Genetic diversity testing for the St Bernard

Overview

The Veterinary Genetics Laboratory (VGL), in collaboration with Dr. Niels C. Pedersen and staff, have developed a panel of short tandem repeat (STR) markers that will measure genetic heterogeneity and diversity across the genome and in the Dog Leukocyte Antigen (DLA) class I and II regions for specified dog populations. This test panel will be useful to dog breeders who wish to use DNA-based testing as a supplement to in-depth pedigrees. Using in-depth pedigrees and DNA based diversity data, along with DNA testing results for desired phenotypes and health traits can aid in informing breeding decisions.

DNA-based testing of the St Bernard breed is now in the preliminary results phase with the objective of building a snapshot of individual- and breed-wide genetic heterogeneity and diversity. Eighty dogs from the USA, Canada, The Netherlands, Australia, Denmark, Great Britain, Belgium, Hungary, Norway and Japan were recruited for this background assessment of the breed and DNA from 30 of these dogs has been received to date and used for this preliminary report. This data base will be progressively expanded as more dogs are added with the goal of characterizing all the known alleles for the breed at 33 STR loci across the genome as well as all existing DLA class I and II haplotypes identified by seven STRs.

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Results reported as:
Short tandem repeat (STR) loci: A total of 33 STR loci from across the genome were used to gauge genetic heterogeneity and 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: Seven 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 the genetic relatedness of an individual's parents. The value 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 two individuals from different sources may have identical IR values but a very different genetic makeup.

I. Introduction

A. History of the breed [1-7]

1. The Great Saint Bernard Hospice -The earliest written records of the ancestors of the St. Bernard breed were from monks at the Great St Bernard Hospice in 1707. The pass and hospice were named for Bernard of Menthon, the founding 11th century Italian monk. The Great St. Bernard Hospice served as a waystation for people traveling the treacherous Great St. Bernard Pass between Switzerland and Italy. The monks kept a kennel of dogs that purportedly were used as companions, guard dogs, and to help assure the safety of winter travelers through the pass. Male dogs, due to their presumed greater strength and tenacity, usually worked side-by-side with the monks in rescue work. However, rescue duties became so bred into their psyche that packs of 2 to 3 dogs would even work on their own [6]. These early dogs were called "Saint Dogs", "Noble Steeds"or "Alpenmastiff". The first pictorial evidence of these companion and working dogs was two paintings dating to 1690 by the Italian artist Salvator Rosa. The dogs portrayed in these paintings were smaller in size, had shorter reddish-brown coats and white fur and a longer tail than the contemporary St. Bernard. The reputation of these dogs, and their ultimate popularity, was greatly enhanced by stories of Barry der Menschenretter (1800-1814), who reportedly helped save the lives of more than 40 travelers in his career [3,4]. A monument to Barry was placed in the Cimetière des Chiens and his body was preserved in the Natural History Museum in Berne. Rutor, the faithful companion of the Italian priest Pierre Chanoux, was a second famed rescue dog who lived from 1800-1812. The dogs of the hospice were ultimately credited with saving over 2000 lives, with the last documented person a 12-year-old boy in 1897 [3].

Eighteen St. Bernard dogs still belonged to the hospice in 2004 [3]. The Barry Foundation was formed in 2005 and kennels established in the nearby village of Martingy [4, 5]. "Its responsibility is to ensure the continued management of the over three-century-old breeding kennels at their original location and the preservation of the special type of hospice dog. It is our duty to impart the history and the legend of Barry to present and future generations and to ensure that the legacy of Barry lives on." [5]. Several St. Bernard puppies are born every year at the foundation and used for the outreach programs of the foundation. As for rescue efforts on the pass, monks now rely on helicopters.

The severe winters of 1816-1818 led to the deaths of many dogs and greatly reduced the size of the kennel [3]. The kennel was initially supplemented with similar dogs from neighboring farms. These dogs were purportedly crossed starting in 1830 with Newfoundland's originally brought from Canada. This was apparently not a positive solution as the long coats and larger size of the Newfoundland's weighted them down in heavy snow [3, 7].

The St. Bernard became well established in Switzerland during the mid- to late-19th century. The monks of the hospice would give away many of their dogs to local farms, which caught the fancy of a local innkeeper, Heinrich Schumacher from Holligen near Bern [3,5]. Schumacher started his own kennel in 1855 based on a studbook supplied by the hospice and used this information in

1867 to document an ancestry for the breed. In February 1884, the Swiss dog register was started, and the first entry was a St. Bernard called Léon [5]. Twenty-eight additional entries were all also Saint Bernards. On 15th March 1884, the Swiss Saint Bernard Club was founded in Basel and a recommended Swiss St. Bernard standard created shortly thereafter. On the occasion of an International Cynology Congress on 2nd June 1887, the Saint Bernard was officially recognized as a Swiss dog breed and compulsory standards set in 1888.

Dogs from the hospice were exported to England in the 1820s, as part of the 19th century craze for public dog breeding and showing in the UK. English bred dogs of many breeds became a major source of foundation stock elsewhere in Europe and in distant countries such as Russia and the United States. The Saint Bernard Club of America was established in 1888 [6], only a year after its formal recognition in Switzerland. Significant changes in the appearance of the breed occurred as a result of the breed's expansion, both within Switzerland and particularly in England. It is presumed that these changes occurred as a result of crosses with breeds such as the English Mastiff. As a result of outcrossing, the contemporary St. Bernard grew considerably in body and head size [8], the coat has become longer and thicker, and a more uniform and distinctive coat color and pattern achieved. Interestingly, Barry's stuffed body was made bigger, legs stretched, and fur color and texture altered in 1923 because he no longer conformed to the public's perception of the breed [8]. Although great changes have occurred in the breed in its subsequent travels, the St. Bernard is considered the Swiss national dog, just as the Bulldog is considered the national dog of England. However, both of these modern breeds are much different in appearance than their famous ancestors.

