Genetic Diversity Testing for Golden Retrievers

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 may be useful to breeders who wish to track and increase genetic diversity of their breed as a long-term goal.

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

A. Breed history

The origin of the modern Golden Retriever began around 1850 near Glen Affric in Scotland on the highland estate of Dudley Marjoribanks, the first Baron of Tweedmouth. The common hunting dogs of the time were descendants of indigenous trackers and retrievers. Improved firearms increased the need for a specialist retriever that could retrieve fowl from water and land and over greater distances and rougher terrain. Therefore, indigenous retrievers were crossed with outstanding water spaniels. The original cross was of a yellow-colored retriever from the region called Nous with a Tweed Water Spaniel female named Belle. The Tweed Water Spaniel was common in the border country of Scotland during this time, but is now extinct. This mating

produced a litter in 1868 that included four pups, which then were crossed with Irish Setters, sandy-colored Bloodhounds, the St. John's water dog of Newfoundland, and wavy-coated black retrievers. Certain progeny from these various crosses were inbred to solidify Dudley Marjoribanks' vision of the perfect hunting dog. The result was a dog that was stronger and more active than previous retrievers, but with a gentle mouth, good temperament and easy to train.

Golden Retrievers were first registered by The Kennel Club of England in 1903 as Flat Coats – Golden. They were first exhibited in 1908 and 1911 as Golden or Yellow Retrievers. The breed was first registered in Canada in 1927 and the Golden Retriever Club of Ontario (GRCO) was formed in 1958. The GCRO ultimately became the Golden Retriever Club of Canada. The Golden Retriever was recognized by the American Kennel Club in 1925. In 1938, the Golden Retriever Club of America was founded.

Although the Golden Retriever was developed as a retriever of fowl on land and water, it has filled many niches over the last century. They are widely used as guide dogs for the blind, hearing dog for the deaf, detection, and search and rescue operations. As of 2015 is was the third-most popular companion breed in the United States, the fifth-most popular in Australia, and the eighth-most popular in the United Kingdom.

The Golden Retriever is found throughout the world but its appearance can vary by country. British-type Golden Retrievers are prevalent throughout Europe and Australia and are broader and more muscular with a more chiseled muzzle. The coat is generally lighter in color than the American types. The topline and hindquarters tend to be straighter than US dogs and the eyes are rounder and darker. Golden Retrievers from the UK have coat colors with various shades of gold or cream, but white, red and mahogany are prohibited. The Canadian Golden Retriever has a thinner and darker coat and stands taller than other types. American Golden Retrievers are lankier, less muscular and a little taller than UK dogs; their coats are darker in color and of various shades of gold with moderate feathering. There are differences in the gait as well, which is said to be more free-flowing in US dogs, possibly a result of a more sloping topline and angular hindquarters. Males stand between 22 and 24in inches in height at the withers; females are 20 to 22.5inches tall. The weight for Golden Retriever males is between 65-75lbs. and females between 60-70lbs., with the more muscular UK dogs tending to be heavier. The British Kennel Club standard is used in all countries except the USA and Canada. Some Golden Retrievers from the UK are brought to the USA to incorporate more of the temperament and appearance of the British types. However, each country stoutly maintains its preferred type.

B. Performance vs. Conformation

There are a number of breeds such as the Standard Poodle, Irish Setter and Show English Setter that have evolved from performance to show dogs. There are also breeds such as the Brittany that must qualify as champions by outstanding achievement in both activities. In fact, it can be argued that most breeds were used for work of some type before they ever saw a show ring. There is also a growing movement among modern breeders to maintain or re-instill performance traits into their particular breed. Many Golden Retrievers in the US are now used very effectively for both hunting and field trials. There are also Golden Retriever breeders that select for dogs that perform well in both worlds. Re-instilling performance traits is not a difficult undertaking

for breeds that have not gone too far down the conformation path, as many performance traits remain latent in their genomes and can be brought back by altering the direction of positive selection. This reverse selection alters the frequency of alleles in a number of biologic pathways linked to behavior, temperament and appearance. The Golden Retriever Club of America recognizes both conformation and performance and has encouraged kennels to select dogs for any or all skill sets inherent in the original Golden Retriever. Phenotypic differences that began to appear between conformation and performance lines are inevitably associated with genotypic differences, which will become more distinct with time. Selection for performance traits tends to result in smaller dogs with less refined coats and temperaments more suited for the desired tasks.

