McNab Genetic Study

Mars Veterinary, 2017

Acknowledgements:

Mars Veterinary would like to thank all the McNab owners and breeders who have donated samples to make this study possible.

Contents

Introduction & Purpose

In 2014, Mars Veterinary received 31 samples from the McNab dog breed from several breeders/owners throughout the United States. As the breed is increasing in numbers and popularity, in particular in dog sports such as flyball, this is a unique opportunity to examine the breed.

Mars Veterinary has previously examined samples of 12,000+ purebred dogs of 250+ breeds and varieties from the North America, Australia, Europe and Asia for the purposes of breed ancestry detection, disease and trait prevalence, and genetic diversity assessment. The McNab was evaluated using a research process, the findings of which are shared below for the benefit of the study participants.

Materials and Methods

Sample processing. 31 buccal mucosal swab submissions were processed by GeneSeek Inc., (Neogen Inc., Omaha, NE). Each sample was assigned a unique sample ID and the DNA was extracted and genotyped on an Illumina bead array chip. These genotypes were then obtained by Mars Veterinary (Vancouver, WA) for further analysis. Sample genotypes were assessed for quality based on the proportion of successfully genotyped markers (known as the "call rate"). All but one sample (14-304) met the quality threshold of 90% call rate required to be included in the evaluation (see Figure 1). This is the sample which was submitted separately. One other sample, 14-115 met the minimum call rate for breed marker evaluation but disease markers were not examined for this sample.

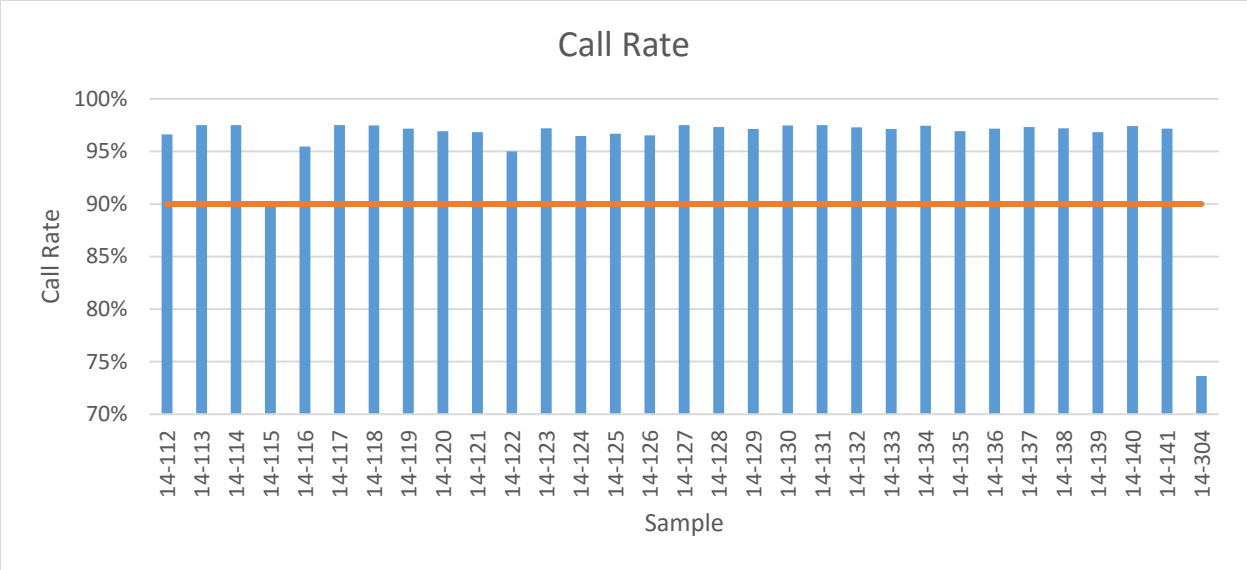


Figure 1: Call Rates of Submitted McNab Dog Samples

Breed similarity analysis. Assessment of how similar the genotypes of McNab were to known genotypes of other breeds in our database was done with Mars Veterinary's proprietary Mixed-Breed algorithm and Principal Component Analysis (PCA).

When the mixed-breed algorithm does not contain the correct breed, it will attempt to fit the closest related breed to help describe the samples in question. This will show us what the closest breeds are which are then used to compare against the McNab samples in the Principle Component Analysis (PCA).

PCA is an unsupervised clustering method of tested genotypes, and allows comparison of DNA similarity. Closely related samples, such as dogs within the same breed, will be expected to cluster together, unlike samples from other breeds. If a sample is within the cluster for the breed, this is a good indication that it is potentially a pure member of this breed or species.

Breed identification. From the PCA-inferred clusters, we identified likely purebreds based on where the majority clustered and added their selected genotypes to our breed database. We could then investigate how the algorithm would behave containing the McNab dogs. The foundational algorithm used in breed identification has been in commercial use for over 9 years during which time is has been used to evaluate 600,000+ samples.

Disease mutation prevalence. The Mars Veterinary (MV) genotyping array tests for over 100 disease mutations. The process to detect disease mutations using this technology has been validated

and in commercial process for more than 2 years, with over 200,000+ samples analyzed. We aimed to identify any disease mutations that might be present in the McNabs.

Trait prevalence. MV have a separate proprietary algorithm to assign phenotypic trait prevalence. The algorithm has been validated and is used in our commercial process, with 100,000+ samples analyzed. This algorithm was used against all samples to identify phenotypic traits exhibited by the McNabs.

Genetic diversity assessment. In genetics, diversity of a breed can be assessed by a variety of measures, but is commonly assessed by comparing the proportion of homozygous genotypes. A homozygous genotype is where the same version of a genetic marker is inherited from both the sire and the dam. Higher values of this proportion (termed as homozygosity) indicate lower genetic diversity. Compared over breed populations, more homozygous breed populations typify less genetic diversity, which is considered to be negative indicator of genetic fitness.

Similarity to Known Breeds

Mixed Breed Algorithm

The mixed breed algorithm used in the Mars Veterinary suite of breed detection products, such as the commercially available Wisdom Panel® tests, was run on the 30 samples above the sample quality threshold. This predicts the closest 8 great-grandparents of ancestry in an attempt to find the closest ancestors to the McNab.

We then counted how many times each breed was called a great-grandparent in each of the dog's ancestries and sorted this to find the breeds which explained the largest proportion of the ancestry and were the best match to the McNab's genetic profile. As expected, we see a lot of herding breeds appearing, though the Border Collie is the predominant breed, showing up 110 time out of the possible 240 great-grandparent slots across all 30 samples. The next highest contributor, though of much lower magnitude, was the Koolie. This is summarized in Table 1 below.

Many of the breeds on the list are likely there because they are also heterozygous breeds, which appear more frequently in the algorithm results as false positives, and thus are not likely contributors to significant, if any proportion, of the McNab's recent breed ancestry.