2. Ancestors of the hospice dogs

The original dogs of the Great St. Bernard Hospice share a history with Sennenhunds, the Alpine Mountain Dog or Alpine Cattle Dog. These were the large multi-use dogs of alpine farmers and dairymen and were used to guard and herd livestock, as small draft animals, and for hunting, search and rescue dogs and watchdogs. These dogs are thought to be descendants of molosser type dogs brought into the Alps by the ancient Romans, and the St. Bernard is recognized internationally today as one of the Molossoid breeds [1]. Related modern breeds include the Bernese Mountain Dog, Great Pyrenees, Greater Swiss Mountain God, English Mastiff and Newfoundland.

B. Breed characteristics [1,2,7]

The St. Bernard is a less popular breed, ranking 48 out of 183 breeds registered by the AKC [2]. Nonetheless, it is still one of the world’s most famous and beloved breeds.

The standard accentuates the breed's muscular, imposing, and massive stature. Females are somewhat smaller (26-28 vs 28-30 inches at the withers) and lighter (120-140 vs. 149-180 lbs) than males [1, 2, 7]. The huge head features a wrinkled brow, a short muzzle, and dark eyes, combining to give St Bernard's an intelligent, friendly expression that would supposedly be a welcome sight to stranded Alpine travelers.

The coat is either smooth or rough. The smooth coat is close and flat, while the rough coat is denser, flatter, and more profuse around the neck and legs. The coat color is typically a red shade with white, or a mahogany brindle with white. Black shading is usually found on the face and ears. The tail is long and heavy, hanging low. Eyes are usually brown, but sometimes can be icy blue, with naturally tight lids and haws (third eyelid) only slightly visible.

Breed Standards:
AKC: https://saintbernardclub.org/breed-standard/
UK: https://www.thekennelclub.org.uk/services/public/breed/standard.aspx?id=5138
FCI: http://www.fci.be/Nomenclature/Standards/061g02-en.pdf

C. Temperament of St. Bernard

St. Bernard are known as gentle giants, being calm, patient and gentle with adults and especially children. However, males of some lines can be more willful and dominant, leading them to be more aggressive to other dogs and people [6-7, 9]. Because of large adult size, it is essential that proper training and socialization begin while the St. Bernard is still small. An unruly full-grown St. Bernard can present problems for even a strong adult, so control needs to be asserted from the beginning of the dog's training. While generally not instinctively protective, a St. Bernard may bark at strangers, and their size makes them good deterrents against possible intruders. Saint Bernards are known (lovingly?) for slobbering, drooling, and loud snoring, a characteristic of many brachycephalic breeds.

II. Genetic studies of contemporary St. Bernard

A. Population genetics based on allele frequencies at 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 [21, 22]. Each STR locus is made up of 7 to 27 known alleles (avg. 15.4 alleles/locus) when tested across many breeds of dogs and other canids. 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 the 30 St. Bernard are listed in Table 1. Link to Table 1

Table 1. Alleles and their frequencies at 33 autosomal STR markers in Saint Bernard (n=30)

AHT121	AHT137	AHTH130	AHTh171-A	AHTh260	AHTk211
92 (0.03)	131 (0.73)	119 (0.03)	219 (0.13)	240 (0.22)	87 (0.02)
96 (0.38)	135 (0.17)	121 (0.35)	221 (0.20)	244 (0.37)	89 (0.02)
100 (0.08)	137 (0.02)	125 (0.25)	229 (0.38)	246 (0.15)	91 (0.28)
106 (0.10)	141 (0.02)	129 (0.13)	233 (0.18)	248 (0.27)	93 (0.47)
108 (0.35)	147 (0.03)	131 (0.13)	235 (0.10)		95 (0.22)
110 (0.02)	153 (0.03)	133 (0.03)			
114 (0.03)		139 (0.07)			

AHTk253	C22.279	FH2001	FH2054	FH2848	INRA21
286 (0.07)	116 (0.27)	132 (0.92)	152 (0.05)	232 (0.03)	95 (0.30)
288 (0.93)	118 (0.18)	144 (0.05)	156 (0.22)	234 (0.42)	97 (0.38)
	126 (0.55)	148 (0.03)	160 (0.22)	236 (0.40)	101 (0.32)
			164 (0.20)	238 (0.02)	
			168 (0.22)	242 (0.13)	
			172 (0.10)		

INU005	INU030	INU055	LEI004	REN105L03	REN162C04
110 (0.02)	144 (0.03)	210 (0.17)	85 (0.42)	231 (0.12)	202 (0.12)
122 (0.18)	146 (0.03)	218 (0.83)	95 (0.35)	233 (0.37)	204 (0.08)
124 (0.15)	148 (0.20)		107 (0.23)	235 (0.08)	206 (0.55)
126 (0.42)	150 (0.57)			237 (0.22)	208 (0.23)
128 (0.02)	152 (0.17)			241 (0.17)	210 (0.02)
130 (0.12)				245 (0.05)	
132 (0.10)					

REN169D01	REN169O18	REN247M23	REN54P11	REN64E19	VGL0760
202 (0.02)	162 (0.25)	268 (0.37)	226 (0.05)	143 (0.13)	12 (0.22)
212 (0.37)	164 (0.10)	270 (0.30)	228 (0.63)	145 (0.47)	13 (0.30)
216 (0.15)	168 (0.48)	272 (0.33)	232 (0.13)	147 (0.17)	19.2 (0.02)
218 (0.38)	170 (0.17)		234 (0.12)	149 (0.05)	20.2 (0.08)
220 (0.08)			238 (0.07)	153 (0.18)	21.2 (0.17)
					22.2 (0.20)
					23.2 (0.02)

VGL0910	VGL1063	VGL1165	VGL1828	VGL2009	VGL2409
12 (0.22)	9 (0.13)	13 (0.02)	15 (0.27)	9 (0.17)	13 (0.02)
17.1 (0.02)	13 (0.02)	14 (0.08)	16 (0.23)	10 (0.02)	17 (0.83)
18.1 (0.30)	14 (0.70)	18 (0.03)	17 (0.03)	13 (0.10)	18 (0.15)
19.1 (0.17)	15 (0.03)	19 (0.23)	19 (0.05)	14 (0.65)	
20.1 (0.23)	19 (0.08)	21 (0.07)	20 (0.23)	15 (0.07)	

