Genetic Diversity Testing for Doberman Pinchers

Overview

The Veterinary Genetics Laboratory (VGL), in collaboration with Dr. Niels C. Pedersen and staff, has developed a panel of short tandem repeat (STR) markers that will determine genetic diversity across the genome and in the Dog Leukocyte Antigen (DLA) class I and II regions. This test panel will be useful to breeders who wish to track and increase genetic diversity of their breed as a long term goal.

Genetic diversity testing of Doberman Pinschers is now in the preliminary results phase. During this phase, we continue to test more registered dogs to build genetic data necessary to provide breeders with an accurate assessment of genetic diversity in their breed. We are accepting Doberman Pinscher from the USA and Canada, as well as Dobermann from other regions of the world. We are especially interested in testing more Dobermann from Western and Eastern Europe. We have currently tested over 233 Dobermans. To avoid confusion, the whole group will be referred to as Doberman Pinschers or Doberman. The name Dobermann will be used in discussions of the breed history to designate dogs that are mostly German (European) in origin. The results are listed below.

**Price: $80**
Price reduced to $70 when combined with a diagnostic test.

**ORDER TEST KITS**
Allow 5-10 business days for results.

**Results reported as:**
Short tandem repeat (STR) loci: A total of 33 STR loci from across the genome were used to gauge genetic diversity within an individual and across the breed. The alleles inherited from each parent are displayed graphically to highlight heterozygosity, and breed-wide allele frequency is provided.

DLA haplotypes: STR loci linked to the DLA class I and II genes were used to identify genetic differences in regions regulating immune responses and self/non-self recognition. Problems with self/non-self recognition, along with non-genetic factors in the environment, are responsible for autoimmune disease.

Internal Relatedness: The IR value is a measure of genetic diversity within an individual that takes into consideration both heterozygosity of alleles at each STR loci and their relative frequency in the population. Therefore, IR values heterozygosity over homozygosity and uncommon alleles over common alleles. IR values are unique to each dog and cannot be compared between dogs. Two dogs may have identical IR values but with very different genetic makeups.

## I. Introduction

The history of the Dobermann and Doberman pinscher is similar to many breeds originating in the Victorian era. Breed histories usually start with an individual who decides to create a type of dog to fits a specific need or desire. This person may be a dog breeder or a relative novice. The proto-breed then catches the fancy of a key dog breeder or breeders who see great value in fostering and refining (standardizing) this proto-breed to a point where it becomes accepted (registered). At this point, the breed is closed to further genetic introgressions from outside the original registry. Many of these new breeds had their origin in Europe, where they persist to this day or have disappeared. The more popular ones will find their way to distant lands where they will often continue to evolve, but sometimes along different paths. Geographic isolation, and in particular philosophical differences between old-world and new-world breeders, has frequently led to subtle differences in breed phenotype and therefore genotype.

The exact ancestry of a breed can vary greatly depending on whose version of the proto-breed's origin and subsequent standardization is believed. Such is the history of the Dobermann Pinscher. Doberman Pinschers were first bred in the town of Apolda, in the German state of Thuringia around 1890 by Karl Friedrich Louis Dobermann. Dobermann served in the dangerous roles of local tax collector, dogcatcher/skinner, and night watchman. Dobermann used dogs from this area to create what he thought would be the perfect dog to help protect people doing his types of work. There appears to be agreement on this part of the breed's origin, but the story on the type of dogs used to create the Dobermann is somewhat less clear. The best account of the origins and evolution of the Doberman breed in Germany can be found in the writings of Phillip Gruenig, who referred to himself as a founding breeder and judge of Doberman (http://www.blitzkrieger.com/breedhistory.html). One story is that Dobermann's first mating involved a black bitch named Bismark (Bissart) and a clever and fearless grey smooth-coated mongrel named Schnupp. An article from 1898 stated the owner of a local gravel pit in Apolda bred his blue-grey bitch with a black "Butcher's dog" and that Dobermann crossed these offspring with German Pinschers to create his breed. Outcrosses to other breeds undoubtedly followed, but the exact breeds vary according to the various historical accounts. The Thueringinn sheepdog, Butchers dog, German Pinscher and Beauceron existed at the time and in the locality, as did the black and tan terrier. A famous bitch whose dam was a cross between a Greyhound stud and a Doberman bitch was also registered in the early 1900s and brought greyhound attributes into the breed. Regardless of the original ancestry, Dobermann's goal was to breed dogs that would combine aggressiveness, protective behavior, loyalty, trainability, and physical prowess. He obviously succeeded directly or indirectly in this effort and a standard for the new "breed" was created by the German Kennel club in 1890.

Dobermann died in 1894 and Otto Goeller christened the "new breed" in his memory. Dobermann's new breed may or may not have been fully developed at the time of Dobermann's death. There is genereal agreement that further development was left to skilled dog breeders such as Otto Goeller, Karl Doberman, Goswin Tischler and Philip Greunig. The appearance of the breed was standardized and refined, while retaining only the "bravest, toughest, and most loyal dogs." Goeller created the National Dobermann Pinscher Club in Germany in 1899 and was influential in writing the first breed standard. The name Pinscher (terrier in German) was later dropped after 1949 by the Germans and the British as it was not appropriate for the breed. The

Dobermann breed was first registered with the American Kennel Club in 1908 as the Doberman Pinscher, but it was not until 1921 that more than 100 individuals were registered each year. The breed's popularity in the USA increased dramatically after the end of WWII, when soldiers brought back their Dobermanns from Germany. The Doberman Pinscher was the 12th most popular dog breed in the USA in 2012 and 2013.

These original Dobermann were of medium size, compact build, muscular, and extremely loyal and distrustful of unfamiliar people. They became known for their keen ability to hunt and kill vermin. This aggressiveness often extended to other dogs and people and this behavior has been often referred to as "sharp." However, as Dobermans became more popular in Germany and other parts of Europe, this temperament was throttled back to make them more suitable as pets. Most of this sharpness has been eliminated from contemporary US Doberman Pinschers. This sharp nature was put to good use by the German military in WWI and by all militaries of WWII.

Two major genetic bottlenecks occurred in Germany and Europe as the results of WWI and WWII. The period between 1914-1918 saw a great decline in the breed and a small number of dogs played a major role in re-establishing the breed in Germany. One sire, Burschel v. Simmenau was credited by Gruenig as proving that one individual dog of this stature can redeem an entire breed (http://www.blitzkrieger.com/breedhistory.html.) The German Dobermann flourished after WWI and many champions were proclaimed, some of which had great genetic influence on subsequent generations. Many champion Dobermanns were exported from Germany during 1920's, including to countries as distant as the USA and the USSR.

The breed in Germany underwent an even more severe genetic bottleneck as the result of WWII and its aftermath, and no litters were registered in West Germany from 1949 to 1958 (https://en.wikipedia.org/wiki/Doberman_Pinscher). German Dobermanns were saved by Werner Jung, who searched farms throughout Germany for remaining breeding stock. Preferring to use native dogs, Jung used Dobermanns he found in the countryside of West Germany, 4 oversized Miniature Pinschers, and a black and red Doberman bitch smuggled from East Germany to re-establish the "original" breed. It is possible that introgressions with other breeds occurred during this time.

