 , LEMD3 , HMG2 , CL031 , LLPH , TMBIM4 , IRAK3 , HELB , GRIPI1 , CAND1
12	58,451,666 – 59,686,574	1,234,908	SIM1, ASCC3 , RPL3, GRIK2
13	59,856,073 – 60,594,321	738,248	AUGT2B31, UGT2A1, MYL9, SULT1B1, SULT1D1, SULT1E1, CSN1S1, CSN2
23	32,925,063 – 34,572,127	1,647,064	PPP2R3A, MSL2, PCCB, STAG1, SLC35G2, NCK1, IL20RB
24	28,326,104 – 29,866,851	1,540,747	MAFB, TOP1, PLCG1, ZHX3
33	6,311,985 – 7,121,321	809,336	DCBLD2, COL8A1, CMSS1, FILIP1L
35	2,119,124 – 2,991,614	872,490	EXOC2

* Genes bolded in red overlap with ROH region; genes bolded in blue overlap with unique coding variants.

Supplemental Table 5. Regions under selection in the Standard Poodle that differ from 49 other dog breeds based on F_{ST} . Regions crossing the top 1% threshold of LOESS-smoothed values were considered as a region under selection

Chr	Region	Length (bp)	Genes*
3	91,411,383 – 92,016,083	604,710	GM3414, ANAPC13, NCAPG, DCAF16, CTBP1, SPON2
6	59,011,272 – 60,955,203	1,943,931	ZNF326, LRRC8D, GBP4, GBP5, HADH, CCDC69, GBP1, KYAT3, GIF2B, SRSF10, PKN2
16	2,477,869 – 4,541,311	2,063,442	CNTNAP2 , CNTNAP5
16	7,114,456 – 11,092,638	3,978,182	SSBP1, WEE2, AGK, TMEM178B, MRPS33, BRAF, NDUFB2, DEVND2A, ADCX2, MKRN4P, MKRN1, RAB19, SLC37A3, KDM7A, PARP12, PARP11, TBXAS1, HIPK2, CLEC2L, KLKG2, LUC7L2, FMC1, UBN2, TTC26, ZC3HAV1, KIAA1549, TMEM213, ATP6V0A2, SVOPL, TRIM24, RPL23A, STARD5, RALGDS, CREB3L2, DGKI, PTN
17	6,956 – 372,247	365,291	FAM110C, SH3YL1, ACP1, ALKAL2
27	42,994,483 – 44,861,142	1,866,659	TFCP2, POU6F1, DAZAP2, SMAGP, BIN2, CELA1, GALNT6, SLC4A8, SCN8A, FIGNL1, ACVRL1, ANKRD33, ACVR1B, GRASP, ATG101, NR4A1, SMIM41, KRT80, KRT5, KRT15, KRT75, KRT6B, KRT6A, KRT17, KRT74, KRT72, KRT73, KRT2, KRT1, KRT79, KRT77, KRT76, KRT3, KRT75, KRT4, KRT18, KRT78, GLTBD2, KRT18, TNS2, SPRYD3, IGFBP6, SOAT2, CSAD, TPK1, ZNF740, RARG, ITGB7, MFSD5, ESPL1, PFND5, AAA3, SP7, SP1, AMHR2
32	40,121,966 – 40,218,640	96,674	TES

* Genes bolded in red overlap with ROH region; genes bolded in blue overlap with unique coding variants.

Supplemental Table 6. Unique coding based on minor allele frequencies in 34 Portuguese Water Dogs (MAF > 0.10) versus 2,692 dogs from breeds excluding poodle mixes, poodle varieties, and Portuguese Water Dogs (MAF < 0.00). Protein predictions were based on polyphen-2 scores and Fisher's exact two-tailed *P*-values from the low pass cohort are provided.

Chr	Position	Variant		Portuguese W. D. MAF	Gene	Mutation	Protein Accession	PhyloP Score	PolyPhen-2 Score	PolyPhen-2 Prediction	<i>P</i> <i>n</i> =101	neuter <i>P</i> <i>n</i> =63	
1	108,372,583	G	A	0.12	FAM83E	R231Q	XP_038384289	3.90	0.953	possibly damaging	0.52	0.54	
1	111,120,628	G	A	0.41	ZNF296	R231Q	XP_038384532	4.01	0.987	probably damaging	0.32	0.10	
2	47,964,886	G	A	0.30	IPO11	A92T	XP_038386631	8.44	0.008	benign	0.76	0.85	
4	20,183,532	G	A	0.34	MYPN	G919R	XP_038390031	8.38	1.000	probably damaging	0.04	0.10	protective
4	23,211,207	C	T	0.34	ZNF488	M64I	XP_038390195	4.58	0.893	possibly damaging	0.08	0.04	protective
4	35,846,321	G	A	0.38	C4H10	R84H	XP_038390492	6.20	0.988	probably damaging	0.66	0.37	
5	58,758,791	G	A	0.34	SMIM1	G56R	XP_038391475	5.96	1.000	probably damaging	0.23	0.26	
6	23,349,043	C	T	0.17	OTOA	R1087Q	XP_038395978	4.50	0.000	benign	0.85	0.81	
6	40,352,860	G	A	0.18	FBXL16	V284M	XP_038396821	8.38	1.000	probably damaging	0.58	0.33	
7	21,366,864	G	C	0.25	RASAL2	P15R	XP_038398328	3.78	0.988	probably damaging	0.74	1.00	
9	30,654,405	C	T	0.34	USP32	I281L	XP_038403727	5.63	0.024	benign	0.04	0.03	protective
9	36,654,405	A	T	0.16	TMEM100	S131N	XP_038403920	6.09	0.334	benign	0.25	0.25	
10	11,201,245	G	A	0.42	TTC7A	A191T	XP_038405895	4.62	0.972	probably damaging	0.25	0.60	
10	45,851,117	C	A	0.22	TMEM131	S1329Y	XP_038407014	8.58	0.916	possibly damaging	0.13	0.06	
10	50,211,859	G	A	0.36	NUP107	R31K	XP_038407146	8.35	0.007	benign	0.24	0.14	
11	2,724,309	C	T	0.23	ADAMTS2	R446W	XP_038407576	2.29	0.001	benign	0.14	0.82	
12	58,963,809	G	C	0.20	ASCC3	T1480R	XP_038410732	8.48	0.998	probably damaging	0.03	0.26	risk
15	15,202,595	G	A	0.15	ZSWIM5	G38R	XP_038414176	7.01	unknown	unknown	1.00	1.00	
15	38,308,748	G	C	0.14	IKBIP	T172S	XP_038414699	3.09	0.000	benign	0.69	1.00	
16	15,856,471	G	A	0.29	FASTK	P133S	NP_001028683	2.72	0.957	probably damaging	0.44	0.31	
17	21,112,928	C	A	0.21	AGBL5	S25R	XP_038416948	4.75	0.900	possibly damaging	0.86	0.14	
18	40,453,449	C	T	0.16	OR5W2B	A76V	NP_001375937	5.19	0.143	benign	0.18	0.66	
20	47,167,619	G	A	0.10	WIZ	D756N	XP_038422937	8.46	1.000	probably damaging	0.82	1.00	
21	16,135,599	G	A	0.14	PCF11	S140L	XP_038424389	8.47	0.982	probably damaging	0.54	1.00	
21	48,310,989	A	G	0.17	SLC5A12	F430L	XP_038425209	6.06	0.002	benign	0.14	0.03	protective
22	60,548,430	C	T	0.12	ATP11A	R473W	XP_038426008	6.36	1.000	probably damaging	1.00	1.00	
24	17,101,758	C	T	0.17	SLC23A2	T29M	NP_001103426	8.55	0.810	possibly damaging	1.00	0.47	
24	18,898,611	C	T	0.11	TMEM239	A79T	XP_038427713	6.73	0.997	probably damaging	0.12	0.14	
26	29,509,255	G	A	0.14	ARVCF	S76N	XP_038431807	6.68	0.001	benign	0.55	0.31	
35	5,600,465	G	C	0.17	PRPF4B	Q1010H	XP_038439980	2.62	0.722	possibly damaging	1.00	0.38	
36	30,906,801	G	T	0.21	COL3A1	D587Y	XP_038441003	8.48	unknown	unknown	0.12	0.19	
37	24,501,345	C	T	0.17	TNS1	R593Q	XP_038441623	2.21	0.029	benign	0.09	0.65	
38	17,508,139	C	A	0.30	HHIPL2	A360S	XP_038442118	4.99	0.179	benign	0.54	1.00	

Supplemental Table 7. Unique coding based on minor allele frequencies in 39 Standard Poodles (MAF > 0.10) versus 2,692 dogs from breeds excluding poodle mixes, poodle varieties, and Portuguese Water Dogs (MAF < 0.00). Protein predictions were based on polyphen-2 scores and Fisher's exact two-tailed *P*-values from the low pass cohort are provided.

Chr	Position	Variant		Standard Poodle MAF	Gene	Mutation	Protein ID	PhyloP Score	PolyPhen-2 Score	PolyPhen-2 Prediction	neuter <i>P</i> <i>n</i> =93	
4	14,746,238	C	G	0.16	ARID5B	P232R	XP_038389961	8.58	1.000	probably damaging	0.02	protective
4	19,041,136	G	A	0.11	LRRTM3	R194Q	XP_038390002	8.48	1.000	probably damaging	1.00	
5	35,010,559	C	T	0.24	MYH1	D347N	NP_001107189	7.86	0.054	benign	0.50	
6	41,313,121	G	A	0.13	CEPT1	T238M	XP_038396933	4.67	0.002	benign	0.49	
6	42,208,111	C	T	0.14	KCNC4	R582H	XP_038396965	8.45	0.981	probably damaging	0.28	
9	48,841,393	C	T	0.14	DIPK1B	V41M	XP_038404668	6.50	0.951	possibly damaging	0.67	
9	49,232,150	G	A	0.44	QSOX2	V315M	XP_038401982	8.07	1.000	probably damaging	0.13	
9	51,273,314	C	T	0.12	PPP1R26	T450I	XP_038404797	3.15	0.997	probably damaging	0.36	
11	74,086,918	C	A	0.12	CDK5RAP2	S111I	XP_038409167	5.66	0.997	probably damaging	0.11	
17	38,562,905	C	T	0.11	SMYD1	V176M	XP_038417442	6.73	0.999	probably damaging	0.006	risk
20	14,335,356	C	T	0.15	TRNT1	G419S	XP_038421736	8.50	0.217	benign	0.84	
20	42,463,748	G	A	0.23	TMIE	S65L	XP_038422576	6.36	0.065	benign	0.67	
20	44,436,096	G	A	0.21	TMEM161A	R44Q	XP_038422682	8.23	0.955	possibly damaging	0.59	
22	59,060,983	C	T	0.26	CARS2	D308N	XP_038425973	3.92	0.012	benign	0.48	
24	47,125,195	G	A	0.44	OSBPL2	V239M	XP_038428718	8.06	1.000	probably damaging	0.43	
28	1,902,150	T	C	0.24	PARG	R424G	XP_038434005	6.12	0.985	probably damaging	0.59	

Supplemental Table 8. Ensemble IDs, symbol, and name of genes identified from analyses in Portuguese Water Dogs.

Analysis	Ensembl Gene ID	Gene Symbol	Gene Name
DLA	ENSG00000179344	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1
DLA	ENSG00000196126	HLA-DRB1	major histocompatibility complex, class II, DR beta 1
DLA	ENSG00000196735	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1
FST	ENSG00000057019	DCBLD2	discoidin, CUB and LCCL domain containing 2
FST	ENSG00000061987	MON2	MON2 homolog, regulator of endosome-to-Golgi trafficking
FST	ENSG00000073711	PPP2R3A	protein phosphatase 2 regulatory subunit B"alpha
FST	ENSG00000100316	RPL3	ribosomal protein L3
FST	ENSG00000101335	MYL9	myosin light chain 9
FST	ENSG00000107742	SPOCK2	SPARC (osteonectin), cwcv and kazal like domains proteoglycan 2
FST	ENSG00000107745	MICU1	mitochondrial calcium uptake 1
FST	ENSG00000107758	PPP3CB	protein phosphatase 3 catalytic subunit beta
FST	ENSG00000109193	SULT1E1	sulfotransferase family 1E member 1
FST	ENSG00000111110	PPM1H	protein phosphatase, Mg ²⁺ /Mn ²⁺ dependent 1H
FST	ENSG00000111530	CAND1	cullin associated and neddylation dissociated 1
FST	ENSG00000112246	SIM1	SIM bHLH transcription factor 1
FST	ENSG00000112685	EXOC2	exocyst complex component 2
FST	ENSG00000114054	PCCB	propionyl-CoA carboxylase subunit beta
FST	ENSG00000118007	STAG1	stromal antigen 1
FST	ENSG00000118596	SLC16A7	solute carrier family 16 member 7
FST	ENSG00000118600	RXYLT1	ribitol xylosyltransferase 1
FST	ENSG00000120457	KCNJ5	potassium inwardly rectifying channel subfamily J member 5
FST	ENSG00000122861	PLAU	plasminogen activator, urokinase
FST	ENSG00000122882	ECD	ecdysoneless cell cycle regulator
FST	ENSG00000122884	P4HA1	prolyl 4-hydroxylase subunit alpha 1
FST	ENSG00000124181	PLCG1	phospholipase C gamma 1
FST	ENSG00000126545	CSN1S1	casein alpha s1
FST	ENSG00000134909	ARHGAP32	Rho GTPase activating protein 32
FST	ENSG00000134954	ETS1	ETS proto-oncogene 1, transcription factor
FST	ENSG00000135222	CSN2	casein beta
FST	ENSG00000135655	USP15	ubiquitin specific peptidase 15
FST	ENSG00000135677	GNS	glucosamine (N-acetyl)-6-sulfatase
FST	ENSG00000138279	ANXA7	annexin A7
FST	ENSG00000138286	FAM149B1	family with sequence similarity 149 member B1
FST	ENSG00000138303	ASCC1	activating signal cointegrator 1 complex subunit 1
FST	ENSG00000138308	PLA2G12B	phospholipase A2 group XIIb
FST	ENSG00000138315	OIT3	oncoprotein induced transcript 3
FST	ENSG00000144810	COL8A1	collagen type VIII alpha 1 chain
FST	ENSG00000146731	CCT6A	chaperonin containing TCP1 subunit 6A
FST	ENSG00000148660	CAMK2G	calcium/calmodulin dependent protein kinase II gamma
FST	ENSG00000148719	DNAJB12	DnaJ heat shock protein family (Hsp40) member B12
FST	ENSG00000149571	KIRREL3	kirre like nephrin family adhesion molecule 3
FST	ENSG00000151702	FLI1	Fli-1 proto-oncogene, ETS transcription factor
FST	ENSG00000151743	AMN1	antagonist of mitotic exit network 1 homolog
FST	ENSG00000153179	RASSF3	Ras association domain family member 3
FST	ENSG00000156026	MCU	mitochondrial calcium uniporter
FST	ENSG00000156042	CFAP70	cilia and flagella associated protein 70
FST	ENSG00000156110	ADK	adenosine kinase
FST	ENSG00000156650	KAT6B	lysine acetyltransferase 6B
FST	ENSG00000158092	NCK1	NCK adaptor protein 1
FST	ENSG00000164418	GRIK2	glutamate ionotropic receptor kainate type subunit 2
FST	ENSG00000166148	AVPR1A	arginine vasopressin receptor 1A
FST	ENSG00000166295	ANAPC16	anaphase promoting complex subunit 16
FST	ENSG00000166317	SYNPO2L	synaptopodin 2 like
FST	ENSG00000166321	NUDT13	nudix hydrolase 13
FST	ENSG00000166343	MSS51	MSS51 mitochondrial translational activator
FST	ENSG00000166348	USP54	ubiquitin specific peptidase 54