II. Baseline genetic diversity testing and what it tells us about American Golden Retrievers

A. Standard genetic assessments based on 33 STR loci on 25 chromosomes and allele frequencies

STR markers are highly polymorphic and have great power to determine genetic differences among individuals and breeds. The routine test panel contains 33 STRs, 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 STR locus manifests several different genetic configurations known as alleles. Each dog inherits one of these alleles from the sire and the other from the dam. Table 1 lists the alleles recognized at each STR locus among 691 Golden Retrievers tested to date, as well as listing the frequency of any given allele in the population. One allele occurred at a higher incidence (30-60%) than all other alleles at each of the 33 loci, which is something that is commonly seen in almost all breeds of dogs and reflects shared genotypes required to meet the breed standard (breed phenotype). No allele was fixed or nearly fixed at any of the 33 loci.

Table 1: Genomic STR Locus designations, allele sizes, and allele frequencies for Golden Retrievers.

(link to table 1)

1. Standard genetic assessment values for individual STR loci

The allele and allele frequencies can be used to do a standard genetic assessment of heterozygosity at each STR locus (Table 2). The value Na is the number of alleles that are observed at each locus for a specific breed, while Ne is the number of effective alleles observed at each locus. Effective alleles are those alleles that contribute the bulk of the diversity. The Na values for individual STR loci for this population of 691 Golden Retrievers ranged from a low of 3 to a high of 13, while the Ne ranged from 2.136 (AHTk211) to 7.494 (AHT137).

Observed heterozygosity (Ho) is based on the actual allele frequencies at each STR locus and their distribution, while the expected heterozygosity (He) is the value that would be predicted if allele frequencies at each locus were in Hardy-Weinberg equilibrium (HWE). HWE is achieved when all alleles are segregating randomly either at a single locus or across all loci tested. A Ho value of 1.0 would be observed when alleles at each locus are unique for each dog in the

population. A Ho value of 0.00 would occur if there is no heterozygosity, e.g. every individual has the same alleles at each locus.

Ho ranged from 0.525 (AHTh171-A, AHTk211) to 0.863 (AHT137) and He from 0.532 (AHTk211) to 0.867 (AHT137)) between each of the 33 STR locus (Table 2). The Ho and He values were used to calculate the F value (1-Ho/He), a measure of deviation from HWE. More alleles had positive FIS values than negative FIS values, with seven alleles being greater than 0.080 and three of these greater than 0.010. These higher FIS values were responsible for the population-wide F value of 0.053 shown in Table 3. Alleles with the highest FIS scores were likely to be found in the inbred dogs, while alleles with the lowest FIS values were apt to be found among the more outbred dogs (Tables 2, 3).

Table 2: Genetic assessments for individual STR loci of Golden Retrievers. Na= alleles/locus; Ne= effective alleles/locus; Ho=observed heterozygosity; He=expected Heterozygosity; FIS=coefficient of inbreeding (deviation from HWE expectation).

#	Locus	N	Na	Ne	Ho	He	F
1	**AHT121**	713	10	3.251	0.647	0.692	0.066
2	**AHT137**	713	12	7.508	0.836	0.867	0.036
3	**AHTH130**	713	9	3.264	0.647	0.694	0.067
4	**AHTh171-A**	713	9	2.309	0.529	0.567	0.066
5	**AHTh260**	713	10	2.699	0.538	0.629	0.145
6	**AHTk211**	713	6	2.136	0.528	0.532	0.007
7	**AHTk253**	713	5	3.027	0.647	0.670	0.033
8	**C22.279**	713	6	2.870	0.583	0.652	0.105
9	**FH2001**	713	10	4.592	0.741	0.782	0.053
10	**FH2054**	713	9	4.382	0.751	0.772	0.026
11	**FH2848**	713	7	2.638	0.545	0.621	0.122
12	**INRA21**	713	7	4.065	0.756	0.754	-0.002
13	**INU005**	713	6	2.862	0.634	0.651	0.026
14	**INU030**	713	3	2.298	0.534	0.565	0.055
15	**INU055**	713	5	3.209	0.668	0.688	0.030
16	**LEI004**	713	8	2.768	0.607	0.639	0.049
17	**REN105L03**	713	7	2.694	0.579	0.629	0.080
18	**REN162C04**	713	5	3.430	0.647	0.708	0.086
19	**REN169D01**	713	6	3.335	0.643	0.700	0.081
20	**REN169O18**	713	8	3.341	0.729	0.701	-0.040
21	**REN247M23**	713	6	2.880	0.612	0.653	0.062
22	**REN54P11**	713	8	3.180	0.646	0.686	0.058