The Doberman pinscher of the USA has its origins firmly in Europe, but geographic isolation and differences in breeding objectives and standards have led to what are essentially two different varieties. The European Doberman pinscher is larger, more uniform in size, and heavier boned, while the American Doberman pinscher is much more variable in size. The German Dobermann has been bred more for personal (guard) protection and police/military work, with less emphasis on showing. European breeders adhere more strictly to the original German standards, while standards are more loosely defined in America. A sudden increase in the breed's popularity in the USA in the 1970s resulted in a rapid increase in the number of dogs needed to meet demand, resulting in more indiscriminate breeding and greater variations in size, color and appearance. The creations of varieties of the same breed are best exemplified by the American and Japanese Akitas or the American and European Italian Greyhounds. Comparisons of European Dobermann and American Doberman Pinschers can be found at several websites:

1) http://www.blitzkrieger.com/breedhistory.html
2) https://www.youtube.com/watch?v=-UXD6o-nLDg
3) https://doberman-chat.com/threads/american-vs-european-doberman.6991/
4) http://www.dobermanblog.com/american-vs-european-doberman/

**II. Genetic diversity studies of contemporary Doberman**

**A. Population genetics based on 33 STR loci on 25 chromosomes**

STR markers are highly polymorphic and have great power to determine genetic differences among individuals and breeds. The routine test panel contains 33 STRs consisting of those that are recommended for universal parentage determination for domestic dogs by the International Society of Animal Genetics (ISAG) and additional markers developed by the VGL for forensic purposes. Each of these STR loci is known to contain from 7 to 27 different alleles when tested across many breeds of dogs. Each breed, having evolved from a small number of founders and having been exposed to artificial genetic bottlenecks will end up with only a portion of the total available diversity. Artificial genetic bottlenecks include such things as popular sire effects, geographic isolation, catastrophes, outbreaks of disease, and ups and downs in popularity and resulting increases and decreases in population size. The alleles identified at each of the 33 STR loci and their relative frequencies were determined for 218 Doberman from around the world and listed in Table 1.

**Table 1 link**

**B. Assessment of population diversity using standard genetic parameters**

Allele and allele frequencies were used to determine basic genetic parameters such as the number of alleles found at each STR locus (Na); the number of effective alleles (Ne) per locus, i.e., the number of alleles that contribute most to genetic differences; the observed or actual heterozygosity (Ho) that was found; and the heterozygosity that would be expected (He) if the existing population is in Hardy Weinberg equilibrium (HWE). HWE is achieved when the selection of mates is entirely random and subject to no positive or negative human selection pressure. The value F is a coefficient of inbreeding derived from the Ho and He values. A value of +1.0 would occur only if every individual were genetically indistinguishable at each of the 33 STR loci, while a value of -1.0 would be seen when all of the dogs were completely different at each of the 33 loci.

The allele frequency data obtained from the 33 STR panels can also be used to assess heterozygosity within a population (Table 2). Using the 33-marker panel, the 521 Doberman Pinschers had an average of 7.30 alleles/loci (Na). However, the average number of alleles is less important than the number of alleles that have the greatest effect on heterozygosity, a figure known as average effective alleles/loci or Ne. The Ne in this group of dogs averaged 2.31 effective alleles per locus, indicating that Doberman lack genetic diversity. The observed heterozygosity (Ho) across the 218 Doberman was 0.457, while the expected heterozygosity (He) was 0.501, yielding a coefficient of inbreeding (F) of +0.087. A positive F value of 0.087

indicates an 8.7% excess in population-wide homozygosity over what would be expected for a random breeding population.

Table 2. Standard Genetic assessment of 521 Doberman using allele and allele frequencies from 33 STRs on 25 of 39 canine autosomes.

| | | N | Na | Ne | Ho | He | F |
|---|---|---|---|---|---|---|---|
| Doberman Pinscher | **Mean** | 521 | 7.303 | 2.306 | 0.457 | 0.501 | 0.087 |
| | **SE** | | 0.349 | 0.142 | 0.032 | 0.035 | 0.011 |

**C. Standard genetic assessment values for individual STR loci**

The allele frequencies can be also used to do a standard genetic assessment of heterozygosity at each STR locus (Table 3). This provides an estimate of genetic similarities in the specific regions of the genome that are associated with each STR marker. Phenotypic differences equate to genotypic differences. Therefore, alleles that are widely shared across the population are indicators that positive selection is occurring for certain desired traits. Twenty nine of the 33 STR loci had positive F values, which could only occur if traits associated with each locus (i.e., region of the genome) were under a degree of positive rather than random or negative selection. All Doberman are closely related when this is coupled with a small pool of widely distributed breeding dogs, breeders may find it difficult to identify and access the most unrelated mates.

The Na values for an individual STR locus for this population of 521 Doberman Pinschers ranged from a low of 4 to a high of 12 alleles on average per locus, while the Ne ranged from 1.098 to 3.95 alleles per locus. The fact that one-fourth to one-half of the alleles were contributing to most of the genetic diversity is indicative of the large genetic contribution of a small proportion of founders. The observed heterozygosity (Ho) for an individual STR locus ranged from 0.055 to 0.683, while He ranged from 0.058 to 0.749 (Table 3). Thirty-one loci had positive F values and only one had a negative value. Alleles at 9 loci with high F values (> 0.100) were contributing an inordinately high proportion of genetic diversity, indicating that certain regions of the genome (and certain dogs with those alleles) were under deliberate or inadvertent positive selection (i.e., non-random) selection.

Table 3. Standard genetic assessment of Doberman (n=521) based on the number and frequency of alleles at each of the STR 33 loci

| # | Locus | N | Na | Ne | Ho | He | F |
|---|---|---|---|---|---|---|---|
| **1** | **AHT121** | 521 | 7 | 1.488 | 0.298 | 0.328 | 0.092 |
| **2** | **AHT137** | 521 | 9 | 2.559 | 0.605 | 0.609 | 0.008 |
| **3** | **AHTH130** | 521 | 8 | 1.835 | 0.422 | 0.455 | 0.072 |
| **4** | **AHTh171-A** | 521 | 7 | 2.238 | 0.502 | 0.553 | 0.093 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **5** | **AHTh260** | 521 | 7 | 1.297 | 0.225 | 0.229 | 0.019 |
| **6** | **AHTk211** | 521 | 6 | 1.278 | 0.206 | 0.217 | 0.053 |
| **7** | **AHTk253** | 521 | 5 | 1.780 | 0.279 | 0.438 | 0.364 |
| **8** | **C22.279** | 521 | 7 | 3.740 | 0.625 | 0.733 | 0.147 |
| **9** | **FH2001** | 521 | 5 | 1.098 | 0.081 | 0.089 | 0.095 |
| **10** | **FH2054** | 521 | 7 | 1.798 | 0.412 | 0.444 | 0.073 |
| **11** | **FH2848** | 521 | 7 | 1.079 | 0.060 | 0.073 | 0.186 |
| **12** | **INRA21** | 521 | 4 | 1.358 | 0.267 | 0.263 | -0.015 |
| **13** | **INU005** | 521 | 5 | 2.960 | 0.642 | 0.662 | 0.030 |
| **14** | **INU030** | 521 | 4 | 2.346 | 0.571 | 0.574 | 0.004 |
| **15** | **INU055** | 521 | 6 | 2.680 | 0.548 | 0.627 | 0.126 |
| **16** | **LEI004** | 521 | 5 | 1.928 | 0.438 | 0.481 | 0.089 |
| **17** | **REN105L03** | 521 | 8 | 1.114 | 0.094 | 0.102 | 0.078 |
| **18** | **REN162C04** | 521 | 9 | 2.333 | 0.521 | 0.571 | 0.088 |
| **19** | **REN169D01** | 521 | 7 | 3.951 | 0.643 | 0.747 | 0.139 |
| **20** | **REN169O18** | 521 | 7 | 2.830 | 0.562 | 0.647 | 0.130 |
| **21** | **REN247M23** | 521 | 4 | 1.252 | 0.188 | 0.201 | 0.065 |
| **22** | **REN54P11** | 521 | 7 | 2.507 | 0.546 | 0.601 | 0.091 |
| **23** | **REN64E19** | 521 | 7 | 2.359 | 0.517 | 0.576 | 0.102 |
| **24** | **VGL0760** | 521 | 9 | 3.943 | 0.690 | 0.746 | 0.075 |
| **25** | **VGL0910** | 521 | 10 | 1.808 | 0.408 | 0.447 | 0.088 |
| **26** | **VGL1063** | 521 | 11 | 2.929 | 0.596 | 0.659 | 0.095 |
| **27** | **VGL1165** | 521 | 11 | 2.708 | 0.565 | 0.631 | 0.104 |
| **28** | **VGL1828** | 521 | 8 | 2.304 | 0.550 | 0.566 | 0.028 |
| **29** | **VGL2009** | 521 | 7 | 2.904 | 0.617 | 0.656 | 0.058 |
| **30** | **VGL2409** | 521 | 8 | 3.451 | 0.631 | 0.710 | 0.112 |
| **31** | **VGL2918** | 521 | 12 | 2.885 | 0.588 | 0.653 | 0.099 |
| **32** | **VGL3008** | 521 | 10 | 2.259 | 0.556 | 0.557 | 0.003 |
| **33** | **VGL3235** | 521 | 7 | 3.085 | 0.625 | 0.676 | 0.075 |