FST	ENSG00000166507	NDST2	N-deacetylase and N-sulfotransferase 2
FST	ENSG00000168209	DDIT4	DNA damage inducible transcript 4
FST	ENSG00000168386	FILIP1L	filamin A interacting protein 1 like
FST	ENSG00000168917	SLC35G2	solute carrier family 35 member G2
FST	ENSG00000171858	RPS21	ribosomal protein S21
FST	ENSG00000172586	CHCHD1	coiled-coil-helix-coiled-coil-helix domain containing 1
FST	ENSG00000173597	SULT1B1	sulfotransferase family 1B member 1
FST	ENSG00000173610	UGT2A1	UDP glucuronosyltransferase family 2 member A1 complex locus
FST	ENSG00000174306	ZHX3	zinc fingers and homeoboxes 3
FST	ENSG00000174564	IL20RB	interleukin 20 receptor subunit beta
FST	ENSG00000174579	MSL2	MSL complex subunit 2
FST	ENSG00000176986	SEC24C	SEC24 homolog C, COPII coat complex component
FST	ENSG00000177791	MYOZ1	myozenin 1
FST	ENSG00000183735	TBK1	TANK binding kinase 1
FST	ENSG00000184220	CMSS1	cms1 ribosomal small subunit homolog
FST	ENSG00000184575	XPOT	exportin for tRNA
FST	ENSG00000185009	AP3M1	adaptor related protein complex 3 subunit mu 1
FST	ENSG00000196935	SRGAP1	SLIT-ROBO Rho GTPase activating protein 1
FST	ENSG00000196968	FUT11	fucosyltransferase 11
FST	ENSG00000198242	RPL23A	ribosomal protein L23a
FST	ENSG00000198673	TAFA2	TAFA chemokine like family member 2
FST	ENSG00000198900	TOP1	DNA topoisomerase I
FST	ENSG00000204103	MAFB	MAF bZIP transcription factor B
FST	ENSG00000214655	ZSWIM8	zinc finger SWIM-type containing 8
FST	ENSG00000236959	SULT1D1P	sulfotransferase family 1D member 1, pseudogene
FST	ENSG00000243317	STMP1	short transmembrane mitochondrial protein 1
FST+ROH	ENSG00000035403	VCL	vinculin
FST+ROH	ENSG00000090376	IRAK3	interleukin 1 receptor associated kinase 3
FST+ROH	ENSG00000127311	HELB	DNA helicase B
FST+ROH	ENSG00000139233	LLPH	LLP homolog, long-term synaptic facilitation factor
FST+ROH	ENSG00000149948	HMGA2	high mobility group AT-hook 2
FST+ROH	ENSG00000155957	TMBIM4	transmembrane BAX inhibitor motif containing 4
FST+ROH	ENSG00000155974	GRIP1	glutamate receptor interacting protein 1
FST+ROH	ENSG00000156076	WIF1	WNT inhibitory factor 1
FST+ROH	ENSG00000174106	LEMD3	LEM domain containing 3
ROH	ENSG00000010404	IDS	iduronate 2-sulfatase
ROH	ENSG00000013619	MAMLD1	mastermind like domain containing 1
ROH	ENSG00000063601	MTMR1	myotubularin related protein 1
ROH	ENSG00000102181	CD99L2	CD99 molecule like 2
ROH	ENSG00000104408	EIF3E	eukaryotic translation initiation factor 3 subunit E
ROH	ENSG00000104412	EMC2	ER membrane protein complex subunit 2
ROH	ENSG00000110148	CCKBR	cholecystokinin B receptor
ROH	ENSG00000110169	HPX	hemopexin
ROH	ENSG00000110171	TRIM3	tripartite motif containing 3
ROH	ENSG00000111640	GAPDH	glyceraldehyde-3-phosphate dehydrogenase
ROH	ENSG00000114999	TTL	tubulin tyrosine ligase
ROH	ENSG00000115008	IL1A	interleukin 1 alpha
ROH	ENSG00000120526	NUDCD1	NudC domain containing 1
ROH	ENSG00000120533	ENY2	ENY2 transcription and export complex 2 subunit
ROH	ENSG00000125538	IL1B	interleukin 1 beta
ROH	ENSG00000125571	IL37	interleukin 37
ROH	ENSG00000125611	CHCHD5	coiled-coil-helix-coiled-coil-helix domain containing 5
ROH	ENSG00000125630	POLR1B	RNA polymerase I subunit B
ROH	ENSG00000132254	ARFIP2	ADP ribosylation factor interacting protein 2
ROH	ENSG00000132275	RRP8	ribosomal RNA processing 8
ROH	ENSG00000134057	CCNB1	cyclin B1
ROH	ENSG00000144136	SLC20A1	solute carrier family 20 member 1
ROH	ENSG00000144152	FBLN7	fibulin 7

ROH	ENSG00000144161	ZC3H8	zinc finger CCCH-type containing 8
ROH	ENSG00000147604	RPL7	ribosomal protein L7
ROH	ENSG00000147642	SYBU	syntabulin
ROH	ENSG00000147654	EBAG9	estrogen receptor binding site associated antigen 9
ROH	ENSG00000147655	RSPO2	R-spondin 2
ROH	ENSG00000149050	ZNF214	zinc finger protein 214
ROH	ENSG00000153093	ACOXL	acyl-CoA oxidase like
ROH	ENSG00000153094	BCL2L11	BCL2 like 11
ROH	ENSG00000153107	ANAPC1	anaphase promoting complex subunit 1
ROH	ENSG00000153208	MERTK	MER proto-oncogene, tyrosine kinase
ROH	ENSG00000153214	TMEM87B	transmembrane protein 87B
ROH	ENSG00000154188	ANGPT1	angiotensinogen 1
ROH	ENSG00000155966	AFF2	AF4/FMR2 family member 2
ROH	ENSG00000156009	MAGEA8	MAGE family member A8
ROH	ENSG00000158042	MRPL17	mitochondrial ribosomal protein L17
ROH	ENSG00000158077	NLRP14	NLR family pyrin domain containing 14
ROH	ENSG00000164830	OXR1	oxidation resistance 1
ROH	ENSG00000164841	TMEM74	transmembrane protein 74
ROH	ENSG00000166311	SMPD1	sphingomyelin phosphodiesterase 1
ROH	ENSG00000166313	APBB1	amyloid beta precursor protein binding family B member 1
ROH	ENSG00000166333	ILK	integrin linked kinase
ROH	ENSG00000166337	TAF10	TATA-box binding protein associated factor 10
ROH	ENSG00000166340	TPP1	tripeptidyl peptidase 1
ROH	ENSG00000166341	DCHS1	dachsous cadherin-related 1
ROH	ENSG00000166387	PPFIBP2	PPFIA binding protein 2
ROH	ENSG00000169607	CKAP2L	cytoskeleton associated protein 2 like
ROH	ENSG00000169946	ZFPM2	zinc finger protein, FOG family member 2
ROH	ENSG00000170743	SYT9	synaptotagmin 9
ROH	ENSG00000170955	CAVIN3	caveolae associated protein 3
ROH	ENSG00000171100	MTM1	myotubularin 1
ROH	ENSG00000174417	TRHR	thyrotropin releasing hormone receptor
ROH	ENSG00000174429	ABRA	actin binding Rho activating protein
ROH	ENSG00000179532	DNHD1	dynein heavy chain domain 1
ROH	ENSG00000183431	SF3A3	splicing factor 3a subunit 3
ROH	ENSG00000183801	OLFML1	olfactomedin like 1
ROH	ENSG00000196511	TPK1	thiamin pyrophosphokinase 1
ROH	ENSG00000205038	PKHD1L1	PKHD1 like 1
ROH	ENSG00000256646	H3BT36	novel PSMA2 and C7orf25 readthrough
ROH	ENSG00000269556	TMEM185A	transmembrane protein 185A
ROH	ENSG00000283697	HSFX3	heat shock transcription factor family, X-linked member 3
Unique	ENSG00000011451	WIZ	WIZ zinc finger
Unique	ENSG00000068650	ATP11A	ATPase phospholipid transporting 11A
Unique	ENSG00000068724	TTC7A	tetratricopeptide repeat domain 7A
Unique	ENSG00000075391	RASAL2	RAS protein activator like 2
Unique	ENSG00000075568	TMEM131	transmembrane protein 131
Unique	ENSG00000084693	AGBL5	AGBL carboxypeptidase 5
Unique	ENSG00000089057	SLC23A2	solute carrier family 23 member 2
Unique	ENSG00000105523	FAM83E	family with sequence similarity 83 member E
Unique	ENSG00000112739	PRPF4B	pre-mRNA processing factor 4B
Unique	ENSG00000127585	FBXL16	F-box and leucine rich repeat protein 16
Unique	ENSG00000138347	MYPN	myopalladin
Unique	ENSG00000164896	FASTK	Fas activated serine/threonine kinase
Unique	ENSG00000165494	PCF11	PCF11 cleavage and polyadenylation factor subunit
Unique	ENSG00000170684	ZNF296	zinc finger protein 296
Unique	ENSG00000198326	TMEM239	transmembrane protein 239
Unique	ENSG00000235169	SMIM1	small integral membrane protein 1 (Vel blood group)
Unique	ENSG00000265763	ZNF488	zinc finger protein 488
Unique+FST	ENSG00000112249	ASCC3	activating signal co-integrator 1 complex subunit 3

Supplemental Table 9. Ensemble IDs, symbol, and name of genes identified from analyses in Standard Poodles.

Analysis	Ensembl Gene ID	Gene Symbol	Gene Name
FST	ENSG00000111057	DEFB1	defensin beta 1
FST	ENSG00000139648	DEFB107A	defensin beta 107A
FST	ENSG00000167767	DEFB104A	defensin beta 104A
FST	ENSG00000167768	DEFB103A	defensin beta 103A
FST	ENSG00000170421	DEFB4A	defensin beta 4A
FST	ENSG00000170423	KRT80	keratin 80
FST	ENSG00000170454	KRT81	keratin 81
FST	ENSG00000170477	KRT75	keratin 75
FST	ENSG00000170484	KRT6B	keratin 6B
FST	ENSG00000170486	KRT6A	keratin 6A
FST	ENSG00000172867	KRT71	keratin 71
FST	ENSG00000185069	KRT73	keratin 73
FST	ENSG00000185479	KRT2	keratin 2
FST	ENSG00000185640	KRT1	keratin 1
FST	ENSG00000186049	KRT77	keratin 77
FST	ENSG00000186081	KRT76	keratin 76
FST	ENSG00000186442	KRT3	keratin 3
FST	ENSG00000189182	KRT78	keratin 78
FST	ENSG00000205420	KRT8	keratin 8
FST	ENSG00000205426	KRT18	keratin 18
FST	ENSG00000006459	KDM7A	lysine demethylase 7A
FST	ENSG00000006530	AGK	acylglycerol kinase
FST	ENSG00000035115	SH3YL1	SH3 and SYLF domain containing 1
FST	ENSG00000050438	SLC4A8	solute carrier family 4 member 8
FST	ENSG00000059377	TBXAS1	thromboxane A synthase 1
FST	ENSG00000059378	PARP12	poly(ADP-ribose) polymerase family member 12
FST	ENSG00000064393	HIPK2	homeodomain interacting protein kinase 2
FST	ENSG00000065243	PKN2	protein kinase N2
FST	ENSG00000090263	MRPS33	mitochondrial ribosomal protein S33
FST	ENSG00000090266	NDUFB2	NADH:ubiquinone oxidoreductase subunit B2
FST	ENSG00000094914	AAAS	aladin WD repeat nucleoporin
FST	ENSG00000105894	PTN	pleiotrophin
FST	ENSG00000105939	ZC3HAV1	zinc finger CCCH-type containing, antiviral 1
FST	ENSG00000105948	TTC26	tetratricopeptide repeat domain 26
FST	ENSG00000106028	SSBP1	single stranded DNA binding protein 1
FST	ENSG00000110934	BIN2	bridging integrator 2
FST	ENSG00000111077	TNS2	tensin 2
FST	ENSG00000111224	PARP11	poly(ADP-ribose) polymerase family member 11
FST	ENSG00000117228	GBP1	guanylate binding protein 1
FST	ENSG00000120820	GLT8D2	glycosyltransferase 8 domain containing 2
FST	ENSG00000122778	KIAA1549	KIAA1549
FST	ENSG00000123349	PFDN5	prefoldin subunit 5
FST	ENSG00000123358	NR4A1	nuclear receptor subfamily 4 group A member 1
FST	ENSG00000123395	ATG101	autophagy related 101
FST	ENSG00000132436	FIGNL1	fidgetin like 1
FST	ENSG00000133597	ADCK2	aarF domain containing kinase 2
FST	ENSG00000133606	MKRN1	makorin ring finger protein 1
FST	ENSG00000135269	TES	testin LIM domain protein
FST	ENSG00000135409	AMHR2	anti-Mullerian hormone receptor type 2
FST	ENSG00000135457	TFCP2	transcription factor CP2
FST	ENSG00000135476	ESPL1	extra spindle pole bodies like 1, separase
FST	ENSG00000135503	ACVR1B	activin A receptor type 1B
FST	ENSG00000137944	KYAT3	kynurenine aminotransferase 3
FST	ENSG00000137947	GTF2B	general transcription factor IIB
FST	ENSG00000138796	HADH	hydroxyacyl-CoA dehydrogenase
FST	ENSG00000139567	ACVRL1	activin A receptor like type 1
FST	ENSG00000139610	CELA1	chymotrypsin like elastase 1
FST	ENSG00000139626	ITGB7	integrin subunit beta 7
FST	ENSG00000139629	GALNT6	polypeptide N-acetylgalactosaminyltransferase 6
FST	ENSG00000139631	CSAD	cysteine sulfinic acid decarboxylase

FST	ENSG00000139651	ZNF740	zinc finger protein 740
FST	ENSG00000143727	ACP1	acid phosphatase 1
FST	ENSG00000146955	RAB19	RAB19, member RAS oncogene family
FST	ENSG00000146963	LUC7L2	LUC7 like 2, pre-mRNA splicing factor
FST	ENSG00000146966	DENND2A	DENN domain containing 2A
FST	ENSG00000154451	GBP5	guanylate binding protein 5
FST	ENSG00000155052	CNTNAP5	contactin associated protein family member 5
FST	ENSG00000157680	DGKI	diacylglycerol kinase iota
FST	ENSG00000157703	SVOPL	SVOP like
FST	ENSG00000157741	UBN2	ubinuclein 2
FST	ENSG00000157764	BRAF	B-Raf proto-oncogene, serine/threonine kinase
FST	ENSG00000157800	SLC37A3	solute carrier family 37 member 3
FST	ENSG00000161835	TAMALIN	trafficking regulator and scaffold protein tamalin
FST	ENSG00000162654	GBP4	guanylate binding protein 4
FST	ENSG00000162664	ZNF326	zinc finger protein 326
FST	ENSG00000164898	FMC1	formation of mitochondrial complex V assembly factor 1 homolog
FST	ENSG00000167612	ANKRD33	ankyrin repeat domain 33
FST	ENSG00000167778	SPRYD3	SPRY domain containing 3
FST	ENSG00000167779	IGFBP6	insulin like growth factor binding protein 6
FST	ENSG00000167780	SOAT2	sterol O-acyltransferase 2
FST	ENSG00000170374	SP7	Sp7 transcription factor
FST	ENSG00000170545	SMAGP	small cell adhesion glycoprotein
FST	ENSG00000171492	LRRC8D	leucine rich repeat containing 8 VRAC subunit D
FST	ENSG00000172345	STARD5	StAR related lipid transfer domain containing 5
FST	ENSG00000172819	RARG	retinoic acid receptor gamma
FST	ENSG00000182158	CREB3L2	cAMP responsive element binding protein 3 like 2
FST	ENSG00000182544	MFSD5	major facilitator superfamily domain containing 5
FST	ENSG00000183283	DAZAP2	DAZ associated protein 2
FST	ENSG00000184271	POU6F1	POU class 6 homeobox 1
FST	ENSG00000184731	FAM110C	family with sequence similarity 110 member C
FST	ENSG00000185344	ATP6V0A2	ATPase H+ transporting V0 subunit a2
FST	ENSG00000185591	SP1	Sp1 transcription factor
FST	ENSG00000188529	SRSF10	serine and arginine rich splicing factor 10
FST	ENSG00000188883	KLRG2	killer cell lectin like receptor G2
FST	ENSG00000189292	ALKAL2	ALK and LTK ligand 2
FST	ENSG00000196876	SCN8A	sodium voltage-gated channel alpha subunit 8
FST	ENSG00000198242	RPL23A	ribosomal protein L23a
FST	ENSG00000198624	CCDC69	coiled-coil domain containing 69
FST	ENSG00000214102	WEE2	WEE2 oocyte meiosis inhibiting kinase
FST	ENSG00000214128	TMEM213	transmembrane protein 213
FST	ENSG00000236279	CLEC2L	C-type lectin domain family 2 member L
FST	ENSG00000238222	MKRN4P	makorin ring finger protein 4, pseudogene
FST	ENSG00000261115	TMEM178B	transmembrane protein 178B
FST	ENSG00000284791	SMIM41	small integral membrane protein 41
ROH	ENSG00000174429	ABRA	actin binding Rho activating protein
ROH	ENSG00000155189	AGPAT5	1-acylglycerol-3-phosphate O-acyltransferase 5
ROH	ENSG00000154188	ANGPT1	angiopoietin 1
ROH	ENSG00000091879	ANGPT2	angiopoietin 2
ROH	ENSG00000165272	AQP3	aquaporin 3 (Gill blood group)
ROH	ENSG00000137135	ARHGEF39	Rho guanine nucleotide exchange factor 39
ROH	ENSG00000050327	ARHGEF5	Rho guanine nucleotide exchange factor 5
ROH	ENSG00000205143	ARID3C	AT-rich interaction domain 3C
ROH	ENSG00000169020	ATP5ME	ATP synthase membrane subunit e
ROH	ENSG00000110696	C11orf58	chromosome 11 open reading frame 58
ROH	ENSG00000174038	C9orf131	chromosome 9 open reading frame 131
ROH	ENSG00000107159	CA9	carbonic anhydrase 9
ROH	ENSG00000111530	CAND1	cullin associated and neddylation dissociated 1
ROH	ENSG00000106144	CASP2	caspase 2
ROH	ENSG00000159884	CCDC107	coiled-coil domain containing 107
ROH	ENSG00000185972	CCIN	calicin
ROH	ENSG00000172724	CCL19	C-C motif chemokine ligand 19
ROH	ENSG00000213927	CCL27	C-C motif chemokine ligand 27