21.1 (0.07)	20 (0.03)	23 (0.15)	21 (0.05)
		24 (0.02)	24 (0.07)
		28 (0.17)	25 (0.07)
		29 (0.20)	
		30 (0.03)	

VGL2918	VGL3008	VGL3235
13 (0.07)	15 (0.03)	13 (0.20)
14 (0.40)	17 (0.67)	14 (0.48)
15 (0.20)	18 (0.23)	16 (0.25)
16 (0.03)	19 (0.02)	17 (0.07)
17.3 (0.13)	20 (0.05)	
18.3 (0.02)		
19.3 (0.15)		

The average number of alleles per locus that have been discovered for all canids tested at the VGL to date is 15.4. Therefore, the most striking findings were the comparatively low number (2-7) of alleles found at each locus, and the high incidence of one or two alleles (Table 1). A single allele at three loci (FH2001, INU055 and VL2409) occurred in 82-92% of dogs tested (Table 1). These three loci were under particularly strong and continuous positive selection and signatures of an individual or closely related line that played an important role in the founding of the breed. Although it is likely that allele and allele frequencies may change as more dogs are tested, any additional alleles will be at low number and frequency and unlikely to significantly change these observations.

B. Assessment of population heterozygosity using standard genetic parameters

Allele and allele frequencies at each of the 33 STR loci are listed in Table 1 and used to do a standard genetic assessment of the population as a whole (Table 2). These assessments include the average number of alleles found at each STR locus (Na); the average number of effective alleles (Ne) per locus (i.e., the number of alleles that contribute most to genetic differences/heterozygosity); the observed or actual heterozygosity (Ho) for the entire population; and the heterozygosity that would be expected (He) if the existing population was in a state equivalent to Hardy-Weinberg equilibrium (HWE) (i.e., a state of random breeding in a large wild population).

Table 2. Summary of Standard Genetic Assessment for Saint Bernard using 33 STR loci

	N	Na	Ne	Ho	He	F
Mean	30	5.06	3.14	0.63	0.62	-0.01
SE		0.31	0.21	0.04	0.03	0.02

The alleles identified in this group of 30 dogs (Na) represented 5.06 /15.4=33.2% of all known alleles found in canids tested at the VGL. Therefore, these St. Bernards still possess about one third of all available canid genetic diversity. This is higher than the Berger Picard (15.4%),

similar to less popular breeds such as the English Mastiff (31%), Swedish Vallhund (31.9%), Irish Red and White Setter (34.8%) and Flat Coated Retriever (38.6%); and considerably lower than popular and genetically diverse breeds such as the Golden Retriever (54.5%), Toy Poodle (55.6%) and Standard Poodle (58%).

The 30 St. Bernards had an average of 5.06 alleles/loci (Na), but only 3.14/5.06=62% of the alleles were responsible for existing heterogeneity (heterogeneity=genotypic variation=phenotypic variation). Thirty-eight percent of alleles are common to all St. Bernard and are responsible for maintaining phenotypic uniformity. This is typical of most pure breeds of dogs.

The observed (actual) heterozygosity of this group of 30 dogs was 0.63, while the expected heterozygosity (He) for a population in Hardy-Weinberg equilibrium (HWE) was nearly identical, yielding an average coefficient of inbreeding (F) that was near zero. Ho and He values indicate a reasonably high level of heterogeneity. Therefore, if the 30 St. Bernard selected for preliminary testing are representative of the breed, it can be concluded that St. Bernard breeders have done a good job in selecting the least related parents from within the population.

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 of the 33 autosomal STR loci (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. The Na values for an individual STR locus for this population of 30 dogs ranged from a low of 2 to a high of 7 alleles per locus, while the Ne ranged from 1.13 to 6.29 alleles per locus. The observed heterozygosity (Ho) for an individual STR locus ranged from 0.27 to 0.97, while He ranged from 0.12 to 0.84 (Table 3). Loci with the lowest Ho and He values contributed the least to heterozygosity and are most likely involved with shared traits that are most important in maintaining standard breed characteristics. Loci with high Ho and He values are more genetically variable and associated with phenotypic variation within the breed

Fifteen of the 33 loci had values of $F > 0.00$ and 18 were negative with $F < 0.00$ (Table 3). The loci with positive F values were under greater positive selection (i.e., more conserved) and therefore within regions of the genome that tend to be associated with desired breed-specific traits. However, the influences of these various inbred, neutral and outbred regions of the genome defined by these 33 STR loci have been kept in good balance by St. Bernard breeders as evidenced by the nearly zero F value for the whole (Table 2).