**C. Internal relatedness (IR) of individuals and the population as a whole**

***1. IR testing***

Genetic assessments such as those presented in Tables 1 to 3 are indicators of population-wide heterozygosity and do not reflect the genetic diversity being provided to individuals by their parents. Internal Relatedness (IR) is a calculation that has been used to determine the degree to which the two parents of an individual dog were related. The IR calculation takes into consideration homozygosity at each locus and gives more importance to rare and uncommon alleles. Rare and uncommon alleles would presumably be present in less related individuals. IR scores of all individuals in a population can be graphed to form a curve ranging from -1.0 to +1.0. A dog with a value of -1.0 would have parents that were totally unrelated at all 33 STR loci, while a dog with an IR value of +1.0 has parents that were genetically identical at all loci. An IR value of +0.25 would be found among offspring of full sibling parents from a random breeding population. IR values >0.25 occur when the parents of the full sibling parents were themselves highly inbred. The higher the IR value above 0.25 the more closely related were the parents and grandparents of the siblings.

A graph comparing IR values for 218 Doberman Pinschers from around the world (Fig. 1– red line) confirms that the population tested varies greatly in the degree of parental relatedness with individuals scoring as high as +0.457 and as low as -0.259 (Table 4). One half of the dogs had IR scores equal to or greater than 0.083 and one fourth of the dogs had IR scores of 0.212 or greater. An IR score of 0.25 would be seen in puppies resulting from the mating of full siblings from a randomly breeding and genetically diverse population (e.g., geographically diverse village dogs). The IR curve for Doberman is also biphasic (two overlapping peaks) with one peak close to 0.083 and a second peak near 0.212. This second peak represents the most inbred dogs in the population, and it is this population that is most responsible for the positive F values across the breed (Table 2) and in individual STR loci (Table 3).

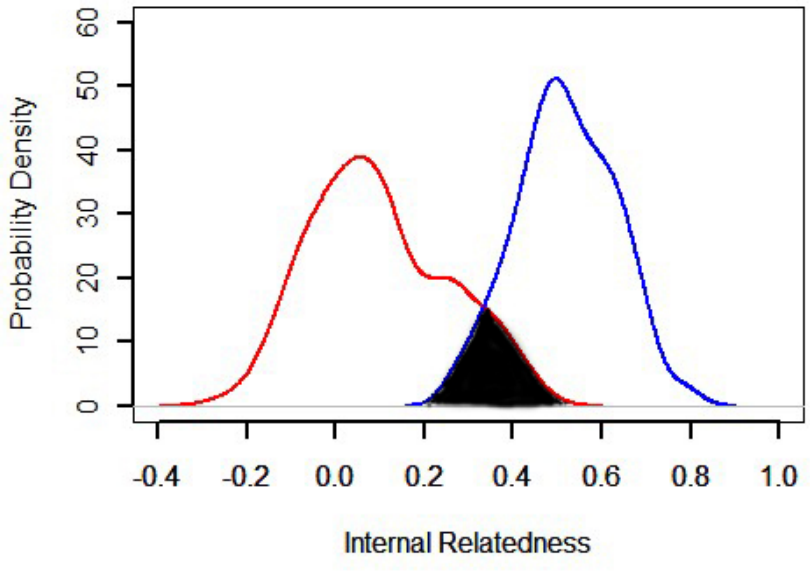


Fig. 1. Distribution of IR estimated in Doberman (n=218) based on intra-breed diversity (red line), compared with IR adjusted to diversity lost during breed development (blue line). Lost diversity was determined by comparing allele frequencies at the same loci between Doberman and village dogs from the Middle East, SE Asia, and the Islands Pacific. Village dogs were the most diverse population studied. The black part of the figure is an estimate of the genetic diversity that exists in village dogs that still exists in Doberman (15.7%).

Table 4. Statistical comparison of IR and IRVD values for 218 Doberman

| | **IR** | **IRVD** |
|---|---|---|
| **Min.** | -0.25906 | 0.2542 |
| **1st Qu** | -0.011 | 0.4358 |
| **Median** | 0.0826 | 0.5246 |
| **Mean** | 0.09639 | 0.5191 |
| **3rdQu** | 0.21185 | 0.5905 |
| **Max.** | 0.45652 | 0.7969 |

***2. Adjusted IR values (IRVD) as a measure of genetic diversity lost during breed evolution from time of origin to the present time.***

All breeds start with a relatively small population of dogs and after registries are closed there are theoretically no further introgressions from outside the breed. Therefore, the goal of breeders is to maintain the original amount of genetic diversity by strict adherence to random mate selection. However, studies have shown that most breeds 87% of their starting diversity. Genetic diversity may be lost through genetic bottlenecks such as natural disasters, loss of popularity, popular sire effects, etc. It is possible to obtain an estimate of how much of the original dog diversity a breed possesses by adjusting the alleles and their frequency to the frequency of those same alleles in a large population of village dogs from across the Middle East, SE Asia and Island Pacific. This is possible because village dogs contain far more of the original genetic diversity of dogs than any current breed and almost all modern breeds trace their ancestry to dogs from these regions. The IR values and IR values adjusted to village dogs (IRVD) can then be graphed and the graphs overlaid. If the IRVD peak overlays the IR peak, the breed has the same diversity as village dogs. If the IRVD and IR peaks are only somewhat overlapping, very little of the original genetic diversity has been retained.

The IRVD curve was shifted well to the right of the IR curve, reflecting a considerable loss of genetic diversity during breed development (Fig. 1). The peak (median) of the IRVD curve was +0.533, with some dogs as high as +0.797 and as low as +0.254 (Table 4). One half of the Doberman tested had IRVD scores equal or greater than 0.525 and one fourth had scores of 0.591or greater. The Doberman with the lowest score (i.e., most outbred) of +0.254 would be equivalent to an offspring of a full sibling parents from among random bred village dogs. In order to attain IRVD scores of +0.797, the parents of the full siblings would also have to be themselves highly inbred. Based on the amount of overlap between IR and IRVD curves, Doberman contain only a small fraction (15.7%) of the genetic diversity found in contemporary village dogs from the region considered to be the ancestral home of most modern breeds (Fig. 1).