ROH	ENSG00000137101	CD72	CD72 molecule
ROH	ENSG00000188037	CLCN1	chloride voltage-gated channel 1
ROH	ENSG00000122705	CLTA	clathrin light chain A
ROH	ENSG00000122756	CNTFR	ciliary neurotrophic factor receptor
ROH	ENSG00000168993	CPLX1	complexin 1
ROH	ENSG00000107175	CREB3	cAMP responsive element binding protein 3
ROH	ENSG00000213145	CRIP1	cysteine rich protein 1
ROH	ENSG00000182809	CRIP2	cysteine rich protein 2
ROH	ENSG00000055130	CUL1	cullin 1
ROH	ENSG00000154832	CXXC1	CXXC finger protein 1
ROH	ENSG00000198876	DCAF12	DDB1 and CUL4 associated factor 12
ROH	ENSG00000137100	DCTN3	dynactin subunit 3
ROH	ENSG00000164825	DEFB105A	defensin beta 105A
ROH	ENSG00000229907	DEFB108A	defensin beta 108A
ROH	ENSG00000206034	DEFB109B	defensin beta 109B
ROH	ENSG00000145214	DGKQ	diacylglycerol kinase theta
ROH	ENSG00000122735	DNAI1	dynein axonemal intermediate chain 1
ROH	ENSG00000137094	DNAJB5	DnaJ heat shock protein family (Hsp40) member B5
ROH	ENSG00000156508	EEF1A1	eukaryotic translation elongation factor 1 alpha 1
ROH	ENSG00000104408	EIF3E	eukaryotic translation initiation factor 3 subunit E
ROH	ENSG00000104412	EMC2	ER membrane protein complex subunit 2
ROH	ENSG00000168913	ENHO	energy homeostasis associated
ROH	ENSG00000146904	EPHA1	EPH receptor A1
ROH	ENSG00000106462	EZH2	enhancer of zeste 2 polycomb repressive complex 2 subunit
ROH	ENSG00000159784	FAM131B	family with sequence similarity 131 member B
ROH	ENSG00000215187	FAM166B	family with sequence similarity 166 member B
ROH	ENSG00000164556	FAM183BP	family with sequence similarity 183 member B, pseudogene
ROH	ENSG00000205108	FAM205A	family with sequence similarity 205 member A
ROH	ENSG00000005238	FAM214B	family with sequence similarity 214 member B
ROH	ENSG00000164970	FAM219A	family with sequence similarity 219 member A
ROH	ENSG00000204930	FAM221B	family with sequence similarity 221 member B
ROH	ENSG00000221829	FANCG	FA complementation group G
ROH	ENSG00000127418	FGFRL1	fibroblast growth factor receptor like 1
ROH	ENSG00000178950	GAK	cyclin G associated kinase
ROH	ENSG00000213930	GALT	galactose-1-phosphate uridylyltransferase
ROH	ENSG00000111640	GAPDH	glyceraldehyde-3-phosphate dehydrogenase
ROH	ENSG00000070610	GBA2	glucosylceramidase beta 2
ROH	ENSG00000122694	GLIPR2	GLI pathogenesis related 2
ROH	ENSG00000159921	GNE	glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase
ROH	ENSG00000171723	GPHN	gephyrin
ROH	ENSG00000150625	GPM6A	glycoprotein M6A
ROH	ENSG00000125675	GRIA3	glutamate ionotropic receptor AMPA type subunit 3
ROH	ENSG00000155974	GRIP1	glutamate receptor interacting protein 1
ROH	ENSG00000197448	GSTK1	glutathione S-transferase kappa 1
ROH	ENSG00000127311	HELB	DNA helicase B
ROH	ENSG00000137133	HINT2	histidine triad nucleotide binding protein 2
ROH	ENSG00000149948	HMGA2	high mobility group AT-hook 2
ROH	ENSG00000196196	HRCT1	histidine rich carboxyl terminus 1
ROH	ENSG00000096384	HSP90AB1	heat shock protein 90 alpha family class B member 1
ROH	ENSG00000127415	IDUA	alpha-L-iduronidase
ROH	ENSG00000211891	IGHE	immunoglobulin heavy constant epsilon
ROH	ENSG00000211899	IGHM	immunoglobulin heavy constant mu
ROH	ENSG00000137070	IL11RA	interleukin 11 receptor subunit alpha
ROH	ENSG00000090376	IRAK3	interleukin 1 receptor associated kinase 3
ROH	ENSG00000197993	KEL	Kell metallo-endopeptidase (Kell blood group)
ROH	ENSG00000186638	KIF24	kinesin family member 24
ROH	ENSG00000186562	KRT4	keratin 4
ROH	ENSG00000171711	KRT5	keratin 5
ROH	ENSG00000176797	KRT72	keratin 72
ROH	ENSG00000176782	KRT74	keratin 74
ROH	ENSG00000186572	KRT79	keratin 79
ROH	ENSG00000178177	LCORL	ligand dependent nuclear receptor corepressor like

ROH	ENSG00000139233	LLPH	LLP homolog, long-term synaptic facilitation factor
ROH	ENSG00000147316	MCPH1	microcephalin 1
ROH	ENSG00000215183	MSMP	microseminoprotein, prostate associated
ROH	ENSG00000182979	MTA1	metastasis associated 1
ROH	ENSG00000111245	MYL2	myosin light chain 2
ROH	ENSG00000215375	MYL5	myosin light chain 5
ROH	ENSG00000164976	MYORG	myogenesis regulating glycosidase (putative)
ROH	ENSG00000136448	NMT1	N-myristoyltransferase 1
ROH	ENSG00000106410	NOBOX	NOBOX oogenesis homeobox
ROH	ENSG00000165271	NOL6	nucleolar protein 6
ROH	ENSG00000159899	NPR2	natriuretic peptide receptor 2
ROH	ENSG00000164978	NUDT2	nudix hydrolase 2
ROH	ENSG00000243641	OR13C7	olfactory receptor family 13 subfamily C member 7 (gene/pseudogene)
ROH	ENSG00000236083	OR13E1P	olfactory receptor family 13 subfamily E member 1 pseudogene
ROH	ENSG00000168828	OR13J1	olfactory receptor family 13 subfamily J member 1
ROH	ENSG00000221858	OR2A12	olfactory receptor family 2 subfamily A member 12
ROH	ENSG00000221938	OR2A14	olfactory receptor family 2 subfamily A member 14
ROH	ENSG00000221933	OR2A25	olfactory receptor family 2 subfamily A member 25
ROH	ENSG00000221836	OR2A5	olfactory receptor family 2 subfamily A member 5
ROH	ENSG00000243896	OR2A7	olfactory receptor family 2 subfamily A member 7
ROH	ENSG00000228960	OR2A9P	olfactory receptor family 2 subfamily A member 9 pseudogene
ROH	ENSG00000213215	OR2F1	olfactory receptor family 2 subfamily F member 1
ROH	ENSG00000221910	OR2F2	olfactory receptor family 2 subfamily F member 2
ROH	ENSG00000273377	OR2Q1P	olfactory receptor family 2 subfamily Q member 1 pseudogene
ROH	ENSG00000221813	OR6B1	olfactory receptor family 6 subfamily B member 1
ROH	ENSG00000164830	OXR1	oxidation resistance 1
ROH	ENSG00000185619	PCGF3	polycomb group ring finger 3
ROH	ENSG00000133256	PDE6B	phosphodiesterase 6B
ROH	ENSG00000155660	PDIA4	protein disulfide isomerase family A member 4
ROH	ENSG00000122733	PHF24	PHD finger protein 24
ROH	ENSG00000174227	PIGG	phosphatidylinositol glycan anchor biosynthesis class G
ROH	ENSG00000165282	PIGO	phosphatidylinositol glycan anchor biosynthesis class O
ROH	ENSG00000159763	PIP	prolactin induced protein
ROH	ENSG00000184838	PRR16	proline rich 16
ROH	ENSG00000100902	PSMA6	proteasome 20S subunit alpha 6
ROH	ENSG00000122707	RECK	reversion inducing cysteine rich protein with kazal motifs
ROH	ENSG00000107185	RGP1	RGP1 homolog, RAB6A GEF complex partner 1
ROH	ENSG00000178222	RNF212	ring finger protein 212
ROH	ENSG00000137075	RNF38	ring finger protein 38
ROH	ENSG00000147604	RPL7	ribosomal protein L7
ROH	ENSG00000164967	RPP25L	ribonuclease P/MRP subunit p25 like
ROH	ENSG00000138326	RPS24	ribosomal protein S24
ROH	ENSG00000147655	RSPO2	R-spondin 2
ROH	ENSG00000198853	RUSC2	RUN and SH3 domain containing 2
ROH	ENSG00000183431	SF3A3	splicing factor 3a subunit 3
ROH	ENSG00000147955	SIGMAR1	sigma non-opioid intracellular receptor 1
ROH	ENSG00000137078	SIT1	signaling threshold regulating transmembrane adaptor 1
ROH	ENSG00000145217	SLC26A1	solute carrier family 26 member 1
ROH	ENSG00000169026	SLC49A3	solute carrier family 49 member 3
ROH	ENSG00000235387	SPAAR	small regulatory polypeptide of amino acid response
ROH	ENSG00000164871	SPAG11B	sperm associated antigen 11B
ROH	ENSG00000137098	SPAG8	sperm associated antigen 8
ROH	ENSG00000118007	STAG1	stromal antigen 1
ROH	ENSG00000101972	STAG2	stromal antigen 2
ROH	ENSG00000165283	STOML2	stomatin like 2
ROH	ENSG00000198420	TCAF1	TRPM8 channel associated factor 1
ROH	ENSG00000170379	TCAF2	TRPM8 channel associated factor 2
ROH	ENSG00000185347	TEDC1	tubulin epsilon and delta complex 1
ROH	ENSG0000009694	TENM1	teneurin transmembrane protein 1
ROH	ENSG00000107140	TESK1	testis associated actin remodelling kinase 1
ROH	ENSG00000125676	THOC2	THO complex 2
ROH	ENSG00000137076	TLN1	talín 1

ROH	ENSG00000162604	TM2D1	TM2 domain containing 1
ROH	ENSG00000155957	TMBIM4	transmembrane BAX inhibitor motif containing 4
ROH	ENSG00000215367	TMED11P	transmembrane p24 trafficking protein 11, pseudogene
ROH	ENSG00000184986	TMEM121	transmembrane protein 121
ROH	ENSG00000178826	TMEM139	transmembrane protein 139
ROH	ENSG00000127419	TMEM175	transmembrane protein 175
ROH	ENSG00000273238	TMEM271	transmembrane protein 271
ROH	ENSG00000137103	TMEM8B	transmembrane protein 8B
ROH	ENSG00000198467	TPM2	tropomyosin 2
ROH	ENSG00000165006	UBAP1	ubiquitin associated protein 1
ROH	ENSG00000137073	UBAP2	ubiquitin associated protein 2
ROH	ENSG00000107341	UBE2R2	ubiquitin conjugating enzyme E2 R2
ROH	ENSG00000198722	UNC13B	unc-13 homolog B
ROH	ENSG00000148429	USP6NL	USP6 N-terminal like
ROH	ENSG00000165280	VCP	valosin containing protein
ROH	ENSG00000150627	WDR17	WD repeat domain 17
ROH	ENSG00000101966	XIAP	X-linked inhibitor of apoptosis
ROH	ENSG00000275591	XKR5	XK related 5
ROH	ENSG00000169946	ZFPM2	zinc finger protein, FOG family member 2
ROH	ENSG00000196946	ZNF705A	zinc finger protein 705A
ROH	ENSG00000159840	ZYX	zyxin
ROH+FST	ENSG00000129055	ANAPC13	anaphase promoting complex subunit 13
ROH+FST	ENSG00000174469	CNTNAP2	contactin associated protein 2
ROH+FST	ENSG00000159692	CTBP1	C-terminal binding protein 1
ROH+FST	ENSG00000163257	DCAF16	DDB1 and CUL4 associated factor 16
ROH+FST	ENSG00000109805	NCAPG	non-SMC condensin I complex subunit G
ROH+FST	ENSG00000160271	RALGDS	ral guanine nucleotide dissociation stimulator
ROH+FST	ENSG00000159674	SPON2	spondin 2
ROH+FST	ENSG00000196511	TPK1	thiamin pyrophosphokinase 1
ROH+FST	ENSG00000122779	TRIM24	tripartite motif containing 24
Unique	ENSG00000150347	ARID5B	AT-rich interaction domain 5B
Unique	ENSG00000134905	CARS2	cysteinyI-tRNA synthetase 2, mitochondrial
Unique	ENSG00000136861	CDK5RAP2	CDK5 regulatory subunit associated protein 2
Unique	ENSG00000134255	CEPT1	choline/ethanolamine phosphotransferase 1
Unique	ENSG00000165716	DIPK1B	divergent protein kinase domain 1B
Unique	ENSG00000116396	KCNC4	potassium voltage-gated channel subfamily C member 4
Unique	ENSG00000198739	LRRTM3	leucine rich repeat transmembrane neuronal 3
Unique	ENSG00000109061	MYH1	myosin heavy chain 1
Unique	ENSG00000130703	OSBPL2	oxysterol binding protein like 2
Unique	ENSG00000227345	PARG	poly(ADP-ribose) glycohydrolase
Unique	ENSG00000196422	PPP1R26	protein phosphatase 1 regulatory subunit 26
Unique	ENSG00000165661	QSOX2	quiescin sulfhydryl oxidase 2
Unique	ENSG00000115593	SMYD1	SET and MYND domain containing 1
Unique	ENSG00000064545	TMEM161A	transmembrane protein 161A
Unique	ENSG00000181585	TMIE	transmembrane inner ear
Unique	ENSG00000072756	TRNT1	tRNA nucleotidyl transferase 1

Supplemental Table 10. Functional enrichment results from DAVID (<https://david.ncifcrf.gov/tools.jsp>) using all genes identified from analyses in Portuguese Water Dogs.

Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
UP_KW_PTM	KW-0597~Phosphoprotein	59.3023256	2.29E-04	1.25152512	0.00412064	0.00435806	0.00435806
GOTERM_MF_DIRECT	GO:0005515~protein binding	78.4883721	2.10E-05	1.22354006	0.00676616	0.00678908	0.00678908
UP_KW_LIGAND	KW-0106~Calcium	10.4651163	0.00312106	2.08326669	0.0606046	0.06242118	0.06242118
KEGG_PATHWAY	hsa04940:Type I diabetes mellitus	2.90697674	7.38E-04	11.9524067	0.14305283	0.08426012	0.08224433
KEGG_PATHWAY	hsa05332:Graft-versus-host disease	2.90697674	8.06E-04	11.6807611	0.15514328	0.08426012	0.08224433
KEGG_PATHWAY	hsa05323:Rheumatoid arthritis	3.48837209	0.00205003	6.56110836	0.34877306	0.1428191	0.13940238
KEGG_PATHWAY	hsa05321:Inflammatory bowel disease	2.90697674	0.00345159	7.90697674	0.51452643	0.15673373	0.15298412
KEGG_PATHWAY	hsa04659:Th17 cell differentiation	3.48837209	0.00374961	5.71059432	0.54394487	0.15673373	0.15298412
SMART	SM00125:IL1	1.74418605	0.00189844	44.0604396	0.18862614	0.20882787	0.20882787
KEGG_PATHWAY	hsa05140:Leishmaniasis	2.90697674	0.00632458	6.67472063	0.73447179	0.22003603	0.21477201
KEGG_PATHWAY	hsa05152:Tuberculosis	4.06976744	0.00759479	3.99741602	0.79676044	0.22003603	0.21477201
KEGG_PATHWAY	hsa04360:Axon guidance	4.06976744	0.00842243	3.91051567	0.82928216	0.22003603	0.21477201
UP_KW_PTM	KW-0007~Acetylation	26.1627907	0.02849077	1.32366599	0.40564659	0.27066231	0.27066231
KEGG_PATHWAY	hsa04658:Th1 and Th2 cell differentiation	2.90697674	0.01171834	5.58645096	0.91487165	0.2721258	0.26561561
KEGG_PATHWAY	hsa04640:Hematopoietic cell lineage	2.90697674	0.01501162	5.19144938	0.95762581	0.31374286	0.30623705
KEGG_PATHWAY	hsa05166:Human T-cell leukemia virus 1 infection	4.06976744	0.02017362	3.22661383	0.98586916	0.38329873	0.37412891
KEGG_PATHWAY	hsa05164:Influenza A	3.48837209	0.02475116	3.58572201	0.99468959	0.39930579	0.38975302
KEGG_PATHWAY	hsa05171:Coronavirus disease - COVID-19	4.06976744	0.02674776	3.02325581	0.99653972	0.39930579	0.38975302
KEGG_PATHWAY	hsa04014:Ras signaling pathway	4.06976744	0.02674776	3.02325581	0.99653972	0.39930579	0.38975302
UP_KW_CELLULAR_COMPO	KW-0491~MHC II	1.74418605	0.01256671	17.3632258	0.34947495	0.42726809	0.42726809
KEGG_PATHWAY	hsa04020:Calcium signaling pathway	4.06976744	0.03519117	2.8328145	0.99943995	0.46346333	0.45237569
KEGG_PATHWAY	hsa05310:Asthma	1.74418605	0.03548045	9.94748687	0.99947397	0.46346333	0.45237569
KEGG_PATHWAY	hsa04142:Lysosome	2.90697674	0.03804918	3.89358703	0.99969873	0.4677811	0.45659017
UP_KW_CELLULAR_COMPO	KW-0458~Lysosome	5.23255814	0.02869621	2.48046083	0.62840241	0.48783551	0.48783551
KEGG_PATHWAY	hsa04114:Oocyte meiosis	2.90697674	0.04461671	3.69750711	0.99992803	0.51804953	0.505656
KEGG_PATHWAY	hsa05330:Allograft rejection	1.74418605	0.05138557	8.11505508	0.9998372	0.56524129	0.55171877
KEGG_PATHWAY	hsa04218:Cellular senescence	2.90697674	0.06424517	3.2735891	0.99999906	0.67136201	0.65530072
OMIM_DISEASE	126200~Multiple sclerosis, susceptibility to, 1	1.1627907	0.01841612	106.210526	0.7653942	0.71822849	0.71822849
OMIM_DISEASE	212750~Celiac disease, susceptibility to	1.1627907	0.01841612	106.210526	0.7653942	0.71822849	0.71822849
KEGG_PATHWAY	hsa04672:Intestinal immune network for IgA production	1.74418605	0.08038747	6.29330802	0.99999998	0.76862608	0.75023789
KEGG_PATHWAY	hsa03010:Ribosome	2.90697674	0.08354585	2.98810168	0.99999999	0.76862608	0.75023789
KEGG_PATHWAY	hsa04066:HIF-1 signaling pathway	2.3255814	0.08731416	3.77213569	0.99999999	0.76862608	0.75023789
KEGG_PATHWAY	hsa05131:Shigellosis	3.48837209	0.0912871	2.47688428	1	0.76862608	0.75023789
KEGG_PATHWAY	hsa05320:Autoimmune thyroid disease	1.74418605	0.09194092	5.81834138	1	0.76862608	0.75023789
GOTERM_MF_DIRECT	GO:0032395~MHC class II receptor activity	1.74418605	0.00538728	26.6752649	0.8262604	0.77444875	0.77444875
GOTERM_MF_DIRECT	GO:0005149~interleukin-1 receptor binding	1.74418605	0.00717082	23.1185629	0.90287111	0.77444875	0.77444875
UP_KW_MOLECULAR_FUNC	KW-0666~Pyrogen	1.1627907	0.01708583	115.427184	0.63195187	0.78816353	0.78816353
UP_KW_MOLECULAR_FUNC	KW-0689~Ribosomal protein	3.48837209	0.02717805	3.51554877	0.79772841	0.78816353	0.78816353
UP_KW_MOLECULAR_FUNC	KW-0494~Milk protein	1.1627907	0.042174	46.1708738	0.91784689	0.81536405	0.81536405
GOTERM_CC_DIRECT	GO:0005829~cytosol	36.627907	0.00319456	1.37834627	0.59824226	0.82474847	0.82474847
GOTERM_CC_DIRECT	GO:0022626~cytosolic ribosome	2.90697674	0.00702618	6.57402745	0.86594838	0.82474847	0.82474847
GOTERM_CC_DIRECT	GO:0012507~ER to Golgi transport vesicle membrane	2.3255814	0.01195376	8.37909939	0.96752707	0.82474847	0.82474847
GOTERM_CC_DIRECT	GO:0005654~nucleoplasm	26.1627907	0.01727819	1.38005638	0.99303823	0.82474847	0.82474847
GOTERM_CC_DIRECT	GO:0042613~MHC class II protein complex	1.74418605	0.01841648	14.2605826	0.99499656	0.82474847	0.82474847
GOTERM_CC_DIRECT	GO:0030669~clathrin-coated endocytic vesicle membrane	2.3255814	0.01960212	6.96291358	0.99645453	0.82474847	0.82474847
GOTERM_CC_DIRECT	GO:0030666~endocytic vesicle membrane	2.3255814	0.02184966	6.6806333	0.99815669	0.82474847	0.82474847
GOTERM_CC_DIRECT	GO:0022625~cytosolic large ribosomal subunit	2.3255814	0.02055636	6.33803672	0.99927696	0.82474847	0.82474847
GOTERM_CC_DIRECT	GO:0030018~Z disc	2.90697674	0.02604469	4.44574518	0.99945847	0.82474847	0.82474847
GOTERM_CC_DIRECT	GO:0098553~luminal side of endoplasmic reticulum memb	1.74418605	0.03216974	10.5935757	0.9999103	0.91683753	0.91683753
UP_SEQ_FEATURE	CARBOHYD:N-acetyl-D-glucosamine	1.74418605	0.00282515	36.7303571	0.92423987	1	1
INTERPRO	IPR000975:IL-1_fam	1.74418605	0.0028815	36.3652941	0.83385291	1	1
GOTERM_BP_DIRECT	GO:0043029~T cell homeostasis	2.3255814	0.00377529	12.6662388	0.98013114	1	1
GOTERM_BP_DIRECT	GO:0002503~peptide antigen assembly with MHC class II p	1.74418605	0.00754141	22.5617378	0.99960732	1	1
GOTERM_BP_DIRECT	GO:0001701~in utero embryonic development	4.06976744	0.01020208	3.81133429	0.99997567	1	1
UP_SEQ_FEATURE	DOMAIN:Immunoglobulin C1-set	1.74418605	0.01023353	19.3317669	0.99991569	1	1
UP_SEQ_FEATURE	DOMAIN:GRAM	1.74418605	0.01131044	18.3651786	0.99996876	1	1
GOTERM_BP_DIRECT	GO:0043123~positive regulation of canonical NF-kappaB si	4.06976744	0.0115546	3.71059418	0.9999941	1	1
GOTERM_BP_DIRECT	GO:0002504~antigen processing and presentation of peptid	1.74418605	0.01168545	18.0493902	0.99999485	1	1
GOTERM_MF_DIRECT	GO:0005509~calcium ion binding	8.13953488	0.01243477	2.16930215	0.98264934	1	1
GOTERM_BP_DIRECT	GO:0009615~response to virus	2.90697674	0.01316445	5.4695122	0.99999891	1	1
UP_SEQ_FEATURE	DOMAIN:Sulfotransferase	1.74418605	0.01360616	16.6956169	0.99999625	1	1
INTERPRO	IPR014756:Ig_E-set	2.90697674	0.01408134	5.3636127	0.99985238	1	1
GOTERM_BP_DIRECT	GO:0045893~positive regulation of DNA-templated transcr	7.55813953	0.01543398	2.19394178	0.99999999	1	1
UP_SEQ_FEATURE	CROSSLINK:Glycyl lysine isopeptide (Lys-Gly) (interchain w	11.0465116	0.0159162	1.82165697	0.99999956	1	1
INTERPRO	IPR003502:IL-1_propep	1.1627907	0.01633533	121.217647	0.99996445	1	1
INTERPRO	IPR014745:MHC_II_a/b_N	1.74418605	0.016394	15.1522059	0.99996574	1	1
GOTERM_BP_DIRECT	GO:0002437~inflammatory response to antigenic stimulus	1.74418605	0.02078959	13.3699187	1	1	1
GOTERM_MF_DIRECT	GO:0023026~MHC class II protein complex binding	1.74418605	0.0224108	12.843646	0.99935334	1	1
INTERPRO	IPR031305:Casein_CS	1.1627907	0.02440324	80.8117647	0.99999979	1	1
GOTERM_BP_DIRECT	GO:0001660~fever generation	1.1627907	0.02457669	80.2195122	1	1	1

GOTERM_BP_DIRECT	GO:0006915~apoptotic process	6.39534884	0.025683	2.23207749	1	1	1
GOTERM_BP_DIRECT	GO:0043484~regulation of RNA splicing	2.3255814	0.02593332	6.25087108	1	1	1
GOTERM_BP_DIRECT	GO:0019886~antigen processing and presentation of exogen	1.74418605	0.02695763	11.6447679	1	1	1
GOTERM_BP_DIRECT	GO:0008015~blood circulation	1.74418605	0.02860138	11.2808689	1	1	1
GOTERM_BP_DIRECT	GO:0035774~positive regulation of insulin secretion involve	1.74418605	0.02860138	11.2808689	1	1	1
GOTERM_BP_DIRECT	GO:0051402~neuron apoptotic process	2.3255814	0.03048104	5.8697204	1	1	1
INTERPRO	IPR008996:IL1/FGF	1.74418605	0.03159497	10.6956747	1	1	1
UP_SEQ_FEATURE	CARBOHYD:N-acetyl-D-glucosamine 2	1.1627907	0.03208499	61.2172619	1	1	1
UP_SEQ_FEATURE	CARBOHYD:N-acetyl-D-glucosamine 1	1.1627907	0.03208499	61.2172619	1	1	1
INTERPRO	IPR020877:IL-1_CS	1.1627907	0.03240537	60.6088235	1	1	1
GOTERM_BP_DIRECT	GO:0050999~regulation of nitric-oxide synthase activity	1.1627907	0.03263477	60.1646341	1	1	1
INTERPRO	IPR000863:Sulfotransferase_dom	1.74418605	0.03510672	10.1014706	1	1	1
GOTERM_BP_DIRECT	GO:0097192~extrinsic apoptotic signaling pathway in abse	1.74418605	0.03556049	10.027439	1	1	1
GOTERM_BP_DIRECT	GO:0043407~negative regulation of MAP kinase activity	1.74418605	0.03739262	9.75642716	1	1	1
GOTERM_BP_DIRECT	GO:0070555~response to interleukin-1	1.74418605	0.03739262	9.75642716	1	1	1
GOTERM_BP_DIRECT	GO:0050778~positive regulation of immune response	1.74418605	0.03739262	9.75642716	1	1	1
UP_SEQ_FEATURE	REGION:Connecting peptide	1.74418605	0.03806094	9.66588346	1	1	1
INTERPRO	IPR036390:WH_DNA-bd_sf	3.48837209	0.03818579	3.23247059	1	1	1
GOTERM_BP_DIRECT	GO:0050870~positive regulation of T cell activation	1.74418605	0.03926025	9.49967908	1	1	1
GOTERM_BP_DIRECT	GO:0019221~cytokine-mediated signaling pathway	2.90697674	0.03980174	3.8815893	1	1	1
GOTERM_BP_DIRECT	GO:0030032~lamellipodium assembly	1.74418605	0.04116267	9.25609756	1	1	1
UP_SEQ_FEATURE	DOMAIN:Ig-like C1-type	1.74418605	0.04178993	9.18258929	1	1	1
GOTERM_CC_DIRECT	GO:0043202~lysosomal lumen	2.3255814	0.04465269	5.04455984	0.99999778	1	1
GOTERM_BP_DIRECT	GO:0045766~positive regulation of angiogenesis	2.90697674	0.0464074	3.69108185	1	1	1
GOTERM_BP_DIRECT	GO:0002181~cytoplasmic translation	2.3255814	0.04645364	4.96203168	1	1	1
GOTERM_CC_DIRECT	GO:0030658~transport vesicle membrane	1.74418605	0.04683759	8.62267786	0.99999885	1	1
UP_SEQ_FEATURE	REPEAT:TPR	2.3255814	0.04684468	4.94684945	1	1	1
GOTERM_BP_DIRECT	GO:0033092~positive regulation of immature T cell prolifera	1.1627907	0.04855298	40.1097561	1	1	1
GOTERM_CC_DIRECT	GO:0098686~hippocampal mossy fiber to CA3 synapse	1.74418605	0.04881483	8.42670791	0.99999936	1	1
GOTERM_BP_DIRECT	GO:0019882~antigen processing and presentation	1.74418605	0.05326971	8.02195122	1	1	1
GOTERM_BP_DIRECT	GO:0045214~sarcomere organization	1.74418605	0.05326971	8.02195122	1	1	1
BIOCARTA	h_il1rPathway:Signal transduction through IL1R	1.74418605	0.05526689	7.37727273	0.98999908	1	1
GOTERM_BP_DIRECT	GO:0031394~positive regulation of prostaglandin biosynthe	1.1627907	0.05641419	34.3797909	1	1	1
INTERPRO	IPR011162:MHC_I/II-like_Ag-recog	1.74418605	0.05684072	7.73729662	1	1	1
GOTERM_CC_DIRECT	GO:0030017~sarcomere	1.74418605	0.05701651	7.72448225	0.99999995	1	1
UP_SEQ_FEATURE	CROSSLNK:Glycyl lysine isopeptide (Lys-Gly) (interchain wi	2.90697674	0.06132654	3.36358582	1	1	1
GOTERM_CC_DIRECT	GO:0000139~Golgi membrane	6.39534884	0.06133881	1.91480123	0.99999999	1	1
GOTERM_BP_DIRECT	GO:0070527~platelet aggregation	1.74418605	0.06195237	7.36709806	1	1	1
GOTERM_CC_DIRECT	GO:1990246~uniplex complex	1.1627907	0.06257384	30.897929	0.99999999	1	1
GOTERM_CC_DIRECT	GO:0032588~trans-Golgi network membrane	2.3255814	0.06309932	4.374928	0.99999999	1	1
INTERPRO	IPR010625:CHCH	1.1627907	0.06376665	30.3044118	1	1	1
UP_SEQ_FEATURE	COMBIAS:Basic residues	6.39534884	0.06395611	1.89954832	1	1	1
GOTERM_BP_DIRECT	GO:0043536~positive regulation of blood vessel endothelial	1.74418605	0.06419366	7.2197561	1	1	1
UP_SEQ_FEATURE	REGION:Beta-2	1.1627907	0.07075579	27.207672	1	1	1
UP_SEQ_FEATURE	REGION:Beta-1	1.1627907	0.07075579	27.207672	1	1	1
GOTERM_BP_DIRECT	GO:1903140~regulation of establishment of endothelial bar	1.1627907	0.07194346	26.7398374	1	1	1
GOTERM_BP_DIRECT	GO:0006027~glycosaminoglycan catabolic process	1.1627907	0.07194346	26.7398374	1	1	1
GOTERM_BP_DIRECT	GO:0006470~protein dephosphorylation	2.3255814	0.07291372	4.11382114	1	1	1
GOTERM_CC_DIRECT	GO:0001673~male germ cell nucleus	1.74418605	0.07470473	6.62098478	1	1	1
GOTERM_MF_DIRECT	GO:0003723~RNA binding	11.0465116	0.07567438	1.50945943	1	1	1
GOTERM_BP_DIRECT	GO:0090266~regulation of mitotic cell cycle spindle assem	1.1627907	0.07961257	24.0658537	1	1	1
GOTERM_BP_DIRECT	GO:0016310~phosphorylation	5.81395349	0.07982937	1.90093631	1	1	1
GOTERM_CC_DIRECT	GO:1904813~ficolin-1-rich granule lumen	2.3255814	0.07999838	3.95493491	1	1	1
UP_KW_BIOLOGICAL_PROC	KW-0053~Apoptosis	5.23255814	0.08124944	1.97584124	0.99326001	1	1
UP_KW_DISEASE	KW-0656~Proto-oncogene	3.48837209	0.08265294	2.50994355	0.93104847	1	1
GOTERM_MF_DIRECT	GO:0003735~structural constituent of ribosome	2.90697674	0.08272355	3.02598991	1	1	1
GOTERM_BP_DIRECT	GO:0032508~DNA duplex unwinding	1.74418605	0.08551224	6.11843737	1	1	1
UP_SEQ_FEATURE	DOMAIN:PNT	1.1627907	0.08579055	22.2608225	1	1	1
GOTERM_BP_DIRECT	GO:0006412~translation	2.90697674	0.08595463	2.97844723	1	1	1
INTERPRO	IPR003118:Pointed_dom	1.1627907	0.08662258	22.0395722	1	1	1
GOTERM_BP_DIRECT	GO:1902237~positive regulation of endoplasmic reticulum s	1.1627907	0.08721869	21.8780488	1	1	1
GOTERM_BP_DIRECT	GO:0051561~positive regulation of mitochondrial calcium i	1.1627907	0.08721869	21.8780488	1	1	1
SMART	SM00251:SAM_PNT	1.1627907	0.08883219	21.3626374	0.99996404	1	1
GOTERM_MF_DIRECT	GO:0004062~aryl sulfotransferase activity	1.1627907	0.09065032	21.0168753	1	1	1
GOTERM_MF_DIRECT	GO:0052629~phosphatidylinositol-3,5-bisphosphate 3-ph	1.1627907	0.09065032	21.0168753	1	1	1
GOTERM_BP_DIRECT	GO:0006468~protein phosphorylation	4.06976744	0.0921271	2.24017255	1	1	1
GOTERM_BP_DIRECT	GO:0032308~positive regulation of prostaglandin secretion	1.1627907	0.09476234	20.054878	1	1	1
GOTERM_BP_DIRECT	GO:0030210~heparin biosynthetic process	1.1627907	0.09476234	20.054878	1	1	1
GOTERM_BP_DIRECT	GO:0030097~hemopoiesis	1.74418605	0.09815087	5.64043445	1	1	1
GOTERM_CC_DIRECT	GO:1990391~DNA repair complex	1.1627907	0.09968963	19.0141102	1	1	1