23	**REN64E19**	713	7	3.860	0.693	0.741	0.065
24	**VGL0760**	713	11	4.562	0.759	0.781	0.028
25	**VGL0910**	713	15	3.227	0.651	0.690	0.057
26	**VGL1063**	713	10	2.307	0.550	0.567	0.030
27	**VGL1165**	713	14	5.052	0.753	0.802	0.061
28	**VGL1828**	713	10	4.143	0.721	0.759	0.050
29	**VGL2009**	713	9	3.981	0.727	0.749	0.030
30	**VGL2409**	713	8	3.567	0.684	0.720	0.050
31	**VGL2918**	713	10	2.783	0.634	0.641	0.010
32	**VGL3008**	713	13	3.844	0.697	0.740	0.058
33	**VGL3235**	713	8	2.796	0.586	0.642	0.088

2. Using allele frequency data to do standard genetic assessments on the population as a whole.

Allele frequencies across all 33 STR loci can also be used to calculate a mean observed heterozygosity (Ho) and an expected heterozygosity (He) for the population (Table 3). The population of 691 Golden Retrievers which were tested had a mean number of alleles (Na) of 8.303 across all 33 genomic STR loci and mean effective alleles per locus of 3.414. Therefore, 41% of the alleles across all 33 STR loci were responsible for most of the genetic. These values for mean Na and Ne indicate a moderate level of heterozygosity that is greater than breeds such as the Akita and lower than more popular breeds with considerable phenotypic and genotypic diversity such as Miniature Poodles and Havanese. The mean observed heterozygosity (Ho) was 0.651, which was lower than the expected heterozygosity (He) of 0.687. This resulted in an FIS value (0.053) that is slightly higher than zero, indicating that breed wide heterozygosity is nearly in line with HWE, except for a small proportion of dogs that are more inbred than the overall population.

Table 3: Genetic assessment parameters of Golden Retriever based on allele frequencies of 33 genomic STRs.

	N	Na	Ne	Ho	He	F
Mean	713	8.394	3.420	0.652	0.687	0.053
SE		0.463	0.177	0.014	0.013	0.006

3. Using allele frequency data from 33 genomic STR to examine the genetic relationship of individuals within a population.

Principal coordinate analysis (PCoA) uses genetic distance based on allele sharing to demonstrate genetic differentiation between individuals in related or unrelated populations. An optimized two-dimensional graph portrays the degree of genetic differentiation between the 691 Golden Retrievers tested (Fig. 1). The more distant two points (dogs) are from each other, the greater the genetic differences and vice versa. This analysis shows that the Golden Retrievers

tested belong to a single breed (population). Although the bulk of the 691 dogs cluster around the intersection of the two coordinates, there are several dogs that appear more distant. These are often referred to as genetic outliers. Because they are somewhat genotypically different, they are likely to possess phenotypic traits that differentiate them from the more tightly clustered dogs. For instance, they may have been selected more for performance in field trials or hunting rather than for conformation or simple companionship. This could be confirmed by testing Golden Retrievers with known performance, conformation or performance/conformation types.

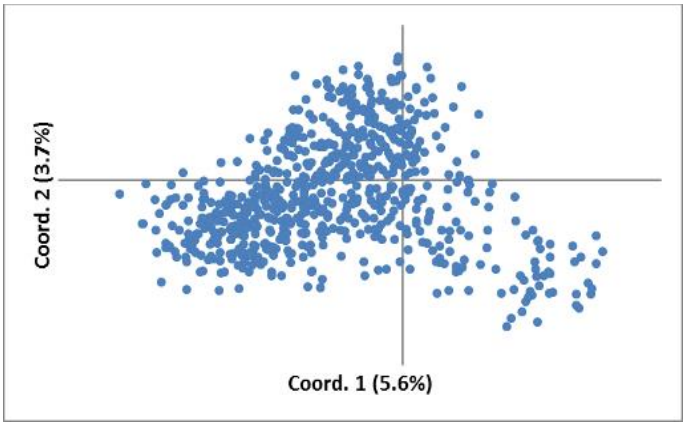


Figure 1: PCoA plot of the Golden Retriever population tested (n=691).