**D. Differences in population structure as determined by principal coordinate analysis (PCoA)**

PCoA is a graphic portrayal of how closely individual dogs within a breed are related to each other. In order to show geographic variation, 218 Doberman from several different regions of the world were plotted (Fig. 2). Individual dogs were scattered across the plot with Doberman from the US and Canada (North America) forming a single diffuse population, which was somewhat unexpected given the literature on Doberman from Europe, Germany, USA and other countries. There appears to be relatively frequent introgressions between Doberman from disparate regions of the world, although there is some evidence for genetic isolation as well. Doberman from Australia tended to form a genetically distinguishable subpopulation, with the exception of a few outliers more closely related to Doberman from North America than Europe. The European Doberman, although too small in number to clearly define, also tended to clump together, but again clearly within the larger North American population. However, the genetic differences in the Australian Doberman were not of a magnitude sufficient to create a "variety", such as seen between Japanese and American Akita. A more appropriate term would be "bloodline." There were too few dogs from the other countries to determine their exact relationship, but they all tended align with dogs from the US and Canada.

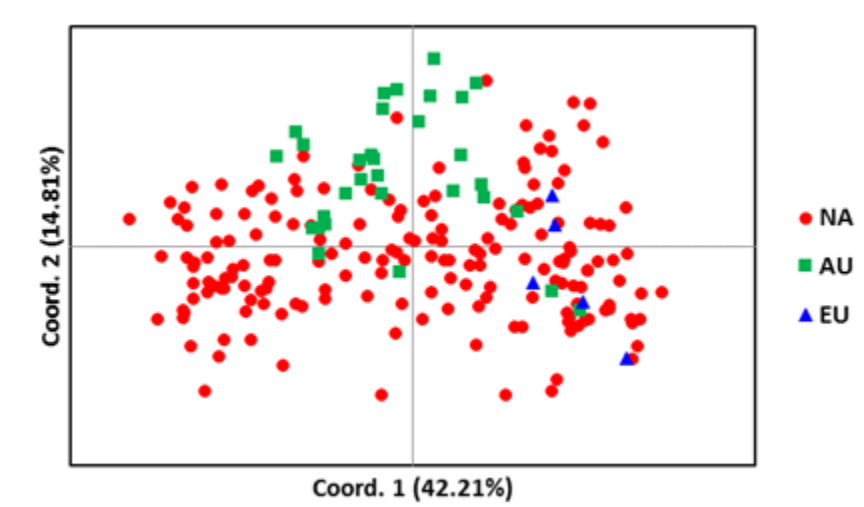



Fig. 2. PCoA of 218 Doberman based on allele and allele frequencies of the 33 STR loci. Dogs were from North America (US=174, Canada=8), Europe (EU=5), and Australia (AU=31).

The question is how much genetic difference must occur for a distinct bloodline or variety to become a breed. The answer is "quite a bit." This can be demonstrated by doing a PCoA plot between Doberman from different geographic regions and a genetically heterogeneous and phenotypically distinct breed such as the Havanese (Fig. 3). There is total segregation between the two breeds and a close relationship between individuals within each breed. Such comparisons between genetically different breeds tend to hide bloodline and variety differences in the breeds being compared.

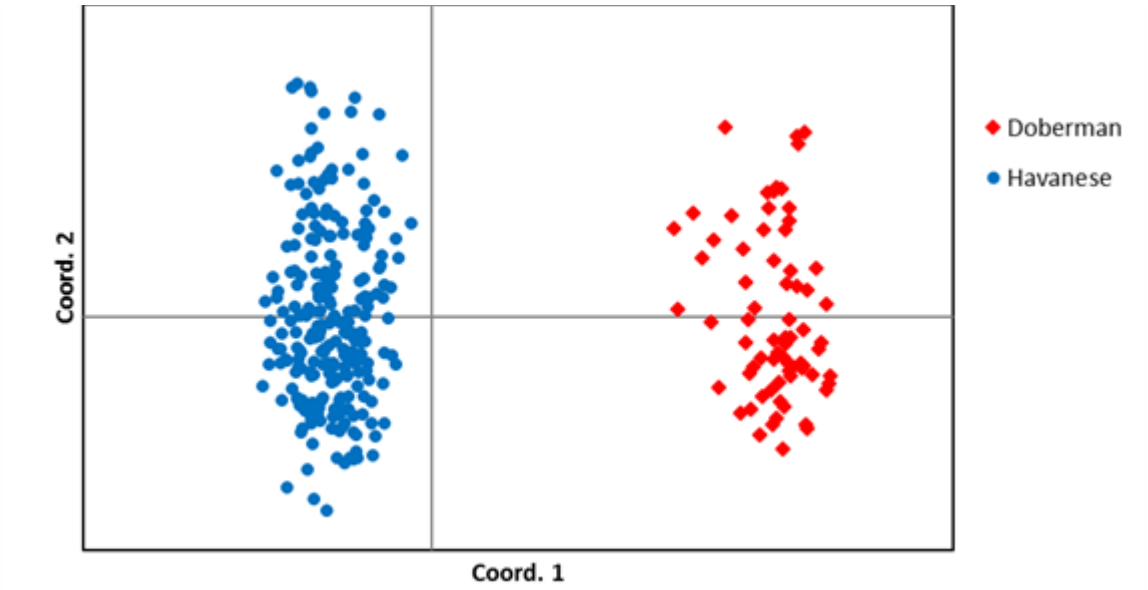



Fig. 3. PCoA of Doberman (n=71) and Havanese (n=242) using the allele and allele frequencies from 33 STR loci.

**E. DLA Class I and II Haplotype frequencies and genetic diversity**

The DLA consists of four gene rich regions making up a small part of canine chromosome 12. Two of these regions contain genes that help regulate normal cell- (Class I) and antibody-mediated (Class II) immunity. Polymorphisms in these regions have also been associated with abnormal immune responses responsible for autoimmune diseases. The Class I region contains several genes, but only one, DLA-88, is highly polymorphic (with many allelic forms) and is therefore most important for immune regulation. Specific alleles at the four STR loci associated with the DLA88 are linked together in various combinations, forming specific haplotypes (Table 4). Groups of genes and their alleles inherited as a block, rather than singly, are called haplotypes. The class II region also contains several genes, three of which are highly polymorphic, DLA-DRB1, DLA-DQB1 and DLA-DQA1. Specific alleles at STR loci associated with each of the three Class II genes are strongly linked and also inherited as a single block or haplotype (Table 6). One haplotype comes from each of the parents. Specific class I and II haplotypes are often linked to each other and inherited as a genetic block. However, there is enough distance between these two regions to allow for a degree of recombination resulting in unusual class I/II combinations. The STR-based haplotype nomenclature used in this breed diversity analysis is based on numerical ranking with the first haplotypes identified in Standard Poodles being named 1001, 1002, ... for class I haplotypes and 2001, 2002, ... for class II haplotypes. It is common for various dog breeds to share common and even rare haplotypes, depending on common ancestry.