Breed	Great-grandparents in 30 dogs	Proportion
Border Collie	110	47.41%
Koolie	14	6.03%
Collie^UK	11	4.74%
Australian Kelpie	10	4.31%
Australian Shepherd	8	3.45%
Rat Terrier	6	2.59%
Australian Cattle Dog	5	2.16%
Dogue de Bordeaux	4	1.72%
Bulldog (American)	4	1.72%
Pomeranian^US	3	1.29%
Old English Sheepdog	3	1.29%

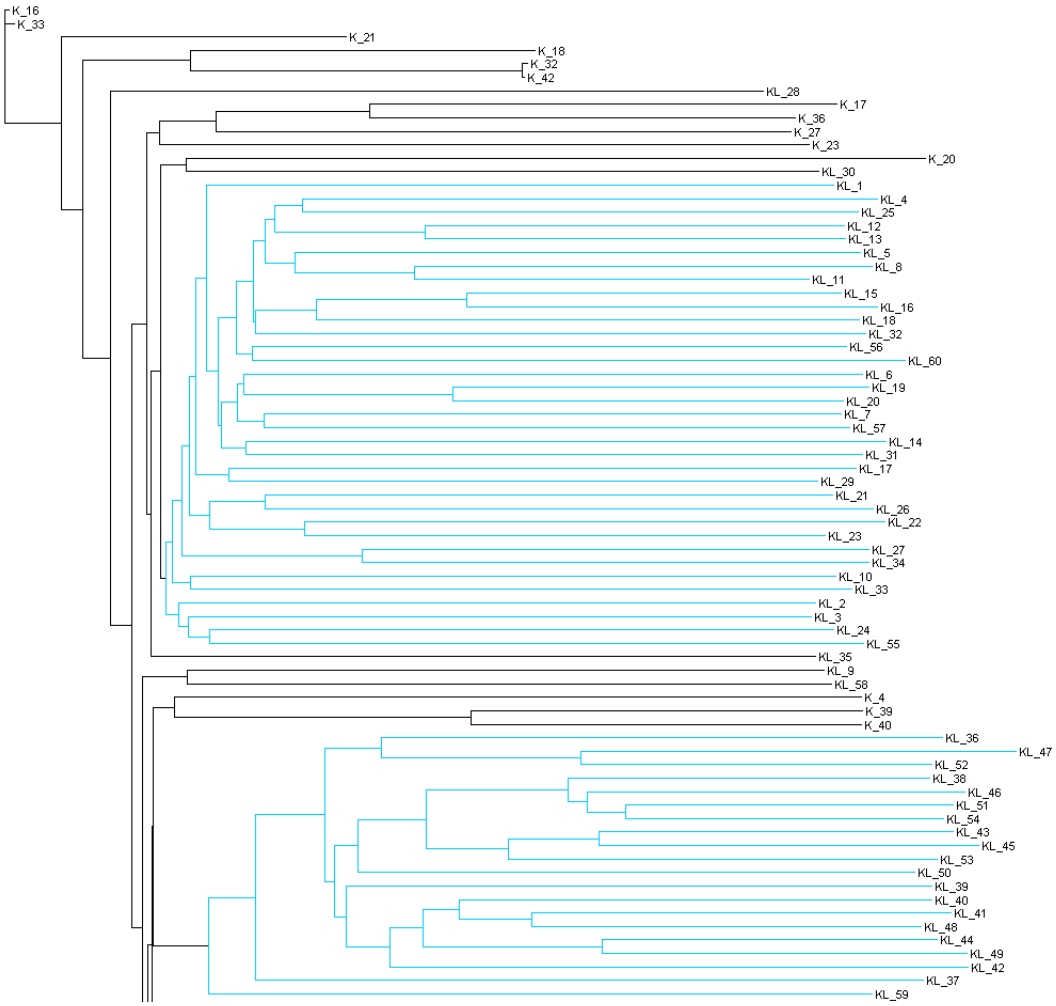
Table 1: Quantity of Great-Grandparents detected in 30 samples when McNab was not an option

The proportion of Border Collie in the different samples was generally less than 50%, with only four samples appearing with more. These are sample 14-121 (7 Great-Grandparents), 14-129 (6 Great-Grandparents), sample 14-136 (6 Great-Grandparents), and sample 14-133 (5 Great-Grandparents).

Clustering

We performed clustering analysis with the top 5 breeds from the breed analysis. The results are in Figure 2 on the next few pages. In summary, most of the McNabs samples cluster together, except for two McNab samples which cluster with the Border Collies; these are 14-121 and 14-133. As most other breeds cluster with themselves, it is good to see the McNab doing the same thing.