B. The use of genomic allele frequencies to determine internal relatedness

1. Internal relatedness of individuals and the population as a whole

Genetic assessments such as those presented in Table 3 are indicators of population-wide heterozygosity and do not reflect the genetic diversity of individuals within the population. The genetic diversity of an individual dog is largely determined by the diversity inherited from each of its parents. Internal Relatedness (IR) is a calculation that has been used to determine the relative genetic contributions of both parents to an individual. The IR calculation evaluates homozygosity and uses allele frequencies to give more importance to rare and uncommon alleles. 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 equivalent to 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 IR values calculated for 226 Golden Retrievers ranged from around -0.234 for the most outbred dog to +0.485 for the most inbred, with a mean value for the population of +0.041 (Table 4, Fig. 2). Therefore, one half of the dogs had IR values over +0.041 and one quarter over +0.114. Only a small proportion of Golden Retrievers were as inbred, or more inbred, than theoretical offspring of full sibling parents.

Table 4: Statistical breakdown of IR and IRVD values used to create population curve shown in Figure 2.

	IR	IRVD
Min.	-0.234	-0.117
1st Qu.	-0.048	0.131
Median	0.039	0.205
Mean	0.041	0.206
3rd Qu.	0.114	0.298
Max.	0.485	0.627

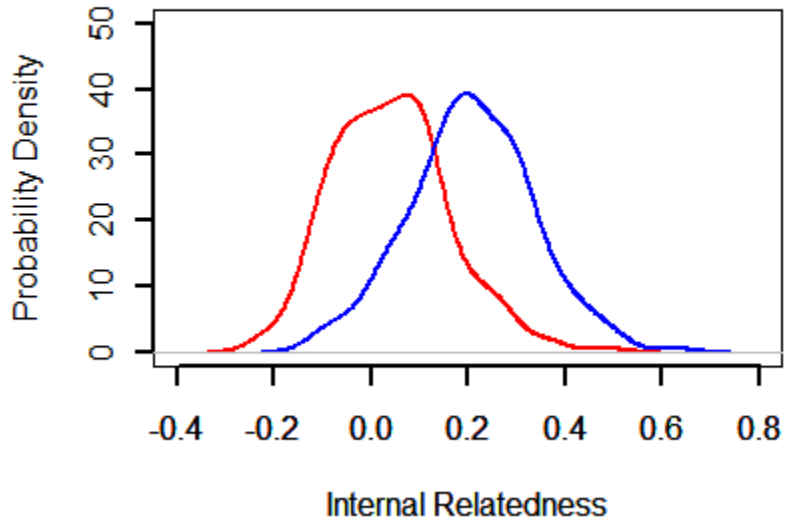


Figure 2: The distribution of IR estimates in 226 Golden Retrievers based on intra-breed diversity (Red line) as compared with IR adjusted for diversity lost during breed development (Blue line). Diversity lost because of breed development was determined by comparing allele frequencies at the same loci between Golden Retrievers and randomly breeding village dogs from the Middle East, SE Asia, and the Pacific Islands. The black area is an estimate (50.4%) of shared genetic diversity with indigenous village dogs.

2. IRVD values as a measure of genetic diversity lost during the entire period of breed evolution from earliest ancestors to present

The IR values can be adjusted in such a way as to provide an estimate of the amount of genetic diversity that has been during breed evolution. This is done by using allele frequencies obtained from DNA of present-day village dogs from the Middle East, SE Asia and Island Pacific nations, which closely reflect the ancestors of dogs before extensive pure breeding. Village dogs are the most random bred and genetically diverse population that has been studied to date. The adjusted IR value is known as IR-village dogs or IRVD.

The IRVD values for the 226 Golden Retrievers are shown in Fig. 2(blue line). The mean IRVD was around 0.206 for the total population with at least one dog having an IRVD value as low as -0.117 (most outbred) and at least one dog with a value as high as +0.627 (most inbred) (Table 4). This shift to the right of the IRVD curve is typical for all pure breeds of dogs and reflects either a small founder population at the time the breed was formed and/or artificial genetic bottlenecks occurring after their registries were officially closed. The estimated loss of genetic diversity (~50% for Golden Retrievers -Fig. 2) that resulted during breed creation and subsequent evolution of is less than for many other pure breeds. Breeds with even small founder populations (e.g., Alaskan Klee Kai, Akita), breeds that have lost much of their genetic diversity (e.g., English Bulldog), or breeds that are overly inbred in certain bloodlines (e.g., Italian Greyhound, Standard Poodle) would have IR curves shifted even more to the right.