***1. DLA class I and II haplotypes existing in Doberman***

The Doberman in this study possessed 12 DLA class I and 12 DLA class II haplotypes (Table 5). The next lower number of haplotypes was found in Flat-coated retriever, with eight class I and

ten class II haplotypes. The 1150-1190 haplotypes, which occur in only 2.6% of Doberman, are unique to the breed. The DLA-I 1094 haplotype, which occurs in 74% of Doberman, occurs at low frequency in Akita and Black Russian Terrier. DLA-II 2089, 2090, 209, 2092 and 2094 haplotypes are so far unique to Dobermans. The other DLA class I and II haplotypes are found in a number of other breeds. In addition to the low number of retained DLA class I and II haplotypes, the frequencies of the 1094 (76%) and 2089 (78%) haplotypes are extremely high. Given their high frequency in the total population, and their uniqueness, the 1094 and 2089 haplotypes were obviously prominent in either a specific founder or founder line and have been retained over the century because of their close association with trait or traits that have strongly defined a highly desirable breed phenotype.

Table 5. DLA class I and II haplotypes identified in Doberman Pinschers and their frequency in the population. A single DLA class I (1194) and II (2089)haplotype are found in three-fourths of all Doberman.

**DLA Class I Haplotype Frequencies (Updated Mar 4, 2019)**

| DLA1 # | STR types | Doberman Pinscher (n=517) |
|---|---|---|
| 1016 | 382 371 277 178 | 0.0145 |
| 1017 | 386 373 289 178 | 0.0909 |
| 1030 | 380 373 293 178 | 0.0977 |
| 1040 | 380 371 277 186 | 0.0106 |
| 1052 | 380 372 289 184 | 0.0019 |
| 1091 | 381 371 277 181 | 0.0010 |
| 1094 | 395 375 277 176 | 0.7563 |
| 1105 | 382 379 277 178 | 0.0010 |
| 1150 | 395 379 277 176 | 0.0232 |
| 1159 | 395 379 277 181 | 0.0010 |
| 1174 | 399 375 277 176 | 0.0010 |
| 1190 | 386 373 291 178 | 0.0010 |

**DLA Class II Haplotype Frequencies (Updated Mar 4, 2019)**

| DLA2 # | STR types | Doberman Pinscher (n=517) |
|---|---|---|
| 2011 | 345 322 284 | 0.0010 |
| 2022 | 339 327 282 | 0.0019 |
| 2023 | 341 323 282 | 0.0977 |
| 2024 | 343 323 280 | 0.0010 |

| | | |
|---|---|---|
| 2033 | 339 323 282 | 0.0010 |
| 2039 | 345 327 276 | 0.0097 |
| 2089 | 343 331 276 | 0.7785 |
| 2090 | 339 322 278 | 0.0880 |
| 2091 | 343 327 288 | 0.0145 |
| 2092 | 343 331 278 | 0.0019 |
| 2094 | 339 322 276 | 0.0039 |
| 2112 | 341 331 276 | 0.0010 |

***2. A genetic assessment of allele and allele frequencies of STRs associated with DLA I and II haplotypes***

Table 5 identifies the specific alleles that form each DLA class I and II haplotype along with the frequency of that haplotype. The most common DLA class I 1094 haplotype is made up of the alleles 395, 375, 277, and 176, while the most common class II 2089 haplotype is made up of alleles 343, 331, and 276. You will notice that some of the alleles for the DLA class I haplotypes are shared between haplotypes, such as 380, 373, 277 and 178. Table 7 provides a genetic assessment of heterozygosity among alleles in the seven DLA-associated STR loci. The average number of alleles for all loci was 5.57, but only 1.56 of these alleles affects most of the diversity. The low number of effective alleles (Ne) was expected given the high frequency of the 1094 and 2089 haplotypes. However, the observed and expected heterozygosity (Ho and He) values were similar and yielded an inbreeding coefficient F of 0.038. This was only slightly positive, meaning that there is only a small subpopulation of Doberman that are more inbred than the population as a whole based on DLA haplotypes. This was also the conclusion of heterozygosity calculations obtained from the 33 STR loci that cover a larger portion of the genome (Table 2). Therefore, the over-representation of the 1094 and 2089 haplotypes probably occurred during the earliest origins of the breed. Periods of strong positive selection (inbreeding) that occur during breed formation are often followed by a return to random breeding. Alternatively, it may be that the original population was far more genetically diverse than it is at this time and that there have been a number of significant artificial genetic bottlenecks that have occurred since the breed was started.

Table 6. F-Statistics for Doberman using 7 STRs in the DLA region

| | | **N** | **Na** | **Ne** | **Ho** | **He** | **F** |
|---|---|---|---|---|---|---|---|
| Doberman Pinscher | **Mean** | 521 | 5.571 | 1.564 | 0.355 | 0.360 | 0.012 |
| | **SE** | | 0.341 | 0.017 | 0.006 | 0.007 | 0.004 |

**III. What does this assessment of genetic diversity tell us about contemporary Dobermann and Doberman Pinschers**

This study confirmed that Doberman from around the world constitute a single breed. However, there is evidence that a genetically distinguishable subpopulation (bloodline) of Doberman is evolving in Australia. The Doberman originated from a common founder population that appears to be relatively small and this has undoubtedly been compounded by artificial genetic bottlenecks that have occurred since the breed was closed to outside blood. Contemporary Doberman not only lack genetic diversity, but there appears to be a significant degree of inbreeding that is still occurring based on DNA analysis. It is hoped that DNA based genetic assessment will be taken more seriously and less emphasis placed on COI's calculated from 3-5 generation pedigrees. Many of the genetic bottlenecks and popular sire effects go far back in the breed history and pedigrees are of limited value in accurately bridging these genetic bottlenecks, especially when genetic diversity is so limited.

The fact that Doberman lack genetic diversity was unexpected, as it has been assumed that the breed had a diverse origin with subsequent known and unknown introgressions with other breeds. Although it can be argued that insufficient dogs were tested, 521 individuals from many parts of the world is a large sampling for a population that lacks genetic diversity. Therefore, it is unlikely that more diversity will be found with further testing, and if it is, it will only be for minor alleles or haplotypes. The lack of genetic diversity helps explain why the breed has developed so many heritable genetic disorders. If genetic diversity is lacking, simple deleterious genetic recessive mutations are much more likely to be linked to desired traits and rapidly spread across the breed by inadvertent positive selection.

This study of 521 Doberman establishes a desperate need for breeders to search the world for pockets of genetic diversity that do not exist in the present population, just as was done by Standard Poodle and Italian Greyhound breeders. Eastern Europe and more isolated areas of Western Europe would be ideal places to search for such diversity. Genetic introgressions with similar dogs may be required, but such outcrossing must be based on sound genetic knowledge and careful monitoring of new diversity to see that it is not lost by backcrossing or contained to only a fraction of the breed.

Internal relatedness (IR) values indicate that one quarter of the Doberman tested were almost as inbred as offspring of full sibling parents. This inbreeding appears to be ongoing and every attempt should be made to rebalance what diversity is remaining by breeding for dogs that will have IR scores of 0 or less. This could be accomplished by careful mate selection without further loss of diversity. The relatively high level of current inbreeding may or may not be associated with attempts to eliminate a large number of serious simple and complex heritable genetic diseases from the breed. In the case of diseases such as DCM, the genetic traits responsible for the disease may already be fixed, reminiscent of hyperuricosuria in the Dalmatian. A lack of genetic diversity greatly limits the ability to find reasonably unrelated mates, but when this lack is combined with the need to select against a large number of heritable traits, the ability to identify genetically suitable mates becomes even more difficult. If the population size is small, it becomes even more difficult to find suitable dogs for breeding that are not too inbred, free of potential genetic defects, or that are close enough to be readily accessible.