As seen in Figure 2, the McNabs seem to form two clusters (highlighted by the encircling square), with one closer to the Border Collie. It is not known if there is any significance to this, such as different breeding lines.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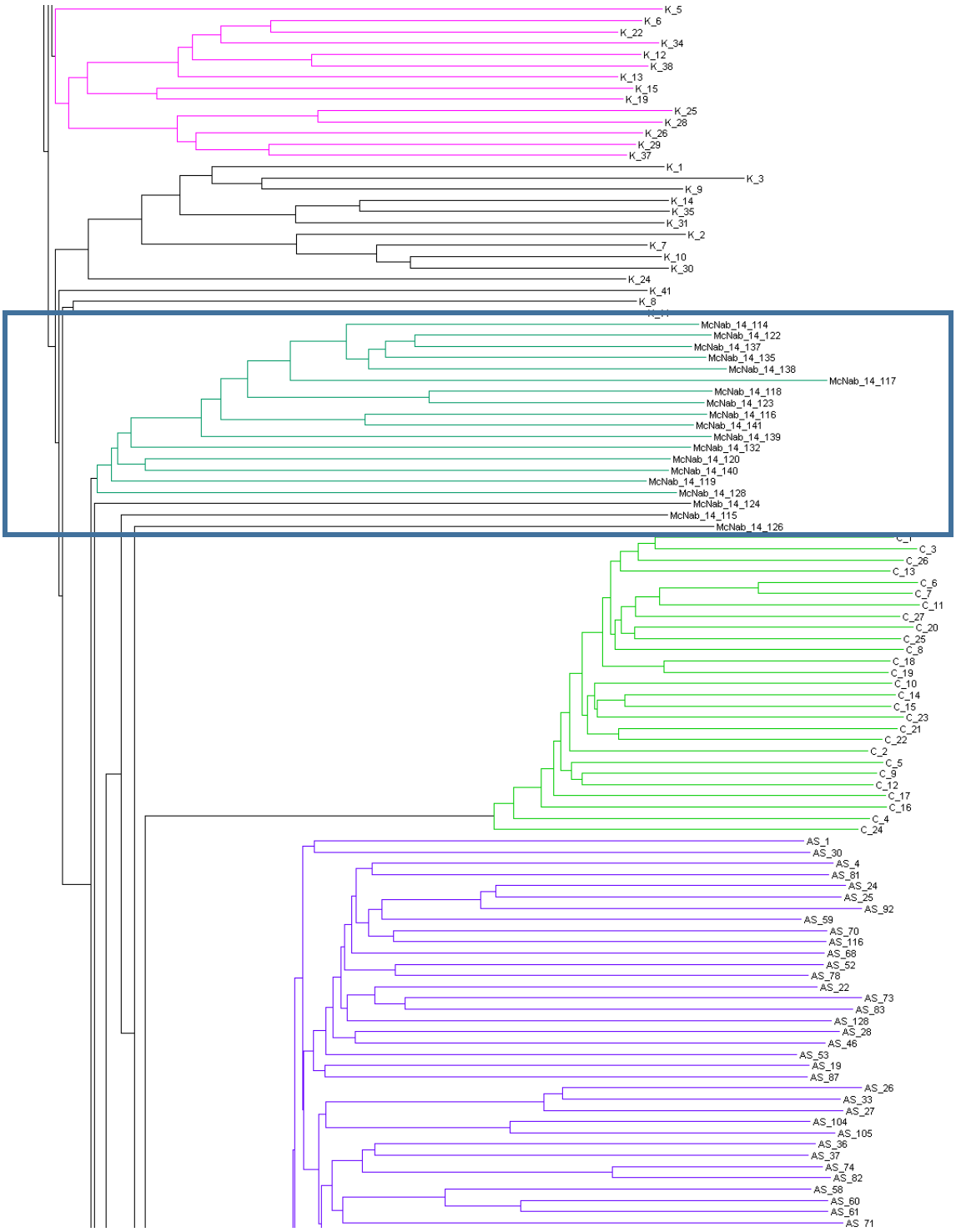
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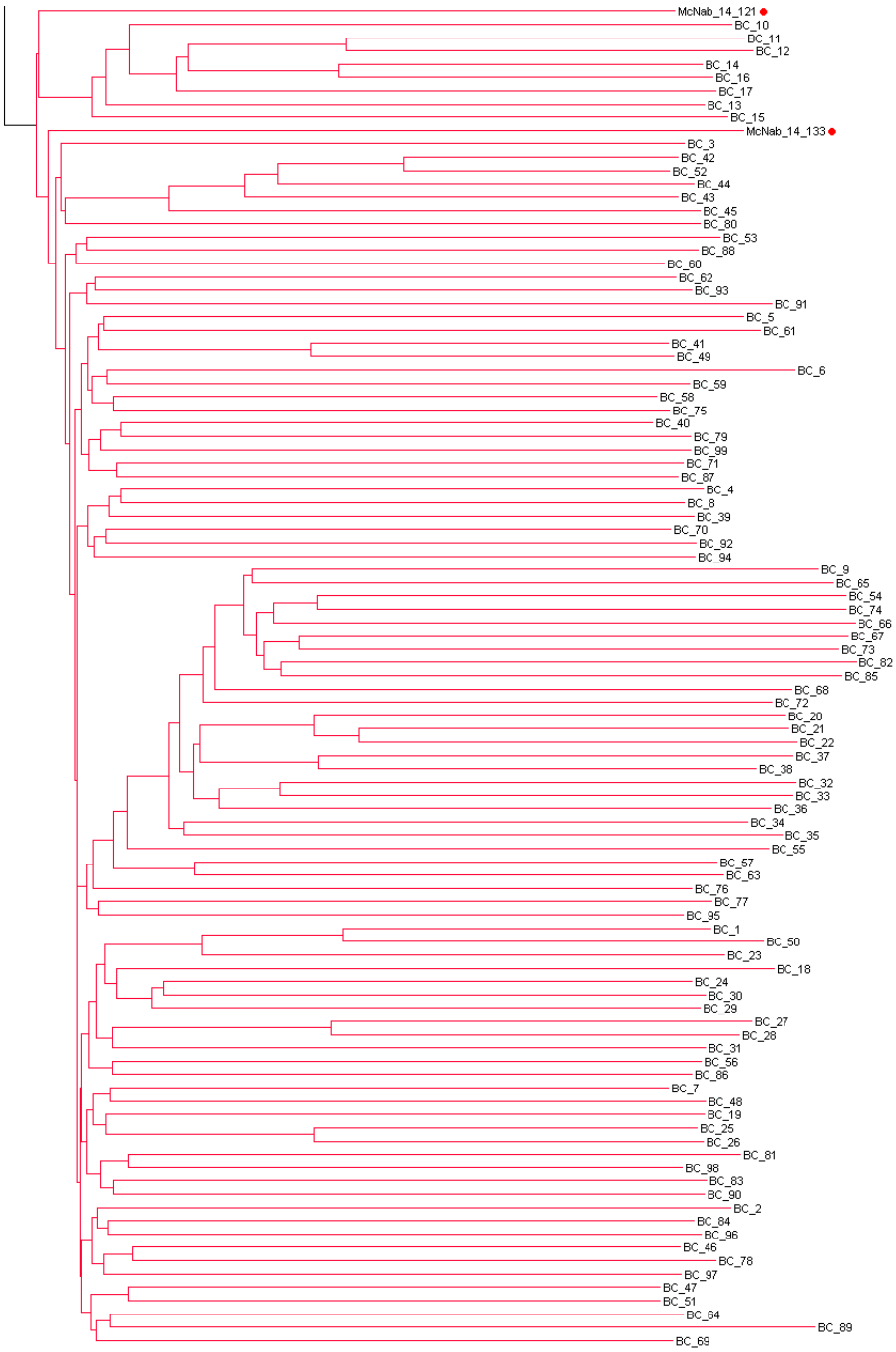

Figure 2: Hierarchical Clustering of McNab Dog samples against related breeds Australian Kelpie (KL), Australian Shepherd (AS), Border Collie (BC), Collie (C), and Koolie (K). The two outliers are marked with a red dot.

Principle Component Analysis (PCA)

The 30 samples were put into a PCA with different breeds taken from the top 11 breeds in Table 1 above. To begin with, we can use the “All Breeds Outgroup” which includes a single sample from each

of the breeds in the database and will generally place the sample of closer related breeds nearer to the samples in question.

In Figure 3 below, we can see that the samples for Border Collie and Collie are most like the McNabs than the other breeds in this analysis. Other herding breeds are being pulled out as well.