Supplemental Table 11. Clusters of pathway enrichment with scores >1.3 from DAVID (<https://david.ncifcrf.gov/tools.jsp>) using all genes from analyses in Portuguese Water Dogs.

Annotation Cluster 1		Enrichment Score: 1.3689769727066363					
Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
GOTERM_CC_DIRECT	GO:0022626~cytosolic ribosome	2.90697674	0.00702618	6.57402745	0.86594838	0.82474847	0.82474847
GOTERM_CC_DIRECT	GO:0022625~cytosolic large ribosomal subunit	2.3255814	0.02505636	6.33803672	0.99927696	0.82474847	0.82474847
KEGG_PATHWAY	hsa05171:Coronavirus disease - COVID-19	4.06976744	0.02674776	3.02325581	0.99653972	0.39930579	0.38975302
UP_KW_MOLECULAR_FUNC	KW-0689~Ribosomal protein	3.48837209	0.02717805	3.51554877	0.79772841	0.78816353	0.78816353
GOTERM_BP_DIRECT	GO:0002181~cytoplasmic translation	2.3255814	0.04645364	4.96203168	1	1	1
GOTERM_MF_DIRECT	GO:0003735~structural constituent of ribosome	2.90697674	0.08272355	3.02598991	1	1	1
KEGG_PATHWAY	hsa03010:Ribosome	2.90697674	0.08354585	2.98810168	0.99999999	0.76862608	0.75023789
GOTERM_BP_DIRECT	GO:0006412~translation	2.90697674	0.08595463	2.97844723	1	1	1
UP_KW_MOLECULAR_FUNC	KW-0687~Ribonucleoprotein	3.48837209	0.13527609	2.1916554	0.99978178	1	1

Annotation Cluster 2		Enrichment Score: 1.3209426024490913					
Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
UP_KW_CELLULAR_COMPO	KW-0458~Lysosome	5.23255814	0.02869621	2.48046083	0.62840241	0.48783551	0.48783551
KEGG_PATHWAY	hsa04142:Lysosome	2.90697674	0.03804918	3.89358703	0.99969873	0.4677811	0.45659017
GOTERM_CC_DIRECT	GO:0043202~lysosomal lumen	2.3255814	0.04465269	5.04455984	0.99999778	1	1
GOTERM_CC_DIRECT	GO:0005764~lysosome	3.48837209	0.10671172	2.3844061	1	1	1

Supplemental Table 12. Clusters of pathway enrichment with scores >1.3 from DAVID (<https://david.ncifcrf.gov/tools.jsp>) using genes identified from ROH in Portuguese Water Dogs.

Annotation Cluster 1		Enrichment Score: 1.7056852685530974					
Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
SMART	SM00125:IL1	4.16666667	3.77E-04	97.7926829	0.02087961	0.02109669	0.02109669
INTERPRO	IPR000975:IL-1_fam	4.16666667	5.17E-04	85.8625	0.13533994	0.14538123	0.14538123
GOTERM_MF_DIRECT	GO:0005149~interleukin-1 receptor binding	4.16666667	0.00124634	55.9536232	0.18801063	0.20813822	0.20813822
INTERPRO	IPR008996:IL1/FGF	4.16666667	0.00611461	25.2536765	0.82155584	0.6443478	0.6443478
GOTERM_BP_DIRECT	GO:0019221~cytokine-mediated signaling pathway	5.55555556	0.01706481	7.27520737	0.99995906	1	1
BIOCARTA	h_il1rPathway:Signal transduction through IL1R	4.16666667	0.01966711	12.2954545	0.49101915	0.66868186	0.66868186
GOTERM_BP_DIRECT	GO:0071222~cellular response to lipopolysaccharide	5.55555556	0.0293395	5.9039641	0.99999997	1	1
GOTERM_BP_DIRECT	GO:0010628~positive regulation of gene expression	6.94444444	0.10258009	2.76929554	1	1	1
GOTERM_MF_DIRECT	GO:0005125~cytokine activity	4.16666667	0.15051259	4.30412486	1	1	1
UP_KW_MOLECULAR_FUNC	KW-0202~Cytokine	4.16666667	0.17541335	3.87179766	0.99858083	1	1
GOTERM_BP_DIRECT	GO:0006955~immune response	5.55555556	0.25926656	2.23298444	1	1	1
KEGG_PATHWAY	hsa04060:Cytokine-cytokine receptor interaction	4.16666667	0.33128707	2.47203579	1	1	1

Supplemental Table 13. Functional enrichment results from DAVID (<https://david.ncifcrf.gov/tools.jsp>) using all genes identified from analyses in Standard Poodle.

Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
INTERPRO	IPR003054:Keratin_II	6.57439446	1.77E-27	49.5862462	1.39E-24	1.39E-24	1.39E-24
INTERPRO	IPR032444:Keratin_2_head	6.2283737	3.33E-26	50.5900164	2.61E-23	1.31E-23	1.30E-23
GOTERM_MF_DIRECT	GO:0030280~structural constituent of skin epidermis	6.57439446	1.33E-23	34.6015094	5.97E-21	5.97E-21	5.97E-21
UP_SEQ_FEATURE	SITE:Stutter	5.88235294	2.87E-21	35.55394	3.98E-18	3.98E-18	3.97E-18
UP_SEQ_FEATURE	REGION:Linker 12	6.92041522	9.28E-21	22.8747776	1.29E-17	4.29E-18	4.28E-18
UP_SEQ_FEATURE	REGION:Coil 2	6.92041522	9.28E-21	22.8747776	1.29E-17	4.29E-18	4.28E-18
UP_SEQ_FEATURE	REGION:Coil 1B	6.92041522	4.62E-20	21.217185	6.40E-17	1.45E-17	1.44E-17
UP_SEQ_FEATURE	REGION:Linker 1	6.92041522	6.26E-20	20.9140824	8.67E-17	1.45E-17	1.44E-17
UP_SEQ_FEATURE	REGION:Coil 1A	6.92041522	6.26E-20	20.9140824	8.67E-17	1.45E-17	1.44E-17
UP_SEQ_FEATURE	REGION:Head	6.92041522	1.51E-19	20.0545995	2.09E-16	2.99E-17	2.98E-17
SMART	SM01391:Filament	6.92041522	1.86E-19	19.2648649	2.62E-17	2.62E-17	2.62E-17
UP_SEQ_FEATURE	REGION:Tail	6.92041522	2.65E-19	19.5198102	3.68E-16	4.60E-17	4.58E-17
INTERPRO	IPR018039:IF_conserved	6.57439446	3.06E-19	21.6939827	2.40E-16	8.00E-17	7.98E-17
UP_SEQ_FEATURE	DOMAIN:IF_rod	6.92041522	3.49E-19	19.2629706	4.84E-16	5.38E-17	5.36E-17
INTERPRO	IPR039008:IF_rod_dom	6.92041522	4.73E-19	18.9803813	3.71E-16	9.29E-17	9.26E-17
UP_KW_CELLULAR_COMPC	KW-0403~intermediate filament	6.92041522	1.92E-18	17.5592092	6.91E-17	6.91E-17	6.91E-17
GOTERM_BP_DIRECT	GO:0045109~intermediate filament organization	6.57439446	4.00E-18	19.0812214	5.37E-15	5.37E-15	5.37E-15
GOTERM_BP_DIRECT	GO:0031424~keratinization	6.57439446	8.56E-18	18.3473282	1.15E-14	5.76E-15	5.76E-15
GOTERM_CC_DIRECT	GO:0045095~keratin filament	6.92041522	1.29E-16	14.3820147	3.85E-14	4.46E-14	4.44E-14
UP_KW_CELLULAR_COMPC	KW-0416~Keratin	6.92041522	2.95E-12	8.40256638	1.06E-10	5.30E-11	5.30E-11
UP_SEQ_FEATURE	DOMAIN:Keratin type II head	2.07612457	2.68E-09	73.1992883	3.71E-06	3.71E-07	3.70E-07
UP_KW_MOLECULAR_FUNC	KW-0211~Defensin	2.76816609	6.97E-06	11.0096076	5.02E-04	5.02E-04	5.02E-04
GOTERM_CC_DIRECT	GO:0005882~intermediate filament	3.80622837	1.30E-05	6.12587319	0.00451625	0.00226323	0.00225018
GOTERM_BP_DIRECT	GO:0042742~defense response to bacterium	3.80622837	5.81E-05	5.14612868	0.07513656	0.02603564	0.02603564
UP_KW_PTM	KW-0488~Methylation	11.4186851	1.65E-04	2.02443182	0.00346729	0.00363841	0.00363841
UP_KW_MOLECULAR_FUNC	KW-0929~Antimicrobial	3.11418685	1.72E-04	5.7082422	0.01230829	0.0061918	0.0061918
INTERPRO	IPR001855:Defensin_beta-typ	1.38408304	1.98E-04	32.4775414	0.14416285	0.03113195	0.03105263
GOTERM_CC_DIRECT	GO:0016363~nuclear matrix	3.11418685	3.83E-04	5.12774141	0.12446836	0.03422781	0.03403053
GOTERM_CC_DIRECT	GO:0005829~cytosol	35.6401384	3.95E-04	1.35049384	0.12797592	0.03422781	0.03403053
UP_KW_MOLECULAR_FUNC	KW-0044~Antibiotic	2.76816609	4.24E-04	5.83509202	0.03008675	0.01018072	0.01018072
GOTERM_MF_DIRECT	GO:0031731~CCR6 chemokine receptor binding	1.38408304	0.00124122	18.2113208	0.42673667	0.23711984	0.23711984
GOTERM_MF_DIRECT	GO:0005515~protein binding	68.5121107	0.00158786	1.13088961	0.50930125	0.23711984	0.23711984
UP_KW_DOMAIN	KW-0175~Coiled coil	20.0692042	0.00211319	1.45382954	0.04547298	0.04649013	0.04649013
UP_KW_MOLECULAR_FUNC	KW-0808~Transferase	15.2249135	0.00228525	1.54889026	0.15187423	0.04113451	0.04113451
UP_SEQ_FEATURE	REGION:GTPase domain (Globular)	1.03806228	0.0037065	31.3711235	0.9941817	0.46701852	0.46657071
INTERPRO	IPR037684:GBP_C	1.03806228	0.00371902	31.3176292	0.94632835	0.48657135	0.48533168
GOTERM_BP_DIRECT	GO:0050918~positive chemotaxis	1.73010381	0.00427347	7.53206107	0.9968493	1	1
GOTERM_BP_DIRECT	GO:0051402~neuron apoptotic process	2.07612457	0.0046449	5.5112642	0.99809247	1	1
GOTERM_CC_DIRECT	GO:0070062~extracellular exosome	15.916955	0.00465528	1.50890137	0.80193357	0.30246802	0.30072469
GOTERM_CC_DIRECT	GO:0045111~intermediate filament cytoskeleton	1.73010381	0.00522999	7.12186307	0.83790464	0.30246802	0.30072469
INTERPRO	IPR003191:Guanylate-bd/ATL_C	1.03806228	0.00626157	24.358156	0.99277917	0.67474851	0.67302941
GOTERM_BP_DIRECT	GO:0060326~cell chemotaxis	2.07612457	0.00687296	5.02137405	0.99990636	1	1
GOTERM_MF_DIRECT	GO:0003714~transcription corepressor activity	3.11418685	0.00737502	3.1980856	0.96371137	0.82600173	0.82600173
INTERPRO	IPR036543:Guanylate-bd_C_sf	1.03806228	0.00775686	21.9223404	0.99778582	0.67474851	0.67302941
GOTERM_BP_DIRECT	GO:0046834~lipid phosphorylation	1.03806228	0.00885855	20.5419847	0.99999365	1	1
UP_SEQ_FEATURE	DOMAIN:WWE	1.03806228	0.00936474	19.9634423	0.99999783	0.998425	0.99554354
UP_SEQ_FEATURE	DOMAIN:GB1/RHD3-type G	1.03806228	0.00936474	19.9634423	0.99999783	0.998425	0.99554354
INTERPRO	IPR015894:Guanylate-bd_N	1.03806228	0.00939578	19.9294004	0.99939517	0.67474851	0.67302941
INTERPRO	IPR030386:G_GB1_RHD3_dom	1.03806228	0.00939578	19.9294004	0.99939517	0.67474851	0.67302941
GOTERM_MF_DIRECT	GO:0004143~ATP-dependent diacylglycerol kinase activity	1.03806228	0.00944664	19.8668954	0.98576729	0.84641916	0.84641916
UP_SEQ_FEATURE	DOMAIN:Fibrinogen C-terminal	1.38408304	0.01093671	8.61168097	0.99999976	1	0.99783394
INTERPRO	IPR002181:Fibrinogen_a/b/g_C_dom	1.38408304	0.0109877	8.59699625	0.99982887	0.67474851	0.67302941
INTERPRO	IPR036056:Fibrinogen-like_C	1.38408304	0.0109877	8.59699625	0.99982887	0.67474851	0.67302941
INTERPRO	IPR000333:TGFbeta_receptor	1.03806228	0.01117418	18.268617	0.99985242	0.67474851	0.67302941
GOTERM_BP_DIRECT	GO:0071346~cellular response to type II interferon	2.07612457	0.01193257	4.38760839	0.9999999	1	1
SMART	SM00109:C1	1.73010381	0.01279231	5.47297297	0.8372194	0.72056562	0.72056562
INTERPRO	IPR004170:WWE-dom	1.03806228	0.01308797	16.8633388	0.99996775	0.68351112	0.68176969
INTERPRO	IPR037197:WWE_dom_sf	1.03806228	0.01308797	16.8633388	0.99996775	0.68351112	0.68176969
INTERPRO	IPR002219:PE/DAG-bd	1.73010381	0.01393144	5.37312265	0.99998352	0.68351112	0.68176969
GOTERM_MF_DIRECT	GO:0004672~protein kinase activity	3.46020761	0.01435751	2.62979361	0.99846433	1	1
GOTERM_BP_DIRECT	GO:0061844~antimicrobial humoral immune response medi	2.07612457	0.01494936	4.14608866	1	1	1
SMART	SM00046:DAGKc	1.03806228	0.01533118	15.480695	0.88678186	0.72056562	0.72056562
KEGG_PATHWAY	hsa04621:NOD-like receptor signaling pathway	2.76816609	0.01555566	3.04211296	0.97015845	1	1
UP_SEQ_FEATURE	DOMAIN:DAGKc	1.03806228	0.0172497	14.6398577	1	1	0.99783394
UP_SEQ_FEATURE	ZN_FING:C3H1-type 4	1.03806228	0.0172497	14.6398577	1	1	0.99783394
INTERPRO	IPR001206:Diacylglycerol_kinase_cat_dom	1.03806228	0.01730581	14.6148936	0.99999888	0.79912121	0.79708523
GOTERM_BP_DIRECT	GO:0045766~positive regulation of angiogenesis	2.42214533	0.02162848	3.23462745	1	1	1
UP_SEQ_FEATURE	DOMAIN:PARP catalytic	1.03806228	0.02194761	12.9175215	1	1	0.99783394
INTERPRO	IPR012317:Poly(ADP-ribose)pol_cat_dom	1.03806228	0.02201833	12.8954944	0.99999997	0.86421962	0.86201778