The lack of genetic diversity in the DLA class I and II region of these 521 Doberman is troublesome, but it is uncertain what it means. Certain DLA class I and II haplotypes have been

associated with specific autoimmune diseases in certain breeds. If those disease risk haplotypes dominate in the breed, such as 1094/2089, this lack of diversity would be a serious problem. However, if disease problems are associated with low incidence haplotypes, lack of DLA diversity would be much less of a problem. Therefore, the effect of low genetic diversity has a lot to do with the disease problems associated with the founding dogs. The predominance of a single DLA haplotype (1094/2089), in the face of 11 lower incidence haplotypes, has one positive effect. This inequality could be rapidly corrected by concentrating on breeding dogs with lower incidence haplotypes, or by using such dogs to mate with high incidence haplotypes, thus reducing the number of puppies homozygous for 1094/2089. Homozygotes, especially for a high incidence haplotype, may have more health problems.

The presence of numerous simple and complex genetic disorders in Doberman indicates that the breed has undergone a number of periods where certain desired traits were under strong positive selection. Some of these periods of inbreeding may have occurred at the founder stage, during WWI or WWII, but most likely they were linked to certain popular sires or lines. For instance, autoimmune diseases in Standard Poodles are concentrated in the two thirds of show-type dogs that possess only one-third of the diversity present across the breed. This genetic imbalance was caused by inbreeding to a famous show line. The population of American Italian Greyhound with the highest incidence of autoimmune disease is the ones with the greatest degree of genomic homozygosity, a result of one of more popular sires. The Flat-coated retriever is a breed that we have studied that also is greatly lacking in genetic diversity and originated with a small group of founders that underwent a period of "refinement." However, genetic diseases are uncommon in the breed, with the exception of a high incidence of certain types of cancer. The lack of genetic diseases in Flat-coated retrievers can be attributed to two things. First, the foundation stock appeared to have been remarkably free of heritable diseases. Second, the breed never achieved a high degree of popularity and was largely bred for performance. Flat-coated retrievers have managed to start with a small amount of genetic diversity, that was fortuitously free of most heritable problems, and maintained that diversity and health by strict random breeding. Whether that will change as Flat-coated retrievers gain popularity in homes and the show ring, will remain to be seen.

## IV. Heritable disorders of Dobermann and Doberman Pinschers

### A. Differences in the incidence of heritable disorders in European Doberman and American Doberman Pinschers

The reported lifespan of the Doberman Pinscher is about 10–11 years, on average. However, they suffer from a number of heritable problems that often manifest later in life. American and European Doberman suffer the same heritable disease problems, but their incidence may be higher or lower in American than West European Doberman depending on the disorder. For instance, American Doberman Pinschers have a higher incidence of heart disease, while European Dobermann have a higher incidence of eye disease. The incidence of many of these disorders is reportedly low in Dobermann from Eastern Europe, but this may indicate less accurate diagnosis and reporting. If true, it would suggest that the incidence of these heritable conditions is increasing with the increasing interchange of show quality breeding dogs between these regions of the world.

A discussion pertinent to the health of European vs. American Dobermans and how heritable diseases have appeared with increasing incidence over the last several decades can be found at: http://dobermanpuppyforsale.com/health.html.

"*Doberman breed was created about 100 years ago from a mixture of different breeds. This provided a wide genetic pool and Heterozygosity of the breed (the variety of genes) was a great health advantage. Up to 1950, there were little health problems, worldwide. The Dobermans lived till 12-15 years of age on average. East Germany and Eastern Europe maintain the healthy population of dobermans up to the nineties.*

*When I purchased my first Doberman in Russia in 1996, nobody heard about the cardio problems of the Doberman breed. The artificial isolation of the Russian Doberman population during the Soviet era produced a robust working type dogs with a life expectancy of 13-15 years. To improve and refine the stock, some Dobermans were imported from Western Europe in the end of the 80's and some of the Russian dams were mated with some of dogs abroad. These efforts did produce a more correct and sound type, but unfortunately some of the health issues unknown before nowadays can be found in the Russian dobermans as well."*

**B. Specific heritable disorders known to occur in the breed**

***1. Hip dysplasia and bloat*** (gastric torsion) are disorders shared by many larger breeds of dogs. However, the incidence of both is low compared to many other breeds.

***2. Dilated cardiomyopathy*** (DCM), a disorder of heart muscle, is the most important heritable disease of Doberman Pinschers, and is becoming increasingly common among Dobermann in Europe. About one-half of Doberman Pinschers in the USA will develop DCM in their lifetime and the average survival after diagnosis is around two months, although some dogs can survive longer. Sixty percent of DCM is in males and 40% females, with an average age at onset 7.5 yrs. However, one-fourth of cases occur in dogs over 10 years. This means that most dogs are well past breeding age before the disease is diagnosed. About one quarter of dogs with DCM experience sudden death due to arrhythmias, while the remainder exhibit more classical signs of congestive heart failure such as cough, wheeze, and labored breathing. Two forms of DCM are recognized; an "attenuated wavy fiber type" that is seen in a number of other breeds, and a "fatty infiltration-degenerative type" that appears to be specific to Doberman Pinscher and Boxer. The causes for the disease are largely unknown, although one assumption is that it is an autosomal dominant trait. Two mutations, PDK4 and NCSU DCM2 have been associated with DCM in Doberman Pinscher. The PDK4 mutation not seen in European Dobermann and appears to be a unreliable predictor of disease or disease risk. The DCM2 mutation, discovered at NCSU, is believed to be of more importance, although whether DCM in the breed is a simple or complex heritable condition remains to be determined and it possible that the associated genetic polymorphisms are now fixed in the American Doberman Pinscher.

Aleksandra Domanjko-Petrič; Polona Stabej; A. Žemva (2002). "Dilated cardiomyopathy in the Dobermann dog: survival, causes of death and a pedigree review in a related line". Journal of Veterinary Cardiology. **4** (1): 17–24.

*Broschk C; Distl O. (Oct 2005). "Dilated cardiomyopathy (DCM) in dogs--pathological, clinical, diagnosis and genetic aspects". Dtsch Tierarztl Wochenschr. (in German). **112** (10).*

*Meurs KM; Fox PR; Norgard M; Spier AW; Lamb A; Koplitz SL; Baumwart RD. (2007). "A prospective genetic evaluation of familial dilated cardiomyopathy in the Doberman pinscher". J Vet Intern Med. **21** (5).*

***3. Cervical vertebral instability*** (Cervical spondylomyelopathy, wobbler syndrome) affects 5.5% of Doberman and 4.2% of Great Danes, but also occurs at a lesser incidence in several large (Rottweiller, Weimaraner, German Shepherd, Bernese) and giant (Great Dane, Mastiff) breeds and rarely in small dogs. The usual age at onset in Doberman Pinschers is around 6 years. The syndrome is associated with an instability in the cervical vertebrae due to bony and ligamentous abnormalities that ultimately lead to intervertebral disk slippage, bony malformation, soft tissue hypertrophy and narrowing of the vertebral canal. The C4-5 C5-6 disk regions are most often affected, moving in order of lesion frequency to C3-4, C6-7 and C2-3. The compression damage to the spinal cord and/or nerve roots results in the characteristic clinical signs. The term wobbler syndrome is used to describe the wobbly gait (walk) that is characteristic of the disorder. In addition to the wobbly gait, there may be neck pain and stiffness, difficulty in arising, weakness in the front limbs, atrophy of shoulder muscles, change in gait, and partial or complete paralysis. Signs may change with the position of the head and neck. The precise cause of the instability in the cervical vertebrae is unknown, but in giant breeds it has been attributed to too rapid of growth. However, this would not seem to be the situation with Doberman, Rottweilers, and Bassett hounds. The cause is more likely to involve this specific region of the spine and is genetically complex. Chondrodystrophy is genetically complex and even though it is not a normal trait, it is used to varying degrees in creating the desired phenotype in many breeds.