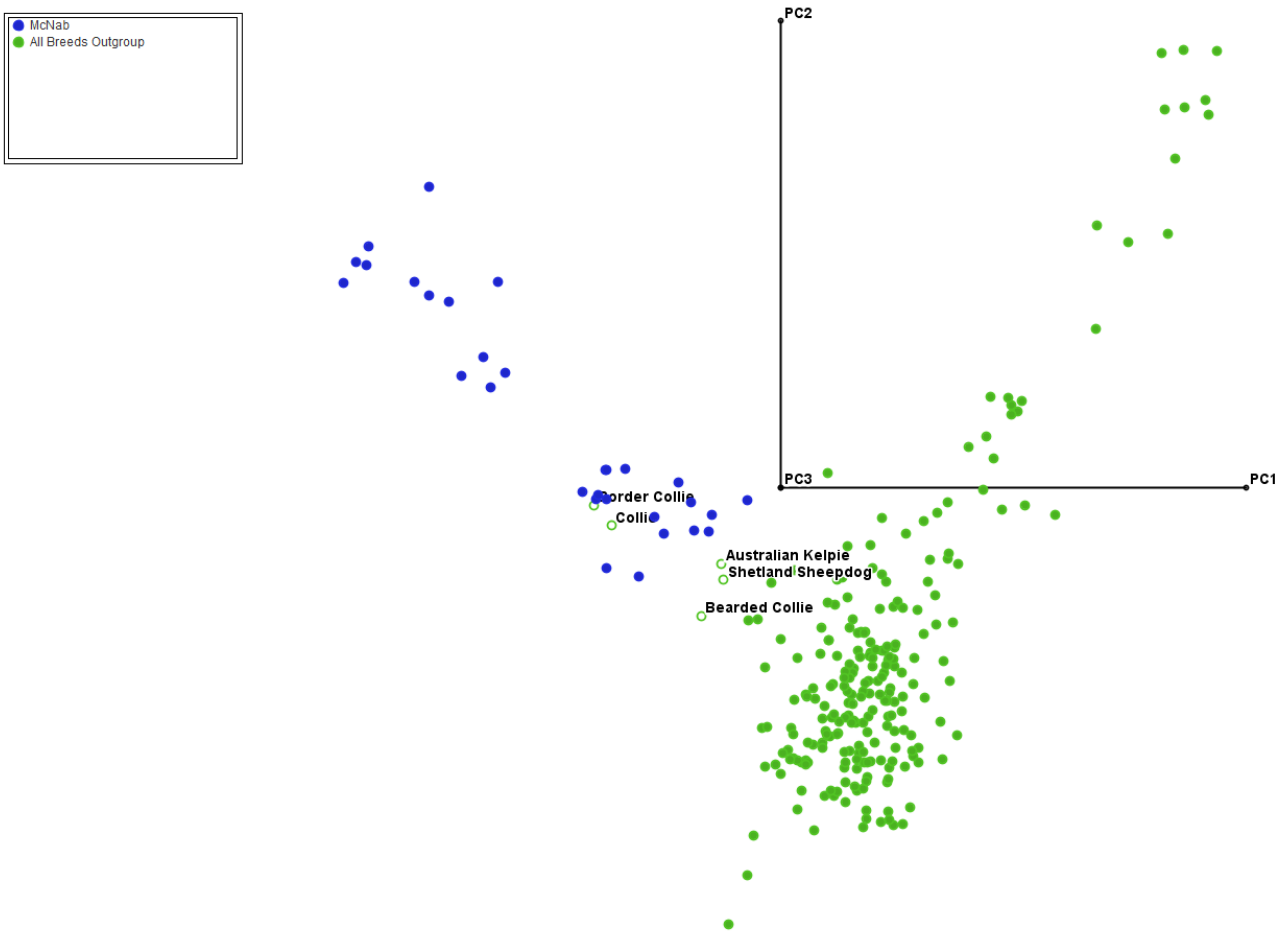

Figure 3: PCA Comparison of McNab against the All Breeds Outgroup.

Figure 4 below shows the McNab samples compared to the Border Collie. Sample 14-121 is the closest to Border Collie. This is the sample which matched with 7 great grandparents of Border Collie as described above.

We note that there is some subclustering between the McNab dog samples. Generally this may indicate family lines or closely related dogs. It appears that one family line clusters together furthest away from the Border Collie, with a second group of family lines in the center and then the rest being closest to the Border Collies. It is possible that the inter-relatedness of the family line is what is pulling them further out of the cluster.

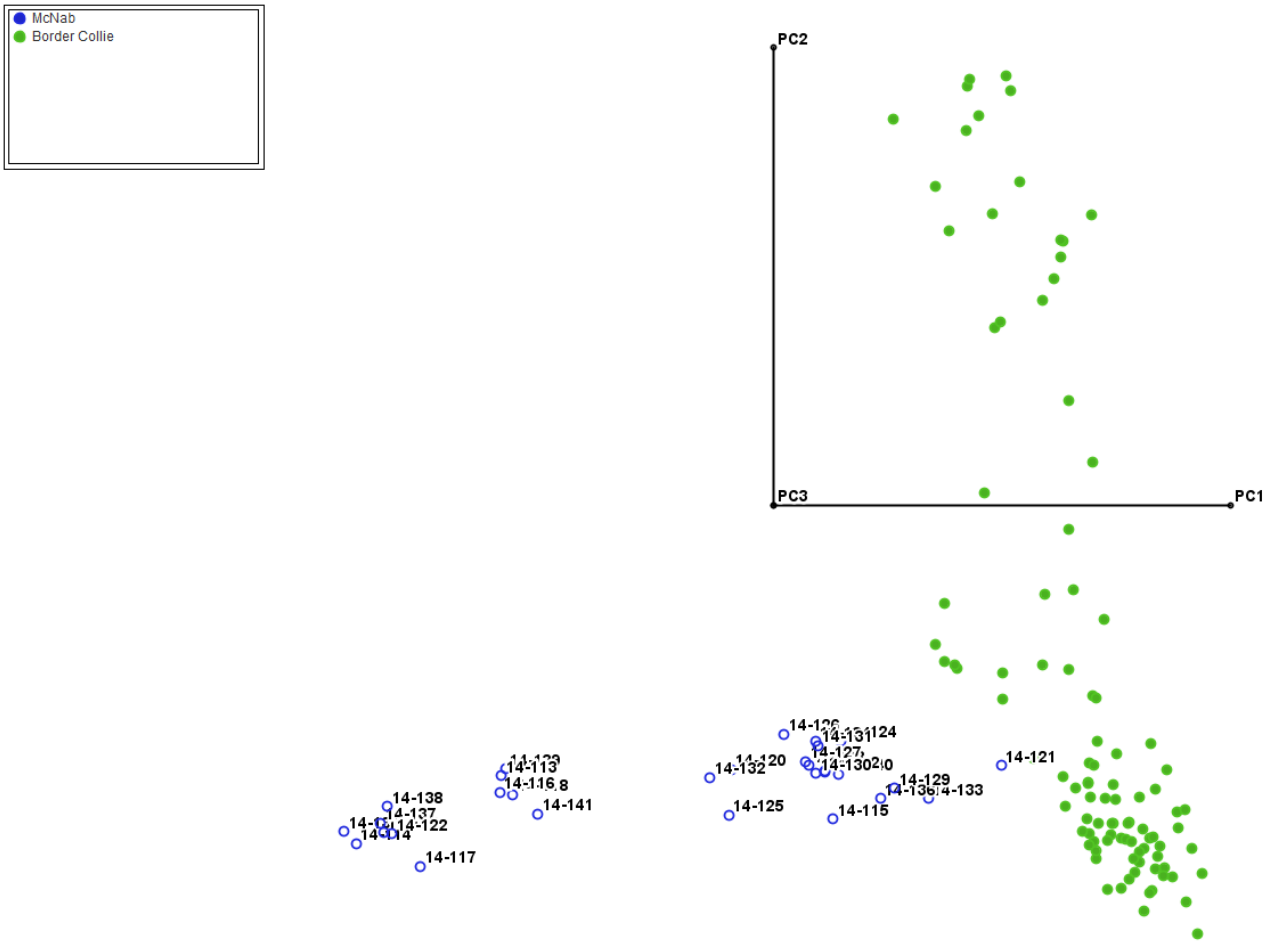

Figure 4: PCA Comparison of McNab against Border Collie

Figure 5 includes the second most common breed matched, the Koolie. This PCA pulls out another two samples (14-131 and 14-134) closer to the Koolie cluster though it seems to maintain the family subclusters identified in Figure 4 above.