INTERPRO	IPR017438:ATP-NAD_kinase_N	1.03806228	0.02201833	12.8954944	0.99999997	0.86421962	0.86201778
INTERPRO	IPR016064:NAD/diacylglycerol_kinase_sf	1.03806228	0.02201833	12.8954944	0.99999997	0.86421962	0.86201778
GOTERM_MF_DIRECT	GO:0042056~chemoattractant activity	1.38408304	0.02217771	6.62229846	0.9999567	1	1
GOTERM_CC_DIRECT	GO:0031410~cytoplasmic vesicle	3.46020761	0.02240255	2.43642684	0.99961493	1	0.99710983
GOTERM_CC_DIRECT	GO:0005856~cytoskeleton	4.84429066	0.02375533	2.00182097	0.99976184	1	0.99710983
GOTERM_MF_DIRECT	GO:1990404~NAD+-protein ADP-ribosyltransferase activity	1.03806228	0.02467986	12.1408805	0.99998626	1	1
UP_KW_LIGAND	KW-0547~Nucleotide-binding	12.8027682	0.02580718	1.36795636	0.46607752	0.61937227	0.61937227
GOTERM_BP_DIRECT	GO:1990114~RNA polymerase II core complex assembly	0.69204152	0.02627755	75.3206107	1	1	1
UP_SEQ_FEATURE	SITE:Breakpoint for translocation to form KIAA1549-BRAF fus	0.69204152	0.02704078	73.1992883	1	1	0.99783394
UP_SEQ_FEATURE	DOMAIN:Peptidase M60	0.69204152	0.02704078	73.1992883	1	1	0.99783394
GOTERM_CC_DIRECT	GO:1904813~ficolin-1-rich granule lumen	2.07612457	0.02707125	3.55523404	0.99992687	1	0.99710983
INTERPRO	IPR042279:Pep_M60_3	0.69204152	0.02708699	73.0744681	1	0.9244909	0.92213551
INTERPRO	IPR035423:M60-like_N	0.69204152	0.02708699	73.0744681	1	0.9244909	0.92213551
INTERPRO	IPR031161:Peptidase_M60_dom	0.69204152	0.02708699	73.0744681	1	0.9244909	0.92213551
SMART	SM01276:M60-like	0.69204152	0.02730944	72.2432432	0.97984267	0.96265771	0.96265771
GOTERM_MF_DIRECT	GO:0046332~SMAD binding	1.38408304	0.02783857	6.07044025	0.99999679	1	1
KEGG_PATHWAY	hsa05016:Huntington disease	3.46020761	0.02787817	2.31092986	0.99822403	1	1
GOTERM_CC_DIRECT	GO:0016020~membrane	28.7197232	0.03015242	1.2178273	0.99997567	1	0.99710983
GOTERM_BP_DIRECT	GO:0050830~defense response to Gram-positive bacterium	2.07612457	0.03024116	3.44979896	1	1	1
UP_SEQ_FEATURE	ZN_FING:PHD-type	1.38408304	0.03058009	5.85594306	1	1	0.99783394
GOTERM_BP_DIRECT	GO:0051496~positive regulation of stress fiber assembly	1.38408304	0.03142402	5.79389313	1	1	1
GOTERM_CC_DIRECT	GO:0098688~parallel fiber to Purkinje cell synapse	1.03806228	0.03200877	10.5810537	0.99998749	1	0.99710983
GOTERM_MF_DIRECT	GO:0042802~identical protein binding	11.7647059	0.03353373	1.42587198	0.99999977	1	1
GOTERM_BP_DIRECT	GO:0045104~intermediate filament cytoskeleton organization	1.03806228	0.03673132	9.82442748	1	1	1
GOTERM_BP_DIRECT	GO:0050829~defense response to Gram-negative bacterium	1.73010381	0.037391	3.96424267	1	1	1
GOTERM_CC_DIRECT	GO:0005886~plasma membrane	31.1418685	0.03759625	1.1920715	0.99999832	1	0.99710983
UP_SEQ_FEATURE	ZN_FING:C3H1-type 3	1.03806228	0.03871197	9.54773325	1	1	0.99783394
GOTERM_BP_DIRECT	GO:0160075~non-canonical inflammasome complex assembly	0.69204152	0.03915721	50.2137405	1	1	1
GOTERM_BP_DIRECT	GO:0002408~myeloid dendritic cell chemotaxis	0.69204152	0.03915721	50.2137405	1	1	1
GOTERM_BP_DIRECT	GO:0060491~regulation of cell projection assembly	0.69204152	0.03915721	50.2137405	1	1	1
UP_SEQ_FEATURE	REGION:Necessary for interaction with PNN	0.69204152	0.04028669	48.7995255	1	1	0.99783394
UP_SEQ_FEATURE	DOMAIN:STAG	0.69204152	0.04028669	48.7995255	1	1	0.99783394
GOTERM_BP_DIRECT	GO:0035264~multicellular organism growth	1.73010381	0.0411675	3.8428883	1	1	1
GOTERM_BP_DIRECT	GO:0071363~cellular response to growth factor stimulus	1.38408304	0.04143863	5.19452487	1	1	1
INTERPRO	IPR000719:Prot_kinase_dom	4.4982699	0.0417976	1.90374366	1	1	0.99872449
GOTERM_BP_DIRECT	GO:0006986~response to unfolded protein	1.38408304	0.043246	5.10648208	1	1	1
UP_SEQ_FEATURE	DOMAIN:Protein kinase	4.4982699	0.04435189	1.88807688	1	1	0.99783394
UP_SEQ_FEATURE	DOMAIN:Phorbol-ester/DAG-type	1.38408304	0.04451126	5.04822678	1	1	0.99783394
GOTERM_BP_DIRECT	GO:0031640~killing of cells of another organism	1.38408304	0.04509226	5.02137405	1	1	1
GOTERM_MF_DIRECT	GO:0003950~NAD+ ADP-ribosyltransferase activity	1.03806228	0.04547048	8.74143396	1	1	1
GOTERM_CC_DIRECT	GO:0016604~nuclear body	3.46020761	0.04685962	2.12837287	0.99999994	1	0.99710983
GOTERM_CC_DIRECT	GO:0001533~cornified envelope	1.38408304	0.04703667	4.93782506	0.99999995	1	0.99710983
GOTERM_BP_DIRECT	GO:0043524~negative regulation of neuron apoptotic process	2.07612457	0.05050636	2.99287195	1	1	1
GOTERM_MF_DIRECT	GO:0019900~kinase binding	1.73010381	0.05144155	3.57084721	1	1	1
GOTERM_BP_DIRECT	GO:0048014~Tie signaling pathway	0.69204152	0.05186716	37.6603053	1	1	1
GOTERM_BP_DIRECT	GO:1900194~negative regulation of oocyte maturation	0.69204152	0.05186716	37.6603053	1	1	1
GOTERM_BP_DIRECT	GO:0072012~glomerulus vasculature development	0.69204152	0.05186716	37.6603053	1	1	1
KEGG_PATHWAY	hsa01100:Metabolic pathways	10.3806228	0.05197301	1.38122842	0.99999358	1	1
UP_KW_MOLECULAR_FUNC	KW-0418~Kinase	5.88235294	0.05215672	1.64232723	0.97886362	0.7054113	0.7054113
GOTERM_CC_DIRECT	GO:0106139~symbiont cell surface	0.69204152	0.05274084	37.0336879	0.99999999	1	0.99710983
GOTERM_BP_DIRECT	GO:0051289~protein homotetramerization	1.38408304	0.05286061	4.70753817	1	1	1
GOTERM_CC_DIRECT	GO:0048471~perinuclear region of cytoplasm	5.88235294	0.05305316	1.65459315	0.99999999	1	0.99710983
INTERPRO	IPR013721:STAG	0.69204152	0.05344282	36.537234	1	1	0.99872449
INTERPRO	IPR012678:Ribosomal_ul23/eL15/eS24_sf	0.69204152	0.05344282	36.537234	1	1	0.99872449
GOTERM_CC_DIRECT	GO:0005615~extracellular space	12.8027682	0.05346204	1.34800438	0.99999999	1	0.99710983
GOTERM_MF_DIRECT	GO:0004713~protein tyrosine kinase activity	1.73010381	0.05452245	3.50217707	1	1	1
INTERPRO	IPR046349:C1-like_sf	1.38408304	0.05478637	4.63964877	1	1	0.99872449
KEGG_PATHWAY	hsa04814:Motor proteins	2.42214533	0.05487594	2.55375346	0.99999677	1	1
UP_KW_DISEASE	KW-0038~Ectodermal dysplasia	1.38408304	0.05767655	4.46846011	0.93097604	1	1
UP_KW_MOLECULAR_FUNC	KW-0514~Muscle protein	1.38408304	0.05878427	4.48853233	0.98724676	0.7054113	0.7054113
KEGG_PATHWAY	hsa00561:Glycerolipid metabolism	1.38408304	0.06043998	4.42276423	0.99999914	1	1
KEGG_PATHWAY	hsa04927:Cortisol synthesis and secretion	1.38408304	0.06043998	4.42276423	0.99999914	1	1
KEGG_PATHWAY	hsa04510:Focal adhesion	2.42214533	0.06169451	2.47827306	0.99999936	1	1
GOTERM_MF_DIRECT	GO:0030246~carbohydrate binding	2.42214533	0.06204998	2.49959304	1	1	1
UP_KW_CELLULAR_COMPO	KW-0206~Cytoskeleton	10.0346021	0.06249393	1.3965869	0.90203584	0.74992714	0.74992714
GOTERM_BP_DIRECT	GO:0007507~heart development	2.42214533	0.06307253	2.4870013	1	1	1
GOTERM_BP_DIRECT	GO:0140639~positive regulation of pyroptotic inflammatory	0.69204152	0.06440962	30.1282443	1	1	1
GOTERM_MF_DIRECT	GO:0005200~structural constituent of cytoskeleton	1.73010381	0.06607233	3.28131905	1	1	1
INTERPRO	IPR003530:Hematopoietin_rcpt_L_F3_CS	0.69204152	0.06635272	29.2297872	1	1	0.99872449
GOTERM_MF_DIRECT	GO:0016361~actin receptor activity, type I	0.69204152	0.06654141	29.1381132	1	1	1