Table 3. Standard Genetic Assessment for Saint Bernard using 33 STR loci

#	Locus	N	Na	Ne	Ho	He	F
1	**AHT121**	30	7	3.46	0.57	0.71	0.203
2	**AHT137**	30	6	1.76	0.47	0.43	-0.08
3	**AHTH130**	30	7	4.40	0.97	0.77	-0.25
4	**AHTh171-A**	30	5	4.03	0.77	0.75	-0.02
5	**AHTh260**	30	4	3.64	0.83	0.73	-0.15
6	**AHTk211**	30	5	2.89	0.53	0.65	0.185
7	**AHTk253**	30	2	1.14	0.13	0.12	-0.07
8	**C22.279**	30	3	2.46	0.63	0.59	-0.07
9	**FH2001**	30	3	1.19	0.17	0.16	-0.07
10	**FH2054**	30	6	5.17	0.90	0.81	-0.12
11	**FH2848**	30	5	2.84	0.67	0.65	-0.03
12	**INRA21**	30	3	2.97	0.73	0.66	-0.11
13	**INU005**	30	7	3.94	0.87	0.75	-0.16
14	**INU030**	30	5	2.56	0.67	0.61	-0.1
15	**INU055**	30	2	1.39	0.27	0.28	0.04
16	**LEI004**	30	3	2.85	0.77	0.65	-0.18
17	**REN105L03**	30	6	4.31	0.77	0.77	0.001
18	**REN162C04**	30	5	2.65	0.60	0.62	0.036
19	**REN169D01**	30	5	3.21	0.67	0.69	0.032
20	**REN169O18**	30	4	3.00	0.60	0.67	0.099
21	**REN247M23**	30	3	2.98	0.80	0.66	-0.2
22	**REN54P11**	30	5	2.28	0.57	0.56	-0.01
23	**REN64E19**	30	5	3.34	0.60	0.70	0.144
24	**VGL0760**	30	7	4.71	0.73	0.79	0.069
25	**VGL0910**	30	6	4.47	0.8	0.78	-0.03
26	**VGL1063**	30	6	1.93	0.43	0.48	0.102
27	**VGL1165**	30	10	6.29	0.77	0.84	0.089
28	**VGL1828**	30	8	5.13	0.87	0.81	-0.08
29	**VGL2009**	30	5	2.15	0.47	0.54	0.128
30	**VGL2409**	30	3	1.39	0.27	0.28	0.057
31	**VGL2918**	30	7	4.06	0.73	0.75	0.027
32	**VGL3008**	30	5	1.99	0.4	0.50	0.196
33	**VGL3235**	30	4	2.94	0.67	0.66	-0.01

D. Differences in population structure as determined by Principal Coordinate Analysis (PCoA)

PCoA measures the genetic relatedness of individuals in a population. The data is computed in a spherical form but often presented in the two dimensions that most closely represent its multi-dimensional form (usually coordinates 1 and 2). The more closely individuals cluster together around the XY axis, the more related they are to each other.

The 30 St. Bernard formed a single population (i.e. breed) in PCoA (Fig. 1). Individual dogs in the group were reasonably dispersed across all four quadrants of the graph. Several individuals appeared as outliers from the main population on the periphery of the graph. It can be assumed, therefore, that this group of 30 dogs were as unrelated to each other as possible given their level of genetic diversity and representative of the breed as a whole.

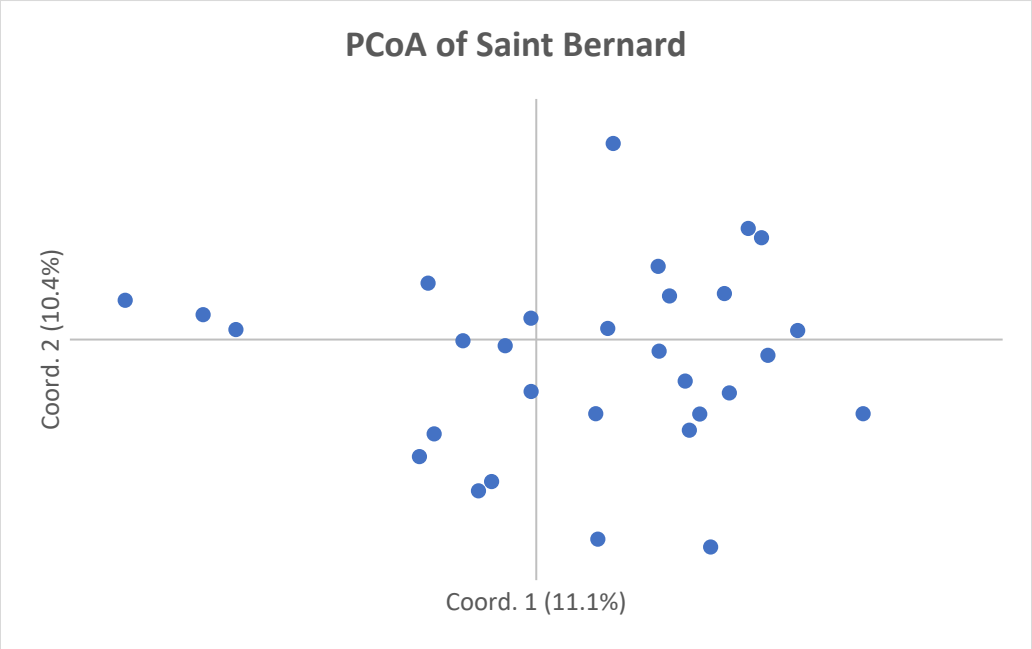

Fig. 1. PCoA of Saint Bernard (n=30) based on the 33 STRs

In order to enhance relatedness between individuals in a breed, English mastiff and Irish wolfhound, were added to the graph (Fig. 3). As expected, the three breeds appeared to be genetically distinct. However, at least one English Mastiff appeared to be almost as closely related to St. Bernard as to its own breed. Also, this comparison caused the St. Bernard to cluster more closely together, something also seen with the Irish wolfhound. However, the English mastiff remained more dispersed. This indicated that English mastiffs have more genotypic and phenotypic variation than either St. Bernard or Irish wolfhound.