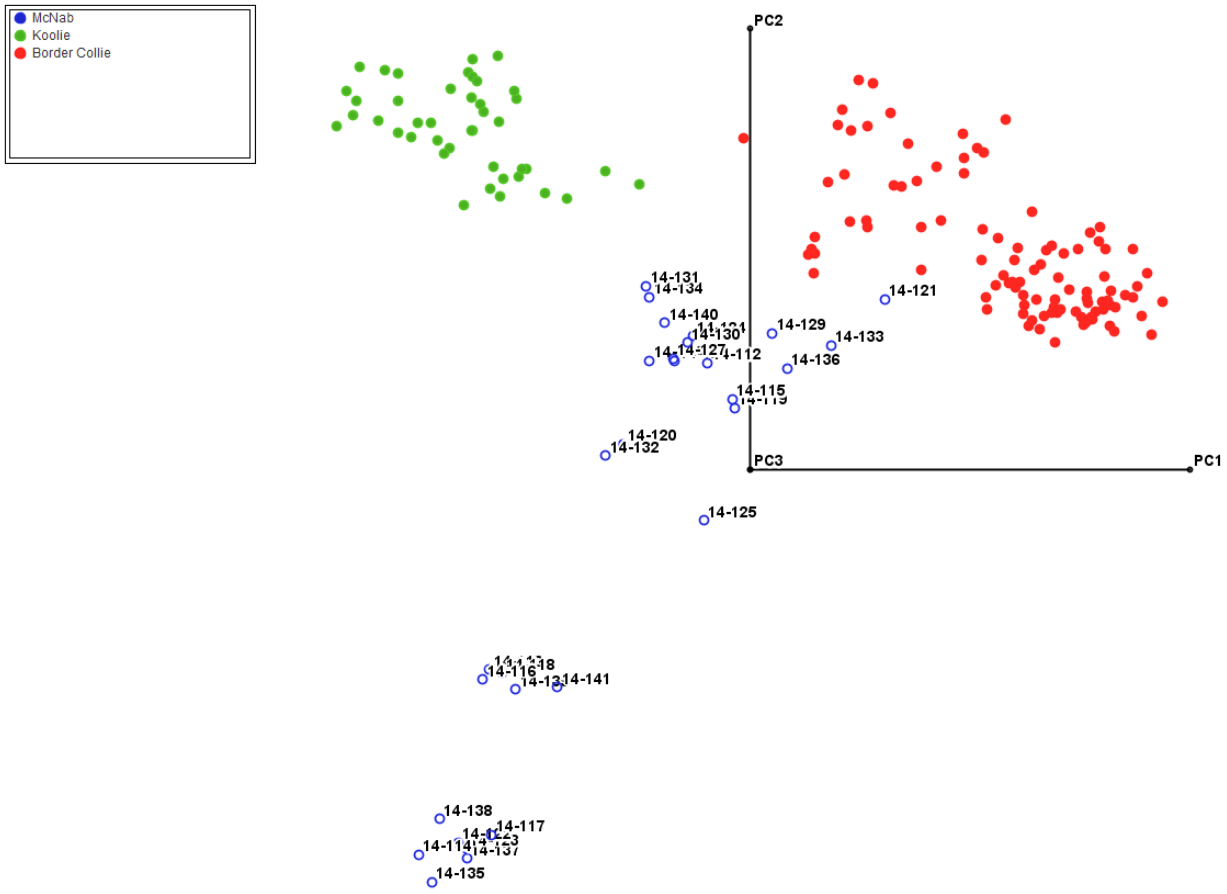

Figure 5: PCA Comparison of McNab against Border Collie and Koolie

Figure 6 shows that the Collie is distinct from the other breeds in the PCA, including the McNab.

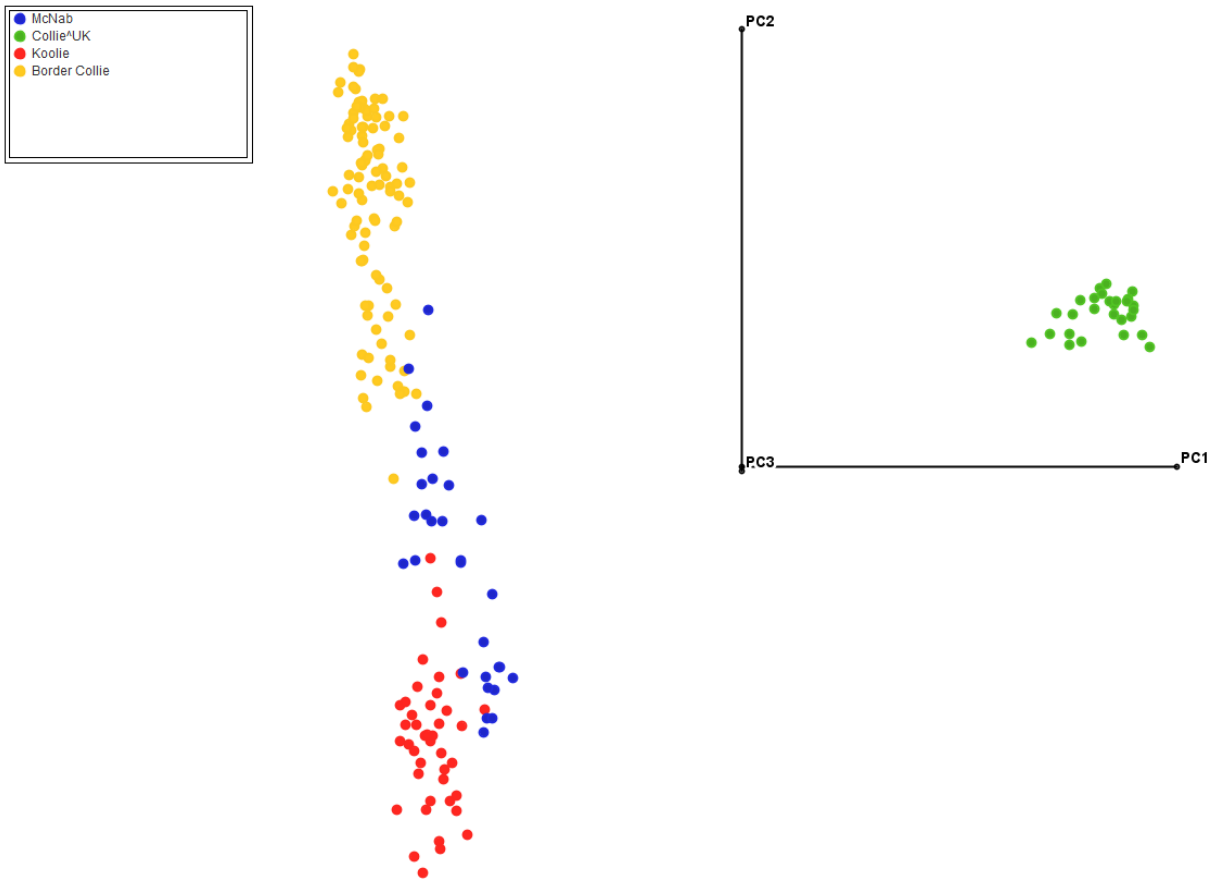

Figure 6: PCA Comparison of McNab against Border Collie, Collie, and Koolie

When the Australian Kelpie is included in the PCA, it shows more of a similarity to the Koolie than either the McNab or Border Collie as seen in Figure 7. Again the McNab samples are separating into the different family subclusters.