C. 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 inherited as a single block or haplotype (Table 5). One haplotype comes from each of the parents.

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.

We have identified 26 different STR-associated DLA Class I (Table 5) and 23 DLA Class II (Table 6) haplotypes among 690 Golden Retrievers tested. The DLA class I haplotypes 1066, 1069, 1071, 1121, 1128, 1129, 1134, 1137 and 1144 and class II haplotypes 2045, 2046, 2047, 2048, 2049, 2050, 2053, 2059, 2079, 2085, 2086 and 2088 are unique to Golden Retrievers among the breeds that have been tested to this time. The remaining DLA class I and II haplotypes are shared with other breeds such as the Standard Poodle. This sharing is perhaps not unusual, as both Golden Retrievers and Standard Poodles were land and water retrievers in the beginning. The number of DLA class I and II haplotypes observed in this group of 690 Golden Retrievers mainly from the USA is reasonable for a breed of this size. Since DLA haplotypes are inherited largely intact and by descent, a lower than expected number of haplotypes suggests either a small founder population, or a subsequent loss of genetic diversity due to artificial genetic bottlenecks such as geographic isolation, popular sire effects, popular bloodline effects, catastrophic events such as world wars, etc.

Although the number of DLA class I and II haplotypes appear large, most occur at low frequency (<1%). However, two DLA class I (1065, 1066) and two DLA class II (2046 and 2048) haplotypes, which have not yet been recognized in other breeds or indigenous dog populations, make up from 45-56% of the total haplotypes in American Golden Retrievers. These two breed specific haplotypes were undoubtedly dominant among the founders of the Golden Retriever breed and have been carefully conserved to modern time.

Tables 5 & 6: DLA Class I & II Haplotype Frequencies in Golden Retrievers. (Note: haplotype 1146 has been renamed 1008 to be consistent with other breeds.)

DLA Class I Haplotype Frequencies (Updated Oct 9, 2019)		
DLA1 #	**STR types**	**Golden Retriever (n=712)**
1002	380 365 281 181	0.0007
1003	387 375 277 186	0.1390
1006	387 375 293 180	0.0140
1008	386 373 289 182	0.0014
1011	376 365 281 180	0.0007
1012	388 369 289 188	0.0014
1014	375 373 287 178	0.0400
1016	382 371 277 178	0.0021
1030	380 373 293 178	0.0007
1040	380 371 277 186	0.0007
1050	380 371 289 182	0.0007
1059	390 371 291 182	0.0007
1062	382 371 277 183	0.0920
1065	380 371 277 181	0.2626
1066	376 375 277 178	0.2795
1067	376 373 277 178	0.0506
1068	380 373 287 181	0.0513
1069	380 365 281 184	0.0400
1070	380 375 291 178	0.0154
1071	380 373 277 178	0.0007
1121	380 371 277 183	0.0007
1128	384 376 287 182	0.0007
1129	382 371 277 181	0.0007
1134	384 365 291 178	0.0007
1137	383 371 281 184	0.0014

1144	390 369 289 182	0.0007
1145	392 373 281 186	0.0007

DLA Class II Haplotype Frequencies (Updated Oct 9, 2019)

DLA2 #	STR types	Golden Retriever (n=712)
2001	343 324 284	0.1397
2003	343 324 282	0.0225
2005	339 322 280	0.0162
2007	351 327 280	0.0140
2012	345 322 280	0.0007
2017	343 322 280	0.0421
2021	339 324 268	0.0920
2022	339 327 282	0.0007
2023	341 323 282	0.0007
2029	337 324 268	0.0007
2045	339 325 284	0.0407
2046	339 329 280	0.2683
2047	339 331 280	0.0105
2048	339 331 282	0.2598
2049	339 331 284	0.0014
2050	341 327 284	0.0400
2051	343 331 282	0.0119
2052	345 321 280	0.0021
2053	343 324 280	0.0302
2059	343 324 276	0.0007
2079	343 323 278	0.0007
2085	345 325 280	0.0014
2086	339 329 284	0.0014
2088	339 329 268	0.0014