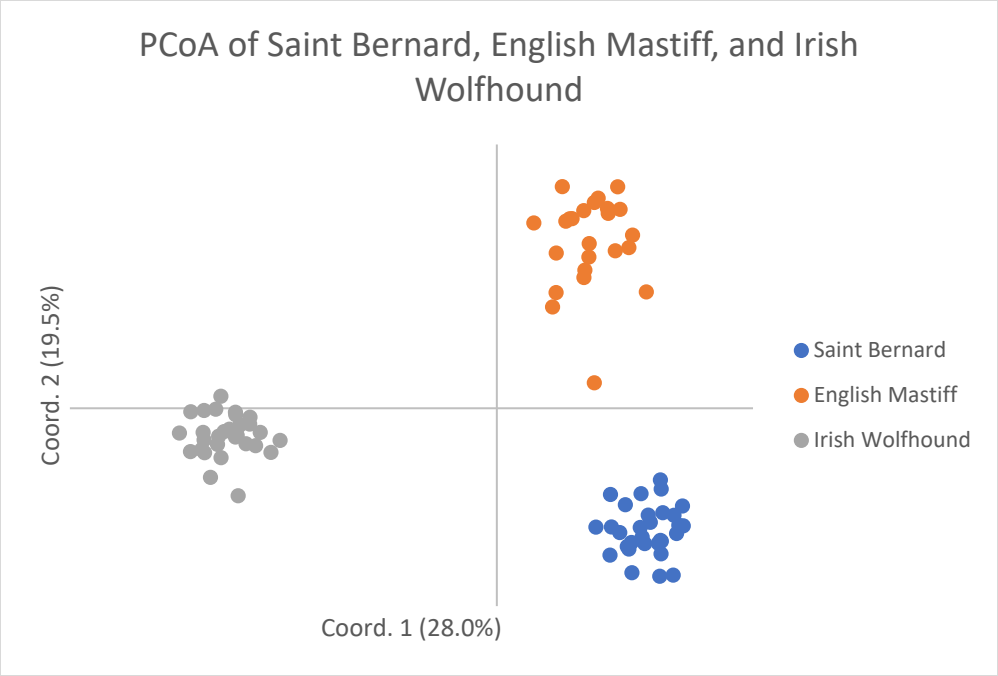

Fig. 2. PCoA of Saint Bernard (n=30), English Mastiff (n=24), and Irish Wolfhound (n=30, randomly selected)

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

1. IR testing

Standard genetic assessments such as those presented in Tables 1-3 are indicators of population-wide (mean/average) heterozygosity and do not reflect the genetic diversity given to individual dogs 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 average 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 sibling parents.

Table 4 summarizes the IR values for the 30 St. Bernard that were initially tested. The most inbred dogs had an IR score of 0.340, while the mean (average) IR score for the group was -.011. One fourth of the population had IR scores between 0.068 and 0.340 and were significantly more inbred than other dogs. In contrast, one fourth of the population had IR scores less than -0.079 to -0.179 and were significantly more outbred others in the population. Therefore, the population appeared to contain equal proportions of dogs that had parents that were as unrelated (most

outbred) or related as possible (most inbred) given the genetic makeup of the population. The existence of both highly inbred and outbred individuals is a typical finding for almost all pure breeds of dogs tested at VGL.

Table 4. Internal relatedness (IR) values calculated using allele numbers and frequencies 30 St. Bernard. The IR values can be adjusted to reflect how these same dogs would score if they were to exist in a large population of village dogs (IRVD).

	IR	IRVD
Min	-0.179	0.017
1st Qu	-0.079	0.155
Mean	-0.011	0.228
Median	-0.032	0.250
3rd Qu	0.068	0.297
Max	0.340	0.631

2. Adjusted IR values based on village dogs (IRVD) as a measure of lost or retained genetic diversity

The IR values obtained from known alleles and their frequencies can be used to approximate the amount of genetic diversity that has been lost as a breed evolves from its oldest common ancestors to the present day. Village dogs that exist throughout the SE Asia, the Middle East and the Island Pacific region are randomly breeding descendants of dogs from which most modern breeds evolved. The known alleles and their frequencies of a given breed can be compared with the same alleles and their frequency in modern village dogs to yield an adjusted IR score (IR-village dog or IRVD). Therefore, the IRVD score approximates how a given St. Bernard IR score would compare to other village dogs if its parents were also village dogs.

The IR values listed in Table 4 are most easily studied in a graph form (Fig. 4). The graphic of IRVD scores for the 30 dogs (blue line) is shifted to the right of their IR scores. All of the 30 St. Bernard have IRVD values above 0.017 and one half had scores of 0.250 and greater (Table 4; Fig. 4). Therefore, if this group of St. Bernard were compared to village dogs, one half of them would be equivalent of offspring of full-sibling parents.

It is noteworthy that the IR graph (red line) is somewhat biphasic with the major population peaking at around -0.1 and a secondary population that peaks at around +0.10. This second peak represents the most inbred portion of the population, while more outbred dogs are poorly resolved and blended with the majority in the first peak. In comparison, 3 peaks were resolved in the IRVD graph (blue line), the first peak being the most outbred dogs (i.e., most genetically diverse), the second peak being the bulk of the population, and the third peak consisting of the most inbred dogs (i.e., least genetically diverse). In this graph, the most outbred population is clearly larger than the most inbred population. The existence of these peaks is due to "population stratification," which is best visualized from the IRVD calculations. Whether this stratification is an artifact resulting from how the test population was selected or typical of all contemporary St.

Bernard, will only be resolved with testing of more dogs from as wide a geographical area as possible.