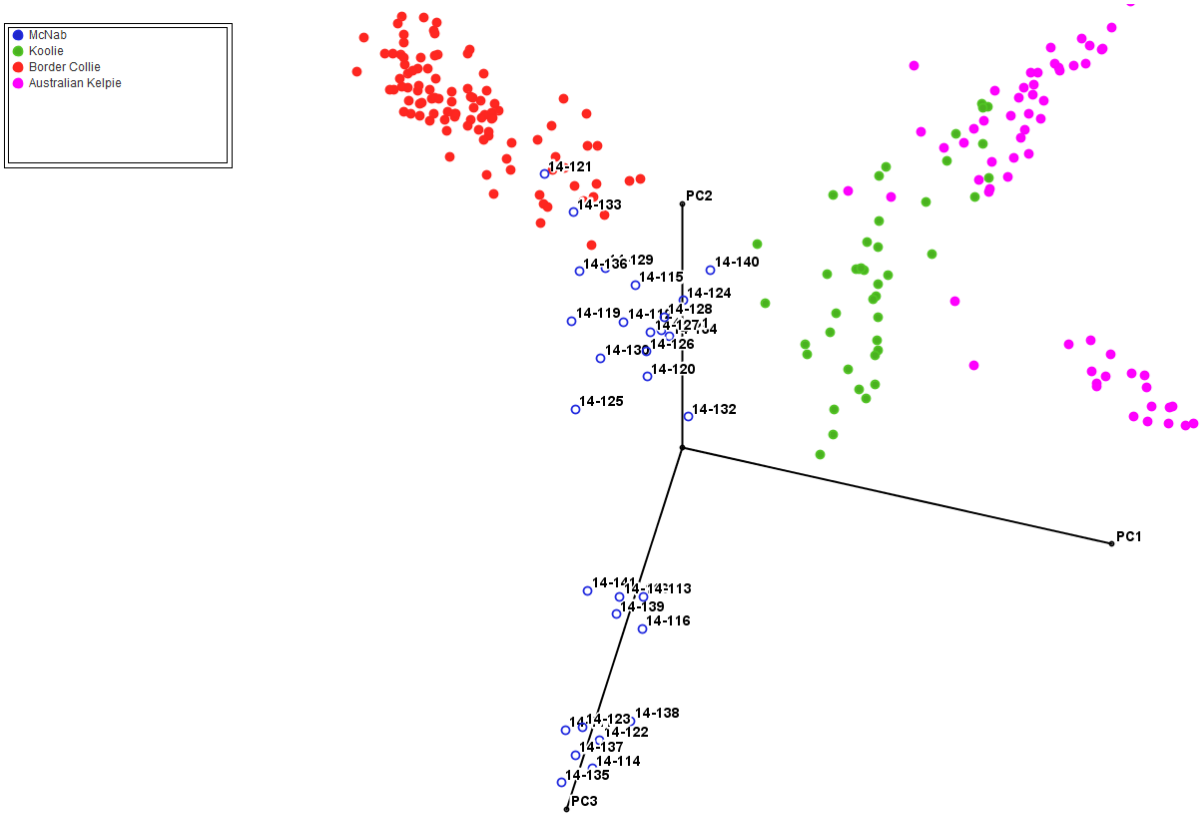

Figure 7: PCA Comparison of McNab against Border Collie, Koolie, and Australian Kelpie

Disease Mutation Prevalence

All samples were screened for 107 genetic diseases except for sample 14-115 (90% CR) and 14-304 (73% CR) as they were below the 95% call rate threshold for disease testing, at which point it is more likely to see false positive calls. These results are in Table 2 below.

Mutation Name	Dog Sample ID										Mode of Inheritance
	14-120	14-122	14-123	14-138	14-116	14-117	14-125	14-141	14-127	14-133	
Bobtail	1	1	1	1	1	0	0	0	0	0	dominant
Primary Lens Luxation, (PLL)	0	0	0	0	0	1	1	1	0	0	recessive but may also affect some heterozygotes
Multi-Drug Resistance 1, (MDR1)	0	0	0	0	0	1	0	0	0	0	dominant
Degenerative Myelopathy, (DM)	0	0	0	0	0	0	0	0	1	0	recessive
Hereditary Footpad Hyperkeratosis, (HFH)	0	0	0	0	fail	0	0	0	0	0	recessive

Table 2: Number of consensus copies of disease mutations detected in McNabs by sample.

There are a couple of mutations here which may cause issues in the breed if unchecked. The bobtail mutation produces a shorter tail in animals; if one copy is inherited, the physical expression of the mutation is visible to the naked eye. However, if a dog inherits two copies, then this is often fatal before birth (resulting in smaller litter sizes) or may have clinical impacts if the puppy survives to birth. If two bobtailed dogs are bred, each puppy in the litter has a 25% chance of inheriting two copies of the bobtail mutation, so it is best to avoid breeding two bobtailed dogs together.

The multi drug resistance 1 (MDR1) mutation is detected in many herding breeds, and only one copy of the mutation is necessary for a dog to experience drug sensitivity and adverse effects to several common medications used in veterinary medicine. An affected dog will appear clinically normal until it is exposed to any of the specific medications that are known to use the pump which is impacted by the mutation. Research done by Dr. Katrina Mealey at Washington State University (WSU) has identified that this mutation has a fairly high prevalence in the McNab breed. Of the McNab samples submitted to her, 30% have been found to be affected. When developing our assay for the MDR1 mutation, we worked directly with Dr. Mealey, actually licensing this test from Washington State University as it is patented. Interestingly, of the 29 dogs tested for disease markers, we found only one dog (3.4%) had the mutation. Though our test was performed on a relatively small sampling (n=29) of McNabs, the finding suggests that the MDR1 mutation may not be as prevalent in the population as previously documented.

It is worth noting however, that many of the samples tested at WSU are tested after the dog exhibits adverse drug reactions, and thus the difference may not be a surprising finding but rather an indication of two sample populations: suspected clinical cases vs. general population samples. To learn more about MDR1, please see the Appendix.

The primary lens luxation (PLL) mutation affects many dog breeds including terriers and Australian Cattle Dogs. Three of the McNabs were found to carry the mutation. It is not yet known if the PLL mutation is clinically significant in the McNab. However, though the condition is a recessive one, requiring a dog inherit two copies of the mutation, the condition has incomplete penetrance and carriers (those with only one copy of the mutation) may be affected, and exhibit luxating ocular lenses. Therefore, it would be a good idea to be aware of the condition and monitor with a veterinarian as needed.

The degenerative myelopathy mutation is quite common across a wide variety of breeds but has been found to be clinically significant in a small number of breeds which carry it. This suggests that there are likely additional genetic and/or environmental factors involved in the expression of this mutation, thus additional follow-up would be required to understand the clinical significance of this finding in the McNab breed. It is worth noting that two of the main breeds in which degenerative myelopathy is known to cause clinical signs are of the herding family: the German Shepherd and Pembroke Welsh Corgi.