The linkages between alleles that make up individual DLA class I or II haplotypes are very strong (Tables 5,6), while linkages between regions of the DLA that are more distant from each other, such as between DLA class I and II haplotypes, are weaker. There are almost two million base pairs separating the DLA class I and II regions, thus allowing for some genetic recombination to occur between DLA class I and II haplotypes. There are also recombination hotspots in this intervening region. As a result, the common DLA class I haplotypes frequently recombine with various common and uncommon DLA class II haplotypes to form different extended class I/II haplotypes that are also unique to a breed (Table 7).

Table 7: Recombination of DLA class I and II halotypes to create different extended haplotypes. These often involve recombination between the most common class I and II haplotypes in the breed (shaded).

Class I/II haplotype	Class I haplotype	Class II haplotype
3003	1003	2001
3010	1006	2007
3021	1069	2045
3027	1030	2023
3090*	1014	2050
3091	1067	2017
3092*	1067	2051
3093*	1066	2046
3094*	1066	2048
3095*	1065	2047
3096*	1065	2048
3097*	1065	2049
3098*	1050	2052
3099*	1071	2017
3100	1068	2053
3101*	1068	2003
3102*	1070	2005
3082	1062	2021
3200*	1129	2048

*Unique to Golden Retrievers

Using standard genetic assessment parameters and DLA class I and II STR allele frequencies to gauge diversity in the entire DLA region.

Genetic diversity can also be assessed by studying the frequency of the DLA class I and II alleles of the four DLA class I and three DLA class II STR loci (Table 8), in the same manner as employed with the 33 genomic STR loci (Table 3). Although these STRs are associated only with the DLA class I and II regions on chromosome 12, the numerous genes and their alleles that make the entire DLA are in strong linkage disequilibrium, meaning that it is inherited as a large block of genes that are less subject to recombination than most other parts of the genome.

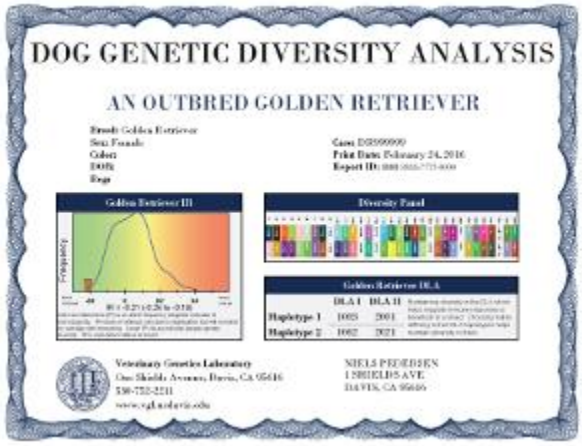
Golden Retrievers have a moderate number of DLA class I and II associated alleles at each of the 7 STR loci (mean Na=7.286), but only about 41% of them (mean Ne=2.959) contribute to most of the diversity (Table 8). Forty-one percent is identical to Ne/Na for the 31 genomic markers, indicating that the DLA region of Golden Retrievers is in equilibrium with the entire genome. The Ho is lower than for the seven DLA-associated STRs, 0.587 vs. 0.614. This has resulted in a somewhat positive value of 0.044 for FIS. This value, 0.044, is very similar to the FIS value of 0.046 for the genomic markers (Table 3), again suggesting that a small population of Golden Retrievers are inbred both in the DLA region and across the genome.

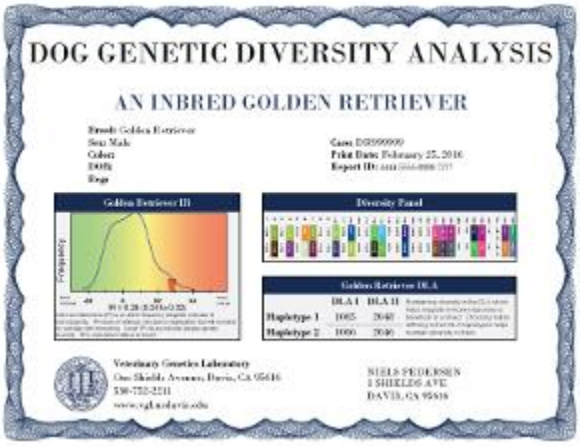
Table 8: Standard genetic assessment of the DLA regions of Golden Retrievers using 7 STR loci associated with the DLA class I and II regions.