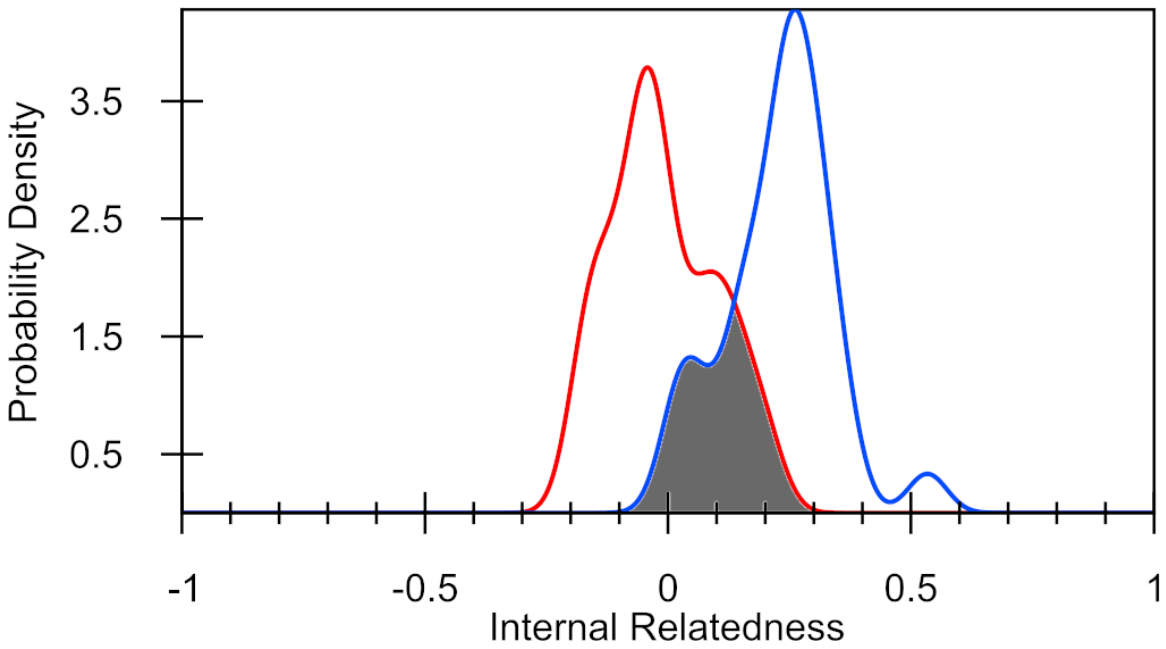

Fig. 4. Distribution of IR (red line) and IR-village dog (IRVD) (blue line) values for St. Bernard (n=30). The area under the curve (black) represents the degree of allele sharing (35.5%) between St. Bernard and village dogs.

The darkened area in Figure 4 representing the overlap of IR and IRVD curves is an estimate of the amount (35.5%) of genetic diversity existing in present-day randomly breeding village dogs that still exists in contemporary St. Bernard. This figure is about the same as the 33.5% retained canid genetic diversity for the breed that was calculated from allele and allele frequencies of the 33 autosomal STRs (Tables 1, 2). It is impossible to determine when this diversity was lost, but it is fair to say that most loss occurred in the decades that preceded breed registration as the "breed" started to take shape, at the time the final founders were registered, and as a result of “refinements” in the breed standard that continue to present time. All these activities required strong positive selection, i.e., inbreeding.

F. 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-mediated (Class I) and antibody-mediated (Class II) immunity. Polymorphisms in these regions have also been associated with abnormal immune responses responsible for autoimmune diseases, allergies, and resistance/susceptibility to infectious diseases.

The Class I region contains several genes, but only one, DLA-88, is highly polymorphic (i.e., with many allelic forms) and is the most important for immune regulation. Specific alleles at the four STR loci associated with the DLA-88 are linked together in various combinations, forming

specific haplotypes (Table 5). 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 the three STR loci associated with the three class II genes are strongly linked and are often 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.

1. DLA class I and II haplotypes

The 30 St. Bernards that were tested possessed 10 DLA class I and 11 DLA class II haplotypes (Table 5). It is likely that several more class I and II haplotypes will be found as more dogs are tested, but they will likely occur at low frequency. The numbers of DLA class I, II haplotypes was higher than the Berger Picard (2, 2), Swedish Vallhund (6, 4) and Shiloh Shepherd (7, 6), somewhat lower than small breeds such as the Giant Schnauzer (14, 15), Samoyed (13, 12) and Shiba Inu (16, 15), and much lower than popular breeds such as the Golden Retriever (26, 23) and Miniature Poodle (33, 23).

The 30 dogs tested possessed no unique DLA class I haplotypes and only one unique DLA class II haplotype (2124) (Table 5). Only one DLA class I (1096) and class II (2023) haplotype occurred at a disproportionately high frequency (33%). These two haplotypes were in linkage disequilibrium (LD), forming and extended 1096/2023 haplotype, which is unique to St. Bernard. All the remaining haplotypes occurred at low and almost equal frequencies.

Table 5: DLA class I and Class II haplotypes and their frequencies in St. Bernard (n=30)

DLA class I	STR alleles	frequency
1011	376 365 281 180	0.10
1017	386 373 289 178	0.07
1040	380 371 277 186	0.03
1062	382 371 277 183	0.08
1068	380 373 287 181	0.13
1096	395 375 277 182	0.33
1128	384 376 287 182	0.02
1160	386 369 289 176	0.13
1165	392 369 281 182	0.08
1221	380 365 293 180	0.02

DLA class II

2001	343 324 284	0.02
2005	339 322 280	0.10
2007	351 327 280	0.02
2014	339 322 284	0.07
2021	339 324 268	0.08
2023	341 323 282	0.32
2028	345 327 288	0.03
2053	343 324 280	0.12
2080	339 325 276	0.08
2098	343 323 282	0.15
2124	341 322 284	0.02

3. DLA class I and II haplotype sharing with other breeds

DLA haplotypes are more conserved than other regions of the genome and inherited as blocks of linked genes, one from each parent, and passed from one generation to the next by descent. Recombination within and between these blocks of genes tends to be low, allowing them to remain much the same over the generations. Therefore, the DLA haplotypes found in a breed can be used to estimate the founder/founder lines that were used to create a breed and the importance of these various founders in subsequent breed evolution. The DLA class I and II regions are frequently shared between breeds, reflecting common distant ancestry (Table 6).

The St. Bernard shares DLA haplotypes with 34 breeds tested at the VGL to date. This is the greatest degree of haplotype sharing that has been observed and suggests that many different types and breeds of dogs were used in the origin and subsequent refinement of modern St. Bernard. Strong sharing of one or more DLA class I haplotypes was with the Lakeland and Biewer terriers, Polish lowland sheepdog, Labrador retriever, Flat coated retriever, Borzoi, Irish wolfhound, Swedish Vallhund, Alaskan Klee Kai, and English bulldog. Strong DLA class II sharing was also observed with Polish lowland sheepdog, Biewer terrier, Irish wolfhound, Alaskan Klee Kai, English bulldog, and Swedish Vallhund. Strong sharing solely of DLA class II haplotypes was seen with the English Mastiff, Mastiff, Llewellin setter, Samoyed, Barbet, and Standard Poodle. The greatest DLA haplotype sharing, regardless of frequency, was with Golden and Labrador retrievers, and Standard Poodle (Table 6). Interestingly, the DLA class I 1221 haplotype was found only in St. Bernard, English mastiff and Mastiff, indicating at least one common and unique ancestor.