Though none of the dogs tested were positive for hereditary footpad hyperkeratosis, one of the dogs (14-116) failed to yield a result for this mutation. Individual markers may fail on occasion and a rerun is necessary to establish the status for the single marker in this individual dog. However, based on the breeds in which this condition has been previously found (Irish Terrier and Kromfohrländer), and the lack of any positive findings for this mutation in any of the other tested McNabs, it is unlikely that this mutation is found in the McNab breed.

Trait Prevalence

All samples were assessed for various traits governing physical phenotype, including coat color, coat length, and morphology. Multiple traits were found to be “fixed” (homozygous) across all individuals. The result of the findings for the 30 successful samples investigated for these trait markers are found below.

Gene Name	Allele	Short Description	# of Copies of the Allele			Allele Frequency	# of Samples with No Call
			0	1	2		
ASIP	A^y	Sable	25	5	0	0.08	0
ASIP	a^t	Tan points	4	13	10	0.61	3
ASIP	a	Recessive black	17	11	0	0.20	2
TYRP1	b^c	Liver	28	2	0	0.03	0
TYRP1	b^s	Liver	15	12	0	0.22	3
MC1R	E^m	Melanistic mask	17	8	3	0.25	2
MC1R	E^g	Grizzle	27	3	0	0.05	0
MC1R	e	Clear red/yellow	28	0	0	0	2
CBD103	k^y	Recessive non-black	9	18	3	0.40	0
MITF	s^p	Piebald/white spotting	24	4	0	0.07	2
PSMB7	H	Harlequin	28	0	0	0.00	2
RALY		Saddle tan	9	16	5	0.43	0
Skull shape		Brachycephaly	27	1	0	0.02	2
KRT71		Curly coat	28	0	0	0	2
Ear morphology		Prick ear carriage	0	0	28	1	2
FGF5		Long coat	22	5	0	0.09	3
IGF1		Small size	22	4	2	0.14	2
IGF1R		Small size (<10")	28	0	0	0	2

Table 3: Trait allelic frequencies in 30 McNabs.

It is worth noting that in some cases a dog may carry a variant but not express it. Generally, this is because of the recessive versus dominant nature of genes as well as the interaction of various different genes, such that one gene will dictate what a separate gene location expresses. As an example, a dog may carry the liver/chocolate color allele found on the B locus but have a black coat. As the black variant is dominant to the recessive liver variant, a dog with even a single copy of the black gene variant will be black and the liver variant will not be expressed. However, if this dog is bred with another dog that is either chocolate or carries chocolate, some of the puppies could be chocolate. Table 4 highlights some of the gene variants, and the dominance hierarchy for the expression of the variants in each series, that are responsible for coat colors and patterns in dogs. Not all mutations responsible for physical features have yet been described while some others (such as merle and dilute) are not presently part of the panel.

Trait	Variants, in descending order of dominance	Comments
Extension (E locus)	$E^m>E^g>E>e$	Determines which areas of the coat show eumelanin vs. which areas show phaeomelanin (red/yellow/tan).
Dominant Black (K locus)	$K^B>k^{br}>k^y$	Currently, the test doesn't distinguish between K^B and k^{br} (brindle). One copy of K^B will prevent any brindling.
Agouti (A locus)	$A^y>a^w>a^t>a$	Controls where eumelanin is expressed in the coat.
Black/Brown (B locus)	$B > b^c, b^s, b^d$	Determines if eumelanin is black or chocolate/liver/brown. Presently cannot test for b^d.
White Spotting (S locus)	$S>s^p$	Determines if the skin cell produces any pigment.
Harlequin (H locus)	H>h	Modifies the merle gene and makes the diluted areas white.
Saddle Tan Pattern (*RALY* gene)	no copy, one copy, two copy	Defines whether tan points or saddle tan is expressed.

Table 4: Subset of genes responsible for coat colors and patterns and their dominance hierarchies.

Genetic Diversity Assessment

We investigated the diversity of individuals using genotype homozygosity. This metric is defined as the ratio of markers that are homozygous (identical) for the copies of both alleles, inherited from sire and dam. Low homozygosity represents high diversity of individuals and vice versa.

The histogram in Figure 8 shows homozygosity on the horizontal (y) axis, with the relative number, or proportion, of individuals who have this diversity level on vertical (x) axis. The less diverse the dog, the farther right on the axis the dog will fall. Most mixed-breed dogs have a homozygosity below 0.59 on this scale; purebred dogs are generally above that so the McNabs are very diverse in comparison to many pure breeds and have a profile that more closely resembles that of the average mixed breed dog population. For comparison purposes, we have graphed the McNab's homozygosity profile against that of the closest breed, the Border Collie.

When the breed population is closed, we would generally see a tendency for the homozygosity to increase slightly and form more of a distribution around a central point (like seen in the Border Collie).

The higher per sample homozygosities of 72% (14-117) and 68% (14-131) are outside the usual distribution of homozygosity for the McNab and may indicate accidental or intentional linebreeding. Although this makes fixing “type” (such as physical characteristics) easier, it also gives a higher potential for recessive disorders or traits to appear more frequently.

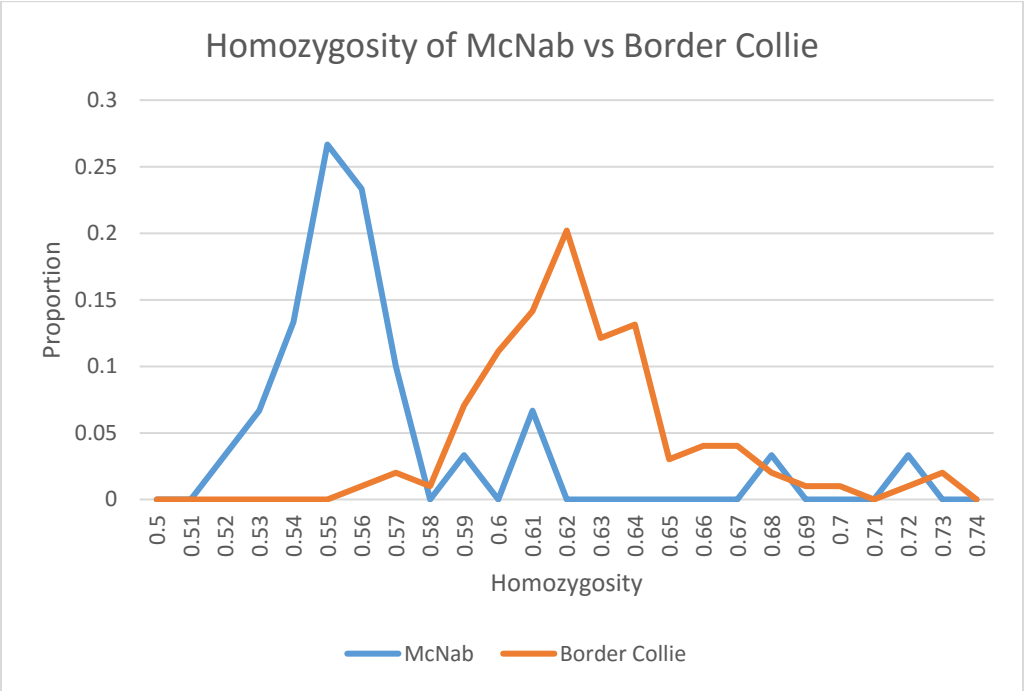

Figure 8: Diversity of McNab vs Border Collie

The average homozygosity for all McNab Dog samples was 56.78%, this places it as the least homozygous breed we have evaluated to date, as seen in Figure 9.