KEGG_PATHWAY	hsa04110:Cell cycle	2.07612457	0.06731609	2.72923742	0.99999983	1	1
GOTERM_CC_DIRECT	GO:0098978~glutamatergic synapse	3.80622837	0.06784754	1.88597485	1	1	0.99710983
GOTERM_BP_DIRECT	GO:0006654~phosphatidic acid biosynthetic process	1.03806228	0.07037949	6.84732824	1	1	1
GOTERM_CC_DIRECT	GO:0098793~presynapse	2.07612457	0.07075421	2.70978204	1	1	0.99710983
GOTERM_MF_DIRECT	GO:0097110~scaffold protein binding	1.38408304	0.07101496	4.1625876	1	1	1
INTERPRO	IPR011009:Kinase-like_dom_sf	4.4982699	0.07119189	1.74306071	1	1	0.99872449
PIR_SUPERFAMILY	PIRSF000654:Integrin-linked_kinase	1.03806228	0.07158777	6.46666667	0.83181762	1	1
GOTERM_CC_DIRECT	GO:0034774~secretory granule lumen	1.73010381	0.07164087	3.19255931	1	1	0.99710983
UP_KW_LIGAND	KW-0067~ATP-binding	9.68858131	0.07247651	1.34799723	0.83563929	0.86971812	0.86971812
UP_SEQ_FEATURE	DOMAIN:LIM zinc-binding	1.38408304	0.07265965	4.12390356	1	1	0.99783394
UP_SEQ_FEATURE	CARBOHYD:O-linked (GlcNAc) serine	1.38408304	0.07265965	4.12390356	1	1	0.99783394
GOTERM_MF_DIRECT	GO:0030971~receptor tyrosine kinase binding	1.38408304	0.07343111	4.10395961	1	1	1
GOTERM_MF_DIRECT	GO:0005524~ATP binding	10.0346021	0.07506739	1.37087165	1	1	1
INTERPRO	IPR019786:Zinc_finger_PHD-type_CS	1.38408304	0.07539166	4.05969267	1	1	0.99872449
GOTERM_BP_DIRECT	GO:0051715~cytolysis in another organism	0.69204152	0.07678678	25.1068702	1	1	1
UP_SEQ_FEATURE	ZN_FING:C3H1-type 1	1.03806228	0.07793233	6.45876073	1	1	0.99783394
UP_SEQ_FEATURE	ZN_FING:C3H1-type 2	1.03806228	0.07793233	6.45876073	1	1	0.99783394
GOTERM_CC_DIRECT	GO:0030892~mitotic cohesin complex	0.69204152	0.07806242	24.6891253	1	1	0.99710983
INTERPRO	IPR025933:Beta_defensin	1.03806228	0.07816349	6.44774718	1	1	0.99872449
UP_SEQ_FEATURE	DOMAIN:SCD	0.69204152	0.07895593	24.3997628	1	1	0.99783394
SMART	SM00132:LIM	1.38408304	0.07905699	3.95853388	0.99999095	1	1
INTERPRO	IPR020839:SCD	0.69204152	0.07908716	24.358156	1	1	0.99872449
GOTERM_MF_DIRECT	GO:0140803~NAD+- protein-cysteine ADP-ribosyltransferase	0.69204152	0.07931063	24.281761	1	1	1
GOTERM_BP_DIRECT	GO:0050832~defense response to fungus	1.03806228	0.08186636	6.27671756	1	1	1
INTERPRO	IPR001781:Znf_LIM	1.38408304	0.08549677	3.84602464	1	1	0.99872449
GOTERM_CC_DIRECT	GO:0015629~actin cytoskeleton	2.76816609	0.08574806	2.10867974	1	1	0.99710983
GOTERM_BP_DIRECT	GO:0032481~positive regulation of type I interferon production	1.03806228	0.08581543	6.10707654	1	1	1
GOTERM_CC_DIRECT	GO:0005634~nucleus	32.8719723	0.08609859	1.13949809	1	1	0.99710983
GOTERM_BP_DIRECT	GO:0061469~regulation of type B pancreatic cell proliferation	0.69204152	0.08900082	21.5201745	1	1	1
GOTERM_BP_DIRECT	GO:0034087~establishment of mitotic sister chromatid cohesion	0.69204152	0.08900082	21.5201745	1	1	1
UP_KW_CELLULAR_COMPONENT	KW-0628~Postsynaptic cell membrane	2.07612457	0.09143319	2.50539937	0.96831548	0.82289875	0.82289875
UP_SEQ_FEATURE	DOMAIN:GS	0.69204152	0.0914975	20.9140824	1	1	0.99783394
INTERPRO	IPR003605:GS_dom	0.69204152	0.09164851	20.8784195	1	1	0.99872449
INTERPRO	IPR039662:Cohesin_Scc3/SA	0.69204152	0.09164851	20.8784195	1	1	0.99872449
SMART	SM00467:GS	0.69204152	0.09238526	20.6409266	0.99999884	1	1
UP_KW_DOMAIN	KW-0440~LIM domain	1.38408304	0.09273714	3.70435224	0.88247535	1	1
GOTERM_MF_DIRECT	GO:0001221~transcription coregulator binding	1.03806228	0.0950466	5.7509434	1	1	1
KEGG_PATHWAY	hsa04721:Synaptic vesicle cycle	1.38408304	0.09553355	3.63898323	1	1	1
GOTERM_CC_DIRECT	GO:0032993~protein-DNA complex	1.03806228	0.09662569	5.69749045	1	1	0.99710983
GOTERM_MF_DIRECT	GO:0016779~nucleotidyltransferase activity	1.03806228	0.09931491	5.60348331	1	1	1

Supplemental Table 14. Functional enrichment results from DAVID (<https://david.ncifcrf.gov/tools.jsp>) using genes except keratin and β -defensin family member that were identified from analyses in Standard Poodle.

Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
UP_KW_MOLECULAR_FUNC	KW-0808~Transferase	16.7938931	8.89E-04	1.61839174	0.06201566	0.06399357	0.06399357
GOTERM_BP_DIRECT	GO:0051402~neuron apoptotic process	2.29007634	0.00292116	6.14447327	0.97840391	1	1
UP_SEQ_FEATURE	REGION:GTPase domain (Globular)	1.14503817	0.00306192	34.5697479	0.98322386	1	1
INTERPRO	IPR037684:GBP_C	1.14503817	0.00307448	34.4983259	0.90860404	0.76810331	0.76810331
GOTERM_CC_DIRECT	GO:0005886~plasma membrane	33.9694656	0.00328441	1.30364316	0.67000158	0.87462297	0.87462297
GOTERM_MF_DIRECT	GO:0003714~transcription corepressor activity	3.4351145	0.00401334	3.54599449	0.83025229	1	1
INTERPRO	IPR003191:Guanylate-bd/ATL_C	1.14503817	0.00518508	26.8320313	0.98239002	0.76810331	0.76810331
GOTERM_CC_DIRECT	GO:0016363~nuclear matrix	2.67175573	0.00519064	4.4105279	0.82688542	0.87462297	0.87462297
INTERPRO	IPR036543:Guanylate-bd_C_sf	1.14503817	0.00642867	24.1488281	0.9933371	0.76810331	0.76810331
GOTERM_BP_DIRECT	GO:0046834~lipid phosphorylation	1.14503817	0.00717606	22.9021277	0.99992066	1	1
SMART	SM00109:C1	1.90839695	0.00754789	6.37795276	0.65115777	0.79428244	0.79428244
GOTERM_MF_DIRECT	GO:0004672~protein kinase activity	3.81679389	0.00762376	2.91587995	0.96578051	1	1
GOTERM_BP_DIRECT	GO:0071346~cellular response to type II interferon	2.29007634	0.0076777	4.89171659	0.9999591	1	1
GOTERM_MF_DIRECT	GO:0004143~ATP-dependent diacylglycerol kinase activity	1.14503817	0.00773665	22.0281476	0.96745492	1	1
UP_SEQ_FEATURE	DOMAIN:GB1/RHD3-type G	1.14503817	0.00776214	21.9989305	0.99996918	1	1
UP_SEQ_FEATURE	DOMAIN:WWE	1.14503817	0.00776214	21.9989305	0.99996918	1	1
INTERPRO	IPR015894:Guanylate-bd_N	1.14503817	0.00779346	21.9534801	0.99771008	0.76810331	0.76810331
INTERPRO	IPR030386:G_GB1_RHD3_dom	1.14503817	0.00779346	21.9534801	0.99771008	0.76810331	0.76810331
UP_SEQ_FEATURE	DOMAIN:Fibrinogen C-terminal	1.52671756	0.00839595	9.48973472	0.99998685	1	1
INTERPRO	IPR036056:Fibrinogen-like_C	1.52671756	0.00844393	9.47012868	0.9986243	0.76810331	0.76810331
INTERPRO	IPR002181:Fibrinogen_a/b/g_C_dom	1.52671756	0.00844393	9.47012868	0.9986243	0.76810331	0.76810331
INTERPRO	IPR000333:TGFB_receptor	1.14503817	0.00927629	20.1240234	0.99928363	0.76810331	0.76810331
INTERPRO	IPR002219:PE/DAG-bd	1.90839695	0.0100445	5.91883042	0.99960792	0.76810331	0.76810331
INTERPRO	IPR037197:WWE_dom_sf	1.14503817	0.01087405	18.5760216	0.9997956	0.76810331	0.76810331
INTERPRO	IPR004170:WWE-dom	1.14503817	0.01087405	18.5760216	0.9997956	0.76810331	0.76810331
SMART	SM00046:DAGKc	1.14503817	0.01142852	18.0404949	0.79764104	0.79428244	0.79428244
GOTERM_MF_DIRECT	GO:0005515~protein binding	66.7938931	0.01151186	1.10825843	0.9939408	1	1
UP_KW_PTM	KW-0488~Methylation	9.54198473	0.01160598	1.69550404	0.21741361	0.25533157	0.25533157
GOTERM_CC_DIRECT	GO:0031410~cytoplasmic vesicle	3.81679389	0.01244898	2.69440144	0.98532544	1	1
GOTERM_BP_DIRECT	GO:0045766~positive regulation of angiogenesis	2.67175573	0.01327187	3.6062655	0.99999998	1	1
GOTERM_MF_DIRECT	GO:0042802~identical protein binding	12.5954198	0.01418855	1.53448812	0.9981673	1	1
UP_SEQ_FEATURE	ZN_FING:C3H1-type 4	1.14503817	0.01434532	16.132549	1	1	1
UP_SEQ_FEATURE	DOMAIN:DAGKc	1.14503817	0.01434532	16.132549	1	1	1
INTERPRO	IPR001206:Diacylglycerol_kinase_cat_dom	1.14503817	0.01440222	16.0992188	0.99998727	0.93254404	0.93254404
GOTERM_CC_DIRECT	GO:0016020~membrane	29.7709924	0.01442573	1.26564277	0.99253013	1	1
UP_SEQ_FEATURE	DOMAIN:PARP catalytic	1.14503817	0.01828238	14.2346021	1	1	1
INTERPRO	IPR016064:NAD/diacylglycerol_kinase_sf	1.14503817	0.01835428	14.205193	0.99999944	0.9507517	0.9507517
INTERPRO	IPR012317:Poly(ADP-ribose)pol_cat_dom	1.14503817	0.01835428	14.205193	0.99999944	0.9507517	0.9507517
INTERPRO	IPR017438:ATP-NAD_kinase_N	1.14503817	0.01835428	14.205193	0.99999944	0.9507517	0.9507517
GOTERM_MF_DIRECT	GO:1990404~NAD+~protein ADP-ribosyltransferase activity	1.14503817	0.0203376	13.4616457	0.99988393	1	1
GOTERM_MF_DIRECT	GO:0046332~SMAD binding	1.52671756	0.0212998	6.73082287	0.99992475	1	1
INTERPRO	IPR000719:Prot_kinase_dom	4.96183206	0.02206111	2.09709262	0.99999997	1	1
KEGG_PATHWAY	hsa05016:Huntington disease	3.81679389	0.02305097	2.38860818	0.99435631	1	1
UP_SEQ_FEATURE	DOMAIN:Protein kinase	4.96183206	0.02341264	2.08058668	1	1	1
SMART	SM01276:M60-like	0.76335878	0.02343124	84.1889764	0.96295811	1	1
GOTERM_BP_DIRECT	GO:1990114~RNA polymerase II core complex assembly	0.76335878	0.0235754	83.9744681	1	1	1
GOTERM_BP_DIRECT	GO:0051496~positive regulation of stress fiber assembly	1.52671756	0.02375592	6.45957447	1	1	1
UP_SEQ_FEATURE	ZN_FING:PHD-type	1.52671756	0.02381923	6.45301961	1	1	1
UP_SEQ_FEATURE	DOMAIN:Peptidase M60	0.76335878	0.02454546	80.6627451	1	1	1
UP_SEQ_FEATURE	SITE:Breakpoint for translocation to form KIAA1549-BRAF fusion	0.76335878	0.02454546	80.6627451	1	1	1
INTERPRO	IPR035423:M60-like_N	0.76335878	0.02459634	80.4960938	1	1	1
INTERPRO	IPR042279:Pep_M60_3	0.76335878	0.02459634	80.4960938	1	1	1
INTERPRO	IPR031161:Peptidase_M60_dom	0.76335878	0.02459634	80.4960938	1	1	1
GOTERM_MF_DIRECT	GO:0005524~ATP binding	11.0687023	0.02500041	1.52000413	0.99998584	1	1
UP_KW_LIGAND	KW-0547~Nucleotide-binding	14.1221374	0.02580718	1.36795636	0.46607752	0.61937227	0.61937227
GOTERM_CC_DIRECT	GO:0098688~parallel fiber to Purkinje cell synapse	1.14503817	0.02657006	11.7014006	0.99988553	1	1
GOTERM_CC_DIRECT	GO:0016604~nuclear body	3.81679389	0.02721542	2.35373	0.99990846	1	1
GOTERM_BP_DIRECT	GO:0035264~multicellular organism growth	1.90839695	0.02930677	4.28441164	1	1	1
UP_SEQ_FEATURE	TRANSMEM:Helical	31.2977099	0.03069783	1.2145327	1	1	1
UP_KW_CELLULAR_COMPO	KW-0206~Cytoskeleton	10.6870229	0.03128263	1.50335458	0.66060848	0.52868464	0.52868464
GOTERM_BP_DIRECT	GO:0071363~cellular response to growth factor stimulus	1.52671756	0.03150869	5.79134263	1	1	1
UP_SEQ_FEATURE	ZN_FING:C3H1-type 3	1.14503817	0.03240565	10.5212276	1	1	1
GOTERM_BP_DIRECT	GO:0006986~response to unfolded protein	1.52671756	0.03291454	5.69318428	1	1	1
GOTERM_BP_DIRECT	GO:0043524~negative regulation of neuron apoptotic process	2.29007634	0.0341868	3.33673383	1	1	1
UP_SEQ_FEATURE	DOMAIN:Phorbol-ester/DAG-type	1.52671756	0.03491831	5.56294794	1	1	1
KEGG_PATHWAY	hsa01100:Metabolic pathways	11.4503817	0.03514317	1.42765626	0.99964457	1	1
GOTERM_BP_DIRECT	GO:0060491~regulation of cell projection assembly	0.76335878	0.03515473	55.9829787	1	1	1
GOTERM_BP_DIRECT	GO:0160075~non-canonical inflammasome complex assembly	0.76335878	0.03515473	55.9829787	1	1	1
GOTERM_BP_DIRECT	GO:0002408~myeloid dendritic cell chemotaxis	0.76335878	0.03515473	55.9829787	1	1	1
GOTERM_CC_DIRECT	GO:0005829~cytosol	31.6793893	0.03609785	1.20348977	0.99999584	1	1
UP_SEQ_FEATURE	DOMAIN:STAG	0.76335878	0.03659221	53.7751634	1	1	1
UP_KW_MOLECULAR_FUNC	KW-0418~Kinase	6.48854962	0.03719921	1.7160214	0.93474353	1	1
GOTERM_MF_DIRECT	GO:0019900~kinase binding	1.90839695	0.03752934	3.95930757	0.99999995	1	1
GOTERM_MF_DIRECT	GO:0003950~NAD+ ADP-ribosyltransferase activity	1.14503817	0.03769859	9.69238494	0.99999996	1	1
GOTERM_CC_DIRECT	GO:0098978~glutamatergic synapse	4.19847328	0.03911345	2.0856663	0.99999855	1	1
INTERPRO	IPR011009:Kinase-like_dom_sf	4.96183206	0.03945437	1.92009031	1	1	1
GOTERM_MF_DIRECT	GO:0004713~protein tyrosine kinase activity	1.90839695	0.03985531	3.88316704	0.99999998	1	1
GOTERM_BP_DIRECT	GO:0051289~protein homotetramerization	1.52671756	0.04042486	5.24840426	1	1	1
GOTERM_BP_DIRECT	GO:0007507~heart development	2.67175573	0.04106204	2.77274187	1	1	1