Table 6. Sharing of specific DLA class I and II haplotypes between St. Bernard and other breeds tested at the VGL.

DLA Class I Haplotype Frequencies (Updated Oct 23, 2019)

DLA1 #	STR types	Black Russian Terrier (n=133)	Lakeland Terrier (n=71)	Labrador Retriever (n=180)	Irish Red and White Setter (n=60)	Doberman Pinscher (n=609)	Flat Coated Retriever (n=546)	Havanese (n=437)	Samoyed (n=189)	Saint Bernard (n=30)	Shiba Inu (n=106)	Giant Schnauzer (n=214)	Polish Lowland Sheepdog (n=18)	Borzoi (n=49)	English Bulldog (n=163)	Biewer (n=120)	Biewer Yorshire Terrier (n=53)	Biewer Terrier (n=107)	Yorkshire Terrier (n=16)	Italian Greyhound (n=912)	Alaskan Klee Kai (n=545)	Shiloh Shepherd, ISSA (n=182)	Magyar Agar (n=60)	English Mastiff (n=24)	Mastiff (n=5)	Irish Setter (n=49)	Llewellin Setter (n=91)	American Akita (n=100)	Golden Retriever (n=717)	Irish Wolfhound (n=41)	Miniature Poodle (n=287)	Scottish Collie (n=47)	Barbet (n=63)	Swedish Vallhund (n=222)	Poodle (n=2839)	Toy Poodle (n=142)
1011	376 365 281 180	--	--	--	0.033	--	--	0.001	0.272	0.1	--	0.012	--	--	--	--	--	--	--	--	0.0578	--	--	--	--	0.1	--	--	0.0007	--	0.003	--	--	--	0.0187	0.021
1017	386 373 289 178	--	--	0.033	--	0.0846	0.4487	--	--	0.07	--	0.093	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	0.0033	--	
1040	380 371 277 186	--	0.197	--	--	0.0099	--	0.021	--	0.03	--	--	0.61	--	0.04	0.108	0.208	0.075	--	0.0872	0.2147	--	--	--	--	--	--	0.01	0.0007	--	0.007	--	--	--	0.0005	0.004
1062	382 371 277 183	--	--	0.014	--	--	--	--	--	0.08	--	--	--	--	0.187	--	--	--	--	--	0.2147	--	--	--	--	--	--	--	0.0914	--	--	--	--	--	--	--	--
1068	380 373 287 181	--	--	0.047	--	--	0.2711	0.017	0.042	0.13	--	0.035	--	--	--	--	0.009	--	--	--	--	0.247	--	--	--	0.01	--	--	0.0523	0.11	0.016	--	--	0.351	--	--	0.011
1096	395 375 277 182	0.004	--	--	--	--	--	--	--	0.33	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
1128	384 376 287 182	--	--	--	--	--	--	0.002	--	0.02	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	0.0007	--	--	--	--	--	--	--	--
1160	386 369 289 176	0.03	--	--	--	--	--	--	0.016	0.13	0.014	--	--	0.6	--	--	--	--	--	--	--	--	--	--	--	--	--	0.005	--	--	--	--	--	--	--	--	--
1165	392 369 281 182	--	--	0.203	--	--	--	--	--	0.08	--	--	--	--	--	--	--	--	--	--	--	0.245	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
1221	380 365 293 180	--	--	--	--	--	--	--	--	0.02	--	--	--	--	--	--	--	--	--	--	--	--	--	0.02	0.1	--	--	--	--	--	--	--	--	--	--	--	--

DLA Class II Haplotype Frequencies (Updated Oct 23, 2019)

DLA2 #	STR types	Black Russian Terrier (n=133)	Lakeland Terrier (n=71)	Labrador Retriever (n=180)	Irish Red and White Setter (n=60)	Doberman Pinscher (n=609)	Flat Coated Retriever (n=546)	Havanese (n=437)	Samoyed (n=189)	Saint Bernard (n=30)	Shiba Inu (n=106)	Giant Schnauzer (n=214)	Polish Lowland Sheepdog (n=18)	Borzoi (n=49)	English Bulldog (n=163)	Biewer (n=120)	Biewer Yorshire Terrier (n=53)	Biewer Terrier (n=107)	Yorkshire Terrier (n=16)	Italian Greyhound (n=912)	Alaskan Klee Kai (n=545)	Shiloh Shepherd, ISSA (n=182)	Magyar Agar (n=60)	English Mastiff (n=24)	Mastiff (n=5)	Irish Setter (n=49)	Llewellin Setter (n=91)	American Akita (n=100)	Golden Retriever (n=717)	Irish Wolfhound (n=41)	Miniature Poodle (n=287)	Scottish Collie (n=47)	Barbet (n=63)	Swedish Vallhund (n=222)	Poodle (n=2839)	Toy Poodle (n=142)
2001	343 324 284	--	--	0.003	--	--	--	0.047	--	0.02	0.005	0.007	--	--	--	--	--	--	--	--	--	0.005	0.092	--	--	--	--	--	0.1388	--	0.014	--	0.19	--	0.6101	0.007
2005	339 322 280	0.015	0.007	0.05	0.117	--	0.4194	0.002	--	0.1	--	0.009	--	--	0.015	0.046	0.009	0.047	--	--	--	--	--	--	--	0.04	0.808	--	0.016	0.22	--	--	--	--	0.0204	0.004
2007	351 327 280	0.041	--	0.042	0.158	--	--	0.051	0.005	0.02	--	0.051	--	0.14	--	--	--	--	--	--	0.0138	--	--	--	--	--	--	0.06	0.0139	--	0.002	0.01	--	0.27	0.016	0.004
2014	339 322 284	--	0.014	0.003	--	--	0.0302	0.008	--	0.07	--	0.002	0.64	--	0.092	--	--	--	--	0.0016	0.0716	--	--	0.17	0.3	--	--	--	--	--	0.024	--	--	--	0.0176	0.028
2021	339 324 268	--	--	0.014	--	--	--	0.002	--	0.08	--	--	--	--	--	0.004	--	--	--	--	0.2138	--	--	--	--	--	--	--	0.0914	0.28	0.059	--	--	--	0.0021	0.067
2023	341 323 282	0.004	--	0.031	--	0.0928	--	0.003	--	0.32	--	--	--	--	--	0.458	0.349	0.472	0.31	0.0258	--	--	--	0.1	--	--	0.016	--	0.0007	--	--	--	0.024	--	0.0026	--	
2028	345 327 288	--	--	--	--	--	--	--	--	0.03	--	--	--	--	0.037	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	0.007	--	--	--	0.0005	--	
2053	343 324 280	--	--	0.044	--	--	0.1346	0.038	0.558	0.12	--	0.042	--	--	--	--	0.009	--	--	--	--	0.308	--	--	--	0.01	--	--	0.0307	0.11	0.016	--	--	0.498	--	--	0.014
2080	339 325 276	--	--	0.208	--	--	--	--	--	0.08	--	--	--	--	--	0.004	0.009	--	--	0.03	--	0.245	--	--	--	--	--	--	--	--	--	0.01	--	--	--	--	--
2098	343 323 282	--	--	0.003	--	--	--	--	--	0.15	0.014	--	0.03	0.01	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
2124	341 322 284	--	--	--	--	--	--	--	--	0.02	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