*da Costa RC, Parent JM, Partlow Dobson H , Holmberg DL, LaMarre J. (2006). Morphologic and morphometric magnetic resonance imaging features of Doberman Pinschers with and without clinical signs of cervical spondylomyelopathy. AJVR, 67(9), 1601-1612.*
http://www.neuronaldo.com.br/docs/27.pdf.

***4. von Willebrand's disease*** is the most common genetic disorder among all pure breeds of dogs. About 60% of Doberman carry the causative mutation. The von Willebrand's factor (vWF) is a carrier protein for Factor VIII, the latter being important for blood clotting. vWF is encoded by a large and highly mutable gene and a number of different genetic forms are found among and between dog breeds. Fortunately, most of the vWF mutants in dogs do not severely affect blood clotting and are not of great clinical significance (i.e., resembling human type 1 vWF mutants). Bleeding problems are more likely to be seen during teething, estrus, and surgical procedures (tail dock, ear clip) and are seldom severe enough to require clinical intervention with normal whole blood or plasma. A genetic test is available for the vWF mutation found in Doberman Pinschers.

http://www.ufaw.org.uk/dogs/doberman-pinscher-von-willebrand-disease;
http://www.vetgen.com/canine-ref-vwd-faq.html.

***5. Prostatic disease*** is more common in Doberman Pinschers than among males of any other breed. Prostatic disease can manifest by hyperplasia (benign enlargement), cystic changes, infection, and even cancer. Bacterial infections of the prostate may manifest by recurrent urinary tract infection and abscessation. Bleeding from the penis and hematuria are also common signs of prostate disease. Marked enlargement of the prostate may impinge on the colon and interfere with normal defecation. Prostate cancer can occur, but is uncommon compared to other prostate disorders. The reason why Doberman Pinschers are so prone to prostatic disease is unknown, but there is little doubt that he breed is predisposed, which would suggest heritable factors.

*Krawiec DR[1], Heflin D. Study of prostatic disease in dogs: 177 cases (1981-1986). J Am Vet Med Assoc. 1992 Apr 15;200(8):1119-22.*

***6. Autoimmune diseases*** occur in Doberman Pinschers, just as they do in many other pure breeds. The incidence of autoimmune disorders increases as a breed becomes more inbred and loses genetic diversity. A number of autoimmune disorders of dogs have been associated with specific DLA class I or II haplotypes, although this has not been studied in Doberman Pinschers. The predisposition to autoimmunity is genetically complex and involves less-specific genetic polymorphisms that effect self/non-self recognition and specific genetic polymorphisms that affect the forms of autoimmunity that occur in a breed. Many autoimmune disorders are shared by many different breeds, in particular **chronic thyroiditis** leading to hypothyroidism. Doberman Pinschers are one of many breeds that suffer from this disorder. **Pemphigus folliaceus** is seen in many breeds, but is another autoimmune disorder that is often seen in the Doberman. **Systemic lupus erythematosus (SLE) and SLE-like** disorders have been described in Doberman. **Chronic active hepatitis** is a relatively breed specific disease to Dobermans. The condition is usually diagnosed in middle aged dogs around 5.4 years of age, but this can occur in dogs from 2.5 to 10 years. Females are much more likely than males to develop the disorder. The breed specificity and strong predisposition towards females indicate a genetic predisposition Chronic active hepatitis is characterized by inflammation, scarring and destruction of the cells and tissue of the liver, resulting in loss of liver function and ultimately liver failure. Usually, by the time dogs are diagnosed with this condition, the damage to the liver is enough to cause dysfunction, and therefore the survival time and response to treatment is usually poor. There are two theories as to the cause of the disease. The disease has been associated with high levels of copper in the liver and bloodstream, reminiscent to copper toxicosis in Bedlington terriers. However, there is some indication that high copper may be a result rather than cause of disease. A second theory is that the chronic hepatitis seen in Dobermans is an autoimmune disorder, comparable to a human disease. The histologic appearance of the lesion is compatible with autoimmunity. Studies have linked the disease to specific DLA class II haplotypes.

*Mandigers PJ[1], van den Ingh TS, Spee B, Penning LC, Bode P, Rothuizen J.Chronic hepatitis in Doberman pinschers. A review. Vet Q. 2004 Sep;26(3):98-106.*

*Dyggve H, Kennedy LJ, Meri S, Spillmann T, Lohi H, Speeti M.Association of Doberman hepatitis to canine major histocompatibility complex II. Tissue Antigens. 2011 Jan;77(1):30-5.*

***7. Color dilution*** **alopecia (**canine follicular dysplasia) occurs in a number of breeds that use the dilute gene to produce shades of black, brown, or red. The dilute gene is a simple recessive that

affects the transport of melanin via melanosomes from melanocytes in the base of the hair follicle to the hair shaft. It may be associated with an additional mutation in the basic color gene that further impedes the transport of melanin. An example would be production of grey or silver coat color by combining the gene for black with dilute in certain breeds, e.g., blue coats in Italian Greyhound and Dobermans. Interference with the transport of melanin causes melanin to build up in melanocytes in the hair follicle. The effect of this increased build up is to weaken the hair shaft and make it more apt to break or to be prematurely shed. The disorder leads to a thinning of the hair coat, usually starting around 2-4 years of age and especially over the back-line. It occurs in about 93% of blue coated Dobermans and 75% of fawns.

*Milller, WH Jr (2008). "Colour Dilution Alopecia in Doberman Pinschers with Blue or Fawn Coat Colours: A Study on the Incidence and Histopathology of this Disorder". Veterinary Dermatology.* ***1*** *(3): 113–122.*

***8. Mitral valve disease*** or endocardiosis, is a common problem among all dogs, but the incidence is greater in certain pure breeds. This suggests that the genetic polymorphisms responsible for this disease are complex and ancient and have been concentrated by descent in certain breeds. Although the mitral valve is affected in 60% of cases, 30% of affected dogs will have involvement of both mitral (left atrium to left ventricle) and tricuspid (right atrium to right ventricle) valve and 10% only the tricuspid valve. The valves undergo a slow degeneration that is presumed to be heritable. The valves become thickened and deformed and with time the valves cannot form a tight seal preventing backward flow of blood. e progresses leakage occurs between the involved chambers of the heart. This leakage causes the heart to pump harder and this can eventually lead to congestive heart failure. The disorder is most common in small or miniature breeds such as Poodles, Minature Schnauzers, Chihuhua, Fox terrier, Boston terrier and Cocker Spaniel, but also can affect large dogs, in particular the Doberman Pinscher.

Khuly P. (2012). Mitral valve disease (Endocardiosis). http://www.embracepetinsurance.com/health/mitral-valve-disease.

***9. PRA (progressive retinal atrophy)*** is a recessive inherited condition in Dobermans. The disease progresses over months or years, to complete blindness. Clinical signs may not become noticeable until 3 years or older. Visual acuity is diminished, first at dusk, later in daylight. A screening test is available and can be performed by a veterinary ophthalmologist. CERF (Canine Eye Registration Foundation) will certify eyes for 12 months from the date of evaluation. A genetic test for the defect not yet available.

***10. Persistent hyperplastic primary vitreous (PHPV) or persistent hyperplastic tunica vasculosa lentis (PHTVL)*** is a developmental disorder of the eye. PHPV is essentially a failure of normal separation and regression of the fetal vasculature from the iris and developing lens. The inheritance has been described as autosomal incomplete dominant or complex. The disorder can be detected at 7-8 weeks of age by expert examination but screening is often done at 15-20 months of age, prior to breeding. The severity is graded 1-6, and dogs scoring low (i.e., 1) are sometimes bred. In its severest form, PHPV can lead to glaucoma and loss of the eye. However, because of its strong genetic basis, no affected dogs should be bred, regardless of severity score.