INTERPRO	IPR046349:C1-like_sf	1.52671756	0.04321174	5.1108631	1	1	1
GOTERM_CC_DIRECT	GO:0048471~perinuclear region of cytoplasm	6.10687023	0.04621015	1.72215094	0.99999988	1	1
GOTERM_BP_DIRECT	GO:0048014~Tie signaling pathway	0.76335878	0.04659733	41.987234	1	1	1
GOTERM_BP_DIRECT	GO:0072012~glomerulus vasculature development	0.76335878	0.04659733	41.987234	1	1	1
GOTERM_BP_DIRECT	GO:1900194~negative regulation of oocyte maturation	0.76335878	0.04659733	41.987234	1	1	1
GOTERM_CC_DIRECT	GO:0106139~symbiont cell surface	0.76335878	0.04776594	40.954902	0.99999993	1	1
KEGG_PATHWAY	hsa04814:Motor proteins	2.67175573	0.04804769	2.63959391	0.99998211	1	1
INTERPRO	IPR012678:Ribosomal_ul23/eL15/eS24_sf	0.76335878	0.04859001	40.2480469	1	1	1
INTERPRO	IPR013721:STAG	0.76335878	0.04859001	40.2480469	1	1	1
GOTERM_CC_DIRECT	GO:0098793~presynapse	2.29007634	0.05033647	2.99670014	0.99999997	1	1
UP_KW_MOLECULAR_FUNC	KW-0514~Muscle protein	1.52671756	0.05282698	4.68994083	0.97991319	1	1
GOTERM_CC_DIRECT	GO:0034774~secretory granule lumen	1.90839695	0.05331758	3.530595	0.99999999	1	1
KEGG_PATHWAY	hsa04510:Focal adhesion	2.67175573	0.05413115	2.56157635	0.99999569	1	1
SMART	SM00132:LIM	1.52671756	0.05480194	4.6130946	0.99960402	1	1
KEGG_PATHWAY	hsa04927:Cortisol synthesis and secretion	1.52671756	0.05576643	4.57142857	0.99999706	1	1
KEGG_PATHWAY	hsa00561:Glycerolipid metabolism	1.52671756	0.05576643	4.57142857	0.99999706	1	1
GOTERM_CC_DIRECT	GO:0015629~actin cytoskeleton	3.05343511	0.05633387	2.33195171	1	1	1
GOTERM_BP_DIRECT	GO:0030971~receptor tyrosine kinase binding	1.52671756	0.05741211	4.55041546	1	1	1
UP_SEQ_FEATURE	CARBOHYD-O-linked (GlcNAc) serine	1.52671756	0.05765261	4.54438001	1	1	1
UP_SEQ_FEATURE	DOMAIN:LIM zinc-binding	1.52671756	0.05765261	4.54438001	1	1	1
GOTERM_BP_DIRECT	GO:0140639~positive regulation of pyroptotic inflammatory	0.76335878	0.05790479	33.5897872	1	1	1
GOTERM_BP_DIRECT	GO:0006654~phosphatidic acid biosynthetic process	1.14503817	0.05812913	7.63404255	1	1	1
INTERPRO	IPR019786:Zinc_finger_PHD-type_CS	1.52671756	0.05993078	4.47200521	1	1	1
KEGG_PATHWAY	hsa04110:Cell cycle	2.29007634	0.06005495	2.82097649	0.99999893	1	1
GOTERM_MF_DIRECT	GO:0016361~activin receptor activity, type I	0.76335878	0.0601499	32.3079498	1	1	1
INTERPRO	IPR003530:Hematopoietin_rcpt_L_F3_CS	0.76335878	0.06036546	32.1984375	1	1	1
UP_KW_CELLULAR_COMPO	KW-0628~Postsynaptic cell membrane	2.29007634	0.06442495	2.79325376	0.89608615	0.52868464	0.52868464
UP_SEQ_FEATURE	ZN_FING:C3H1-type 2	1.14503817	0.0658142	7.11730104	1	1	1
UP_SEQ_FEATURE	ZN_FING:C3H1-type 1	1.14503817	0.0658142	7.11730104	1	1	1
GOTERM_CC_DIRECT	GO:1904813~filocolin-1-rich granule lumen	1.90839695	0.06645788	3.27639216	1	1	1
UP_KW_DOMAIN	KW-1133~Transmembrane helix	32.8244275	0.06728348	1.14742444	0.78398062	0.61133864	0.61133864
UP_KW_DOMAIN	KW-0440~LIM domain	1.52671756	0.06759566	4.24208079	0.7855657	0.61133864	0.61133864
INTERPRO	IPR001781:Znf_LIM	1.52671756	0.06819764	4.23663651	1	1	1
GOTERM_BP_DIRECT	GO:0051715~cytolysis in another organism	0.76335878	0.06907871	27.9914894	1	1	1
GOTERM_CC_DIRECT	GO:0030892~mitotic cohesin complex	0.76335878	0.07078967	27.303268	1	1	1
GOTERM_BP_DIRECT	GO:0032481~positive regulation of type I interferon product	1.14503817	0.07112122	6.80874066	1	1	1
PIR_SUPERFAMILY	PIRSF000654:Integrin-linked_kinase	1.14503817	0.07158777	6.46666667	0.83181762	1	1
GOTERM_MF_DIRECT	GO:0140803~NAD+- protein-cysteine ADP-ribosyltransferase	0.76335878	0.07174037	26.9232915	1	1	1
UP_SEQ_FEATURE	DOMAIN:SCD	0.76335878	0.07185051	26.8875817	1	1	1
INTERPRO	IPR020839:SCD	0.76335878	0.07199573	26.8320313	1	1	1
UP_KW_LIGAND	KW-0067~ATP-binding	10.6870229	0.07247651	1.34799723	0.83563929	0.86971812	0.86971812
GOTERM_BP_DIRECT	GO:0050911~detection of chemical stimulus involved in ser	3.81679389	0.07380321	1.93936416	1	1	1
GOTERM_CC_DIRECT	GO:0005634~nucleus	33.2061069	0.07622284	1.15403286	1	1	1
GOTERM_BP_DIRECT	GO:0016310~phosphorylation	4.96183206	0.07665408	1.72459413	1	1	1
GOTERM_MF_DIRECT	GO:0061629~RNA polymerase II-specific DNA-binding trans	2.29007634	0.07794849	2.63380025	1	1	1
GOTERM_BP_DIRECT	GO:0045444~fat cell differentiation	1.52671756	0.07807822	3.99878419	1	1	1
GOTERM_CC_DIRECT	GO:0014069~postsynaptic density	2.67175573	0.07823711	2.34987142	1	1	1
UP_KW_CELLULAR_COMPO	KW-0539~Nucleus	33.5877863	0.0792567	1.14692837	0.93964526	0.52868464	0.52868464
SMART	SM00467:GS	0.76335878	0.07965339	24.0539933	0.99999024	1	1
GOTERM_MF_DIRECT	GO:0001221~transcription coregulator binding	1.14503817	0.07967376	6.37656904	1	1	1
GOTERM_BP_DIRECT	GO:0061469~regulation of type B pancreatic cell proliferati	0.76335878	0.08012066	23.9927052	1	1	1
GOTERM_BP_DIRECT	GO:0034087~establishment of mitotic sister chromatid coh	0.76335878	0.08012066	23.9927052	1	1	1
GOTERM_BP_DIRECT	GO:0006468~protein phosphorylation	3.4351145	0.08044999	2.01002716	1	1	1
GOTERM_CC_DIRECT	GO:0032993~protein-DNA complex	1.14503817	0.0813956	6.30075415	1	1	1
GOTERM_MF_DIRECT	GO:0042803~protein homodimerization activity	5.72519084	0.08153372	1.61539749	1	1	1
UP_SEQ_FEATURE	DOMAIN:GS	0.76335878	0.08331528	23.0464986	1	1	1
GOTERM_MF_DIRECT	GO:0016779~nucleotidyltransferase activity	1.14503817	0.08332105	6.21306727	1	1	1
UP_KW_DOMAIN	KW-0812~Transmembrane	32.8244275	0.08336436	1.13602938	0.85265742	0.61133864	0.61133864
INTERPRO	IPR003605:GS_dom	0.76335878	0.0834826	22.9988839	1	1	1
INTERPRO	IPR039662:Cohesin_Scc3/SA	0.76335878	0.0834826	22.9988839	1	1	1
UP_KW_CELLULAR_COMPO	KW-0965~Cell junction	3.81679389	0.08663732	1.87589524	0.95409384	0.52868464	0.52868464
GOTERM_MF_DIRECT	GO:0001530~lipopolysaccharide binding	1.14503817	0.08701846	6.05774059	1	1	1
UP_SEQ_FEATURE	COMPBAS:Basic and acidic residues	30.9160305	0.08790916	1.15476889	1	1	1
KEGG_PATHWAY	hsa04721:Synaptic vesicle cycle	1.52671756	0.08852882	3.76130199	1	1	1
GOTERM_MF_DIRECT	GO:0003723~RNA binding	9.54198473	0.08861961	1.38779853	1	1	1
KEGG_PATHWAY	hsa04820:Cytoskeleton in muscle cells	2.67175573	0.08989079	2.24137931	1	1	1
GOTERM_BP_DIRECT	GO:0001955~blood vessel maturation	0.76335878	0.09103219	20.993617	1	1	1
GOTERM_CC_DIRECT	GO:0097060~synaptic membrane	1.14503817	0.09239925	5.85070028	1	1	1
GOTERM_CC_DIRECT	GO:0031461~cullin-RING ubiquitin ligase complex	0.76335878	0.09325886	20.477451	1	1	1
GOTERM_MF_DIRECT	GO:0004675~transmembrane receptor protein serine/threoc	0.76335878	0.094496	20.1924686	1	1	1
GOTERM_MF_DIRECT	GO:0008307~structural constituent of muscle	1.14503817	0.0945566	5.76927675	1	1	1
UP_SEQ_FEATURE	DOMAIN:SPATA31	0.76335878	0.09463898	20.1656863	1	1	1
UP_SEQ_FEATURE	MUTAGEN:C->S: Loss of function.	0.76335878	0.09463898	20.1656863	1	1	1
INTERPRO	IPR015415:Spast_Vps4_C	0.76335878	0.09482784	20.1240234	1	1	1
GOTERM_BP_DIRECT	GO:0042127~regulation of cell population proliferation	1.90839695	0.0978458	2.85627442	1	1	1
GOTERM_BP_DIRECT	GO:0061077~chaperone-mediated protein folding	1.14503817	0.09950756	5.59829787	1	1	1
UP_KW_CELLULAR_COMPO	KW-0472~Membrane	45.8015267	0.09975471	1.09854584	0.97192827	0.52868464	0.52868464

Supplemental Table 15. Clusters of pathway enrichment with scores >1.3 from DAVID (<https://david.ncifcrf.gov/tools.jsp>) using genes except keratin and β -defensin family member that were identified from analyses in Standard Poodle.

Annotation Cluster 1		Enrichment Score: 2.074280334496577					
Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
UP_SEQ_FEATURE	DOMAIN:Fibrinogen C-terminal	1.52671756	0.00839595	9.48973472	0.99998685	1	1
INTERPRO	IPR036056:Fibrinogen-like_C	1.52671756	0.00844393	9.47012868	0.9986243	0.76810331	0.76810331
INTERPRO	IPR002181:Fibrinogen_a/b/g_C_dom	1.52671756	0.00844393	9.47012868	0.9986243	0.76810331	0.76810331
Annotation Cluster 2		Enrichment Score: 1.8260729484785707					
Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
GOTERM_BP_DIRECT	GO:0046834~lipid phosphorylation	1.14503817	0.00717606	22.9021277	0.99992066	1	1
GOTERM_MF_DIRECT	GO:0004143~ATP-dependent diacylglycerol kinase activity	1.14503817	0.00773665	22.0281476	0.96745492	1	1
SMART	SM00046:DAGKc	1.14503817	0.01142852	18.0404949	0.79764104	0.79428244	0.79428244
UP_SEQ_FEATURE	DOMAIN:DAGKc	1.14503817	0.01434532	16.132549	1	1	1
INTERPRO	IPR001206:Diacylglycerol_kinase_cat_dom	1.14503817	0.01440222	16.0992188	0.99998727	0.93254404	0.93254404
INTERPRO	IPR016064:NAD/diacylglycerol_kinase_sf	1.14503817	0.01835428	14.205193	0.99999944	0.9507517	0.9507517
INTERPRO	IPR017438:ATP-NAD_kinase_N	1.14503817	0.01835428	14.205193	0.99999944	0.9507517	0.9507517
KEGG_PATHWAY	hsa00561:Glycerolipid metabolism	1.52671756	0.05576643	4.57142857	0.99999706	1	1
Annotation Cluster 3		Enrichment Score: 1.8038344308396914					
Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
UP_SEQ_FEATURE	DOMAIN:WWE	1.14503817	0.00776214	21.9989305	0.99996918	1	1
INTERPRO	IPR004170:WWE-dom	1.14503817	0.01087405	18.5760216	0.9997956	0.76810331	0.76810331
INTERPRO	IPR037197:WWE_dom_sf	1.14503817	0.01087405	18.5760216	0.9997956	0.76810331	0.76810331
UP_SEQ_FEATURE	DOMAIN:PARP catalytic	1.14503817	0.01828238	14.2346021	1	1	1
INTERPRO	IPR012317:Poly(ADP-ribose)pol_cat_dom	1.14503817	0.01835428	14.205193	0.99999944	0.9507517	0.9507517
GOTERM_MF_DIRECT	GO:1990404~NAD+-protein ADP-ribosyltransferase activity	1.14503817	0.0203376	13.4616457	0.99988393	1	1
GOTERM_MF_DIRECT	GO:0003950~NAD+ ADP-ribosyltransferase activity	1.14503817	0.03769859	9.69238494	0.99999996	1	1
Annotation Cluster 4		Enrichment Score: 1.5381239291204878					
Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
SMART	SM00109:C1	1.90839695	0.00754789	6.37795276	0.65115777	0.79428244	0.79428244
INTERPRO	IPR002219:PE/DAG-bd	1.90839695	0.0100445	5.91883042	0.99960792	0.76810331	0.76810331
UP_SEQ_FEATURE	DOMAIN:Phorbol-ester/DAG-type	1.52671756	0.03491831	5.56294794	1	1	1
INTERPRO	IPR046349:C1-like_sf	1.52671756	0.04321174	5.1108631	1	1	1
GOTERM_CC_DIRECT	GO:0098793~presynapse	2.29007634	0.05033647	2.99670014	0.99999997	1	1
UP_SEQ_FEATURE	ZN_FING:Phorbol-ester/DAG-type	1.14503817	0.10255699	5.49973262	1	1	1
Annotation Cluster 5		Enrichment Score: 1.4542150932810078					
Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
UP_SEQ_FEATURE	REGION:GTPase domain (Globular)	1.14503817	0.00306192	34.5697479	0.98322386	1	1
INTERPRO	IPR037684:GBP_C	1.14503817	0.00307448	34.4983259	0.90860404	0.76810331	0.76810331
INTERPRO	IPR003191:Guanylate-bd/ATL_C	1.14503817	0.00518508	26.8320313	0.98239002	0.76810331	0.76810331
INTERPRO	IPR036543:Guanylate-bd_C_sf	1.14503817	0.00642867	24.1488281	0.9933371	0.76810331	0.76810331
GOTERM_BP_DIRECT	GO:0071346~cellular response to type II interferon	2.29007634	0.0076777	4.89171659	0.9999591	1	1
UP_SEQ_FEATURE	DOMAIN:GB1/RHD3-type G	1.14503817	0.00776214	21.9989305	0.99996918	1	1
INTERPRO	IPR015894:Guanylate-bd_N	1.14503817	0.00779346	21.9534801	0.99771008	0.76810331	0.76810331
INTERPRO	IPR030386:G_GB1_RHD3_dom	1.14503817	0.00779346	21.9534801	0.99771008	0.76810331	0.76810331
KEGG_PATHWAY	hsa04621:NOD-like receptor signaling pathway	2.29007634	0.1083611	2.35827664	1	1	1
GOTERM_MF_DIRECT	GO:0005525~GTP binding	3.05343511	0.23565166	1.58761424	1	1	1
UP_KW_LIGAND	KW-0342~GTP-binding	2.67175573	0.44874524	1.29332447	0.99999938	1	1
GOTERM_MF_DIRECT	GO:0003924~GTPase activity	1.90839695	0.64241892	1.13440835	1	1	1
UP_KW_BIOLOGICAL_PROC	KW-0399~Innate immunity	2.29007634	0.6514834	1.07979819	1	1	1
INTERPRO	IPR027417:P-loop_NTPase	3.81679389	0.80316972	0.87973873	1	1	1
Annotation Cluster 6		Enrichment Score: 1.3754815929013675					
Category	Term	%	PValue	Fold Enrichm	Bonferroni	Benjamini	FDR
GOTERM_CC_DIRECT	GO:0005886~plasma membrane	33.9694656	0.00328441	1.30364316	0.67000158	0.87462297	0.87462297
UP_KW_CELLULAR_COMPO	KW-0472~Membrane	45.8015267	0.09975471	1.09854584	0.97192827	0.52868464	0.52868464
UP_KW_CELLULAR_COMPO	KW-1003~Cell membrane	22.519084	0.22812066	1.11251846	0.9998498	0.86178915	0.86178915

APPENDIX D

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