	N	Na	Ne	Ho	He	F
Mean	713	7.286	2.954	0.603	0.615	0.015
SE		0.661	0.343	0.056	0.059	0.007

III. 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.





IV. What should you do with this information?

A possible goal for Golden Retriever breeders could be to continue to produce puppies with IR scores less than the present population mean of 0.041, and with time even lower scores. If this is the desired goal, 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.

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.

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.

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, hopefully under the control of the registry. 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.

V. Health problems of US Golden Retrievers

The present study was concerned only with genetic diversity. However, genetic diversity and heritable diseases are related. Heritable disorders have two origins: 1) they occur as spontaneous mutations within a breed, which are concentrated by inadvertent positive selection for a desired phenotypic trait and/or by loss of genetic diversity, and 2) they are of an ancestral origin and are inherited by descent from breed founders or from subsequent introgressions with other breeds. Heritable disorders are also of two common types: 1) complex or polygenic, and 2) simple recessive. The ancestry may be comparatively recent, such as the specific mutations that are responsible for two types of progressive retinal atrophy in Golden Retrievers, or they may have originated in breed ancestors hundreds and even thousands of years ago. It is important to remember that human intervention in the genetic makeup of dogs may go back as far as 14,000 to 40,000 years when a wolf-like species decided to “hook their evolutionary star with humans.” However, as long as a population remains genetically diverse and randomly breeding, deleterious genetic traits will either be lost or remain at low levels and heritable disease at low frequency, a process known as “balancing selection.” This drastically changed with the advent of the Victorian era and the popularity of “pure” breeding. Inbreeding associated with breed development and other artificial genetic bottlenecks has concentrated certain deleterious traits, whether polygenic (complex) or simple recessive (Mendelian). Deleterious traits, whether polygenic or Mendelian, are usually not taken seriously until they affect 1-5% of the population, at which point a quarter or more of the dogs may carry the responsible mutations. If the deleterious traits are genetically linked with highly desired phenotypic traits, this concentration can occur at a very rapid pace.

The Golden Retriever suffers from a number of complex traits, many of which are ancestral in origin and inherited by descent. Cancer, the most common being hemangiosarcoma, followed by lymphosarcoma, mast cell tumor, and osteosarcoma, is the cause of death for 61.4% of American Goldens according to a 1998 health study conducted by the Golden Retriever Club of America, making it the breed's biggest killer. Hip and elbow dysplasia afflict one-fifth of American Golden Retrievers and may be a consequence of selection for more sloping and angular hindquarters and free flowing gait. Eye diseases such as cataracts, two forms of progressive retinal atrophy, glaucoma, distichiasis, entropion, corneal dystrophy, and retinal dysplasia are all heritable problems in the breed, as they are for many other breeds. The two forms of progressive retinal atrophy, GR-PRA1 and GR-PRA2 are associated with known simple recessive mutations that have occurred since the breed was founded. Golden Retrievers also suffer from potentially heritable heart diseases such as subvalvular aortic stenosis and cardiomyopathy and joint diseases that include patella luxation, osteochondritis, panosteitis, and cruciate ligament rupture. A heritable bleeding disorder known as von Willebrand’s disease is widespread among many breeds including Golden Retrievers. Epilepsy, a genetically diverse disorder, is observed in Golden Retrievers and appears to be increasing in incidence in many pure breeds. Many of the heritable disorders of dogs involve the immune system. Golden Retrievers have a predisposition to allergic dermatitis such as "hot spots" of flea bite hypersensitivity as well as seborrhea and self-inflicted lick granuloma. Chronic ear infections, a frequent complication of skin allergies, are common occurrence in the breed. Autoimmune diseases including autoimmune thyroiditis, sebaceous adenitis, autoimmune hemolytic anemia, myasthenia gravis, and lupus-like syndromes have been recognized in Golden Retrievers. Panosteitis, an autoinflammatory disorder, has been reported in young Goldens. The importance of immunologic diseases, which are increasing in frequency in many pure breeds as a result of inbreeding, is often overshadowed by more common and less treatable cancers and orthopedic disorders.