Genetic testing led to a decrease in the incidence of the disorder from 19% to 8% in the Netherlands during the period of 1978-1987.

http://www.dobermanns.info/info/PHTVL.htm.

*Stades FC (1980). Persistent Hyperplastic Tunica Vasculosa Lentis and Persistent Hyperplastic Primary Vitreous (PHTVL / PHPV) in 90 Closely Related Doberman Pinschers: Clinical Aspects. J Small Anim Hosp Assoc. 16: 739-751.*

*Stades FC, Boevé MH, van den Brom WE, van der Linde-Sipman JS (1991). The incidence of PHTVL/PHPV in Doberman and the results of breeding rules. Vet Q. 13(1):24-29.*

***11. Narcolepsy*** is a seizure disorder characterized by transient bouts of seizure activity manifested by rapid transitions between wakefulness and rapid eye movement sleep. Narcoleptic dogs are sleepier than normal, which may go unappreciated. However, more severe attacks may cause cataplexy, a state of generalized and complete muscle relaxation (atonia) with full consciousness but an inability to respond. The disorder is caused by recessive mutations in a gene called hypcretin receptor 2 (*Hcrtr2*) in humans and dogs. The responsible gene was first studied in families of affected Labrador retrievers and Doberman Pinschers. A genetic test is available for narcolepsy in Doberman, Labrador retrievers and Labrador crosses.

***12. Albinism*** in Doberman Pinschers is caused by a deletion in a gene known as SLC45A2 similar to Oculocutaneous Albinism in humans. This mutation traces back to a female, Padula's Queen Sheba or "Sheba", born in 1976. Sheba produced an extensive pedigree as breeders selected for this phenotype. Color-diluted dogs are cream in color with blue-eyes, have little pigmentation around eyes, mouth and nose, and are sensitive to bright light. The trait is considered deliterious with increased risk for skin tumors, in particular melanoma-like cancers. Genetic tests are available for the mutation.

*Winkler PA, Gornik KR, Ramsey DT, Dubielzig RR, Venta PJ, et al. (2014) A Partial Gene Deletion of SLC45A2 Causes Oculocutaneous Albinism in Doberman Pinscher Dogs. PLoS ONE 9(3): e92127*

***13. Cancer.*** They rank anywhere from 4$^{th}$ to 9$^{th}$ among all breeds for cancer incidence, depending on data from various pet insurance companies and cancer registries. This gives them a higher than normal rate of cancer compared to all dogs. However, a study by Fleming and colleagues found that 26% of Doberman Pinscher in North America will die of neoplasia, placing them on par with most large breed dogs. Osteosarcoma is an important cancer in the breed. Doberman can also suffer other common cancers of dogs such as lymphoma, hemangiosarcoma, Mast cell cancer, and melanoma. There appears to be a predisposition for mammary cancer in intact females and prostate cancer in intact males.

Fleming JM, Creevy KE, Promislow DE. (2011). Mortality in North American dogs from 1984 to 2004: an investigation into age-, size-, and breed-related causes of death. J Vet Intern Med. 25(2):187-98.

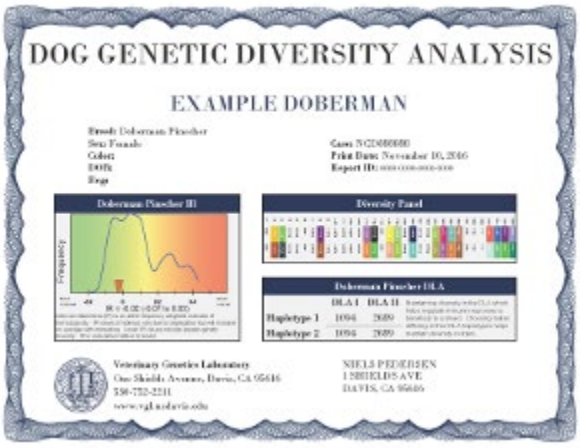
http://www.embracepetinsurance.com/blog/rates-of-cancer-by-dog-breed.

http://dobermansden.com/dobermans-among-top-five-breeds-more-prone-to-cancer/.

**VII. Results of Diversity testing**

**A. How will you be given the results of DNA-based genetic diversity testing on your dog?**

After a sample is submitted for genetic testing, the identity of the dog and owner will be replaced by a laboratory barcode identifier. This identifier will be used for all subsequent activities and each owner will be provided with a certificate that reports the internal relatedness, genomic STR genotypes and DLA class I and II haplotypes for the dog(s) tested. The internal relatedness value for the dog being tested is related to the population as a whole.


DOG GENETIC DIVERSITY ANALYSIS

EXAMPLE DOBERMAN

Doberman Finnsher III

Diversity Panel

Doberman Finnsher DLA

| | DLA I | DLA II |
|---|---|---|
| Haplotype 1 | 1094 | 2089 |
| Haplotype 2 | 1094 | 2089 |

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**B. What should you do with this information?**

The goal for breeders should be to continue to produce puppies with IR scores less than 0, and with time even lower scores. Although most of the individuals tested were randomly bred, there were small subpopulations of dogs that were much more inbred or outbred than the rest of the population. Therefore, there is a possibility to better balance genetic diversity in the breed. Mates should be selected to avoid homozygosity at any genomic loci or DLA class I and II haplotype and encourage the use of dogs with less common genomic alleles or DLA haplotypes. Maintaining existing genomic diversity will require using IR values of potential mates based on the 33 STR loci to assure puppies of equal or greater overall diversity, similar to what is being done by many Standard Poodle breeders. However, IR values, because they reflect the unique genetics of each individual, cannot be used as the criteria for selecting ideal mates. Mates with identical IR values may produce puppies significantly more or less diverse than their parents. Conversely, a mating between dogs with high IR values, providing they are genetically different, may produce puppies having much lower IR scores than either parent. A mating between a dog with a high IR value and a low IR value, providing the latter has few alleles and DLA haplotypes in common, will produce puppies much more diverse than the highly inbred parent. Breeders should also realize that a litter of puppies may have a wide range of IR values, depending on the

comparative contributions of each of the parents. The more genetically diverse and different the parents, the greater the range of IR values in their offspring.

The next step is to compare the DLA class I and II haplotypes. You want to avoid breeding pairs that will produce puppies that will be homozygous for the same haplotypes, and once again, less common haplotypes may offer more diversity than common ones.

Breeders who do not have access to computer programs to predict the outcome of matings based on IR values of sire and dam can also compare values by manual screening. Potential sires and dams should be first screened for genetic differences in alleles and allele frequencies for the 33 genomic STR loci. Some extra weight should be given to rare vs common alleles. This information is included on all certificates and on the breed-wide data on the VGL website.

Puppies, once born, should be tested for their actual IR values, which will reflect the actual genetic impact of each parent on internal diversity. Considerations of mate choices for genetic diversity should be balanced with other breeding goals, but maintaining and/or improving genetic diversity in puppies should be paramount.

An additional goal of this study is to contribute this genetic information to a web repository. The best format for such a repository and testing has been provided by Standard Poodle breeders. This information could be incorporated into a mate selection service that will allow a breeder to identify, among all of the dogs tested, potential mates that would be most ideal for increasing genetic diversity in their litters- https://www.betterbred.com/.