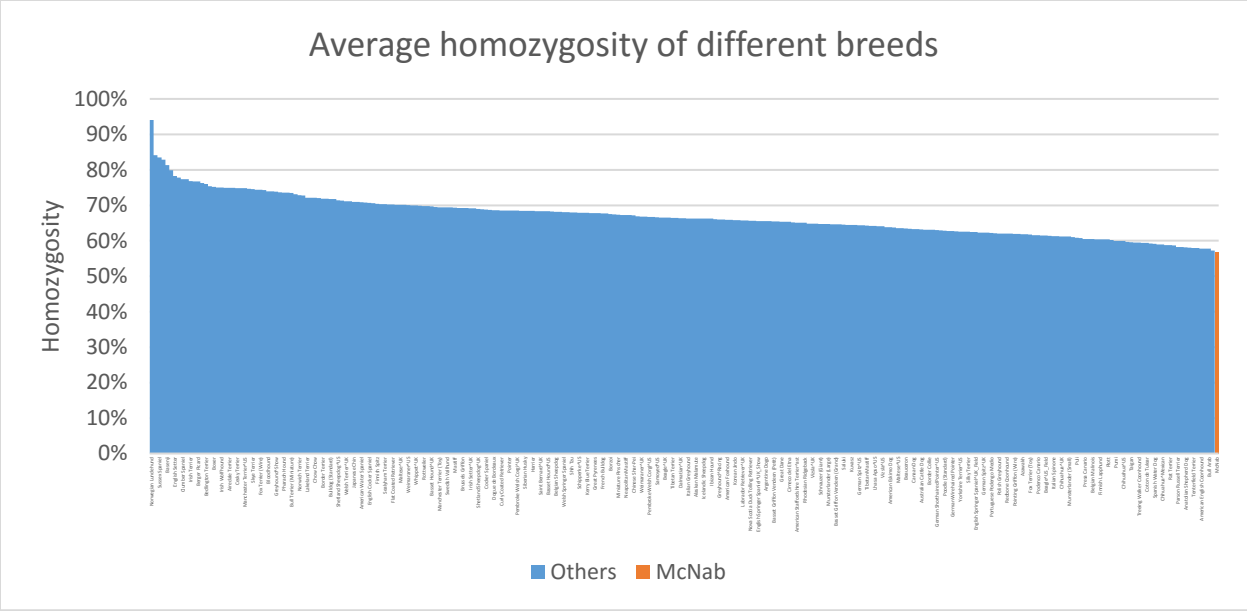

Figure 9: Average homozygosity levels of various breeds

Conclusions

Our analysis of the McNab samples shows that they appear to be a distinct breed, though they have clear ties to herding breeds and the Border Collie in particular. They cluster close together as expected from a breed in the PCA plots as well as in the clustering analysis. There is evidence to support some subclustering within the breed that is likely related to family lines and breeder preferences. As more McNabs are analyzed in the future, we may see the breed's signature shift as the breed's type becomes more fixed.

From a health perspective, the breed appears to be relatively healthy. Overall few carriers or affected dogs were found to have any of the 100+ genetic diseases for which they were tested. The mutations that were observed have low frequencies within the tested population, though it is something to stay vigilant about. Further, there may be more avenues to investigate potential health issues in the breed and determine the clinical significance of some of the mutations that were identified. Lastly, it is worth noting that though the test performed is robust, additional genetic conditions which are not included in the panel or for which a mutation has yet to be found could exist in the McNab. Therefore, the list of potential genetic conditions listed herein should not be considered exclusive.

With regards to diversity, the analysis shows that the breed appears to be quite diverse. Given the high degree of diversity seen in the McNabs tested in this study, it is possible that the representative

population tested does not account for all the phenotypes that occur in the breed. As more dogs are tested, we may find that these individuals carry trait alleles not reported in this study. Additionally, the diversity in the breed is a good thing given it maintains many genetic variants in the populations; we would expect the homozygosity to increase slightly as the breed matures. The analysis also provided evidence of potential backcrossing. This is generally not advisable as it increases the chance of seeing rare mutations in the offspring, and could also negatively impact litter size. Use of pedigree analysis, determination of inbreeding coefficients, or the use of tools such as the Optimal Selection™ Canine Genetic Breeding Analysis can provide valuable information which, when paired with performance and type information, can help preserve and promote a breed's genetic health and integrity while producing quality McNabs who both perform well in the field and fit the breed's standard..

APPENDIX

Multidrug Resistance 1 (MDR1) or Ivermectin Sensitivity

In Brief

Multidrug resistance 1 (MDR1) is a genetic mutation that alters a dog's ability to limit the absorption and distribution of many drugs. Affected dogs are slower to eliminate drugs from the body and can suffer side effects when exposed to certain medications. This mutation is sometimes also called "ivermectin sensitivity." However, the name is a misnomer as several other drugs pose a risk to MDR1 positive dogs. Adverse reactions can occur when affected dogs are exposed to some common drugs such as acepromazine, butorphanol, and macrocyclic lactones. However, all FDA approved heartworm preventatives are safe to administer to MDR1 positive dogs. This mutation is inherited in a dominant fashion though dogs with two copies of the mutation will exhibit more severe clinical signs than dogs who only have one.

Clinical Overview

Dogs that carry this mutation are asymptomatic until they are exposed to a medication that uses the pump that is rendered defective by the mutation in the ABCB1 (MDR1) gene. Drugs known to use this P-glycoprotein pump are macrocyclic lactones (antiparasitic drugs), loperamide (antidiarrheal), erythromycin (antibiotic), acepromazine (tranquilizer), butorphanol (opioid), and certain drugs used in cancer treatment (vincristine, vinblastine, and doxorubicin). When these medications are administered, they accumulate in the brain which in turn results in the clinical signs of the adverse reaction. Typical clinical signs include tremors, loss of balance, seizures, decreased alertness, excessive salivation, dilated pupils, and slow heartrate. If untreated, the condition may lead to respiratory arrest, coma, or death. However, all FDA approved heartworm preventatives are safe to administer to MDR1 positive dogs.

The condition is inherited in an autosomal dominant manner. Dogs with a single mutated MDR1 gene will have reduced P-glycoprotein function while dogs with two mutated copies of the gene will lack any function of this important intracellular pump. Because of the codominant pattern of expression, the most severe cases tend to occur in dogs that are homozygous for the mutation (carry two mutated copies) because they lack any functional P-glycoprotein pumps. However, the condition can be very severe even in dogs that have only one copy of the mutation as they will still show some clinical signs

upon exposure to certain drugs. Though the mutation was originally identified in Collie-related breeds, it has been found in a variety of mixed-breed dogs and thus testing of all dogs is recommended.

References

Online database

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Scientific articles

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