3. Heterogeneity in the DLA region

The 7 loci that define the DLA class I and II haplotypes are in stronger linkage disequilibrium than other parts of the genome that are measured by the 33 autosomal STR markers. However, the expectation is that these loci have achieved an equilibrium with other loci in the genome through random mating and over enough time. This can be tested by doing a standard genetic assessment of each locus (Table 7) and across all loci (Table 8).

A standard genetic assessment of the 7 STR loci confirmed that the DLA region was in random equilibrium with the 33 autosomal STR loci interrogating other regions of the genome (Table 2, 8). The observed and expected heterozygosity at each locus was comparable yielding inbreeding coefficients (F) that were neutral or only slightly negative or positive (Table 7) and yielding a F value of 0.02 across all 7 loci (Table 8). These values also indicated that the disproportionately high incidence of one DLA class I/II haplotype was a result of a single founder or founder line being more extensively used at the foundation of the proto-breed or breed and not some more recent artificial genetic bottleneck. The tendency is for a population to return to HWE over time as random breeding replaces initial artificial selection pressures.

Table 7. Standard Genetic Assessment for Saint Bernard using 7 STRs in the DLA class I/II region

#	Locus	N	Na	Ne	Ho	He	F
1	**DLA I-3CCA**	30	7	4.79	0.83	0.79	-0.05
2	**DLA I-4ACA**	30	6	4.43	0.70	0.77	0.10
3	**DLA I-4BCT**	30	5	3.35	0.70	0.70	0.00
4	**DLA1131**	30	7	4.01	0.77	0.75	-0.02
5	**5ACA**	30	5	3.29	0.7	0.70	-0.01
6	**5ACT**	30	5	3.25	0.67	0.69	0.04
7	**5BCA**	30	6	3.36	0.67	0.70	0.05

Table 7. Summary of Standard Genetic Assessment for Saint Bernard using 7 STRs in the DLA class I/II region

	N	Na	Ne	Ho	He	F
Mean	30	5.86	3.78	0.72	0.73	0.02
SE		0.32	0.22	0.02	0.01	0.02

III. Health problems of heritable nature [9-18]

A. Life expectancy

AKC and UK breed clubs put the average lifespan for a St. Bernard at 8–10 years [12]. A 2003 Danish breed survey (35 dogs) puts the median lifespan at 9.5 years [13]. A study of mortality in pure breed dogs in Sweden showed that 30% of St. Bernard dogs were dead by 5 years of age, 52% by 8 years of age, and 74% by 10 years of age [14].

B. Heritable disorders

1. Polygenic (complex) heritability

A number of health problems in the St. Bernard are associated with anatomic features characteristic of the breed. Osteochondritis dessicans, hip and elbow dysplasia manifest in the breed at a young age, as they do in many other breeds. However, these disorders are compounded by the very fast growth rate and the weight of a St. Bernard and lead to severe secondary degenerative joint disease (osteoarthritis) with age. Hip dysplasia is the biggest problem, with almost 50% of St. Bernard being affected [15]. St. Bernard are at high risk for elbow dysplasia and ranks 11th among the 20 most affected large breeds [16]. Panosteitis occurs in the long bones of growing dogs but does not usually lead to permanent damage.

Like other breeds, about one-third will die from cancer. St. Bernard suffer from many of the cancers seen in dogs, such as lymphoma. However, brain and bone cancers are more common than in smaller and less brachycephalic breeds. Early research attempted to link osteosarcoma with simple Mendelian inheritance. In one study, osteosarcoma occurred in 6 of 148 first-degree relatives of 21 index St. Bernard dogs with histologically proved bone cancer, but not in any of the 110 first-degree relatives of 18 breed-, age-, and sex-matched controls [17]. However, the general consensus is that the predisposition to bone cancer is common within all large and fast-growing breeds and more related to bone growth.

Eyelid problems occur in Saint Bernard's due to excessive skin over the face and eyes. Excessive skin and skin folds causes the eyelids to droop either downwards (ectropion), or in towards the eye (entropion), where the skin rubs and irritates the eye, causing problems. This is a major fault according to the breed standard. Cherry eye (eversion of the third eyelid) has been recognized in young dogs, and cataracts in older dogs.

St. Bernard, being large and deep chested, are more prone to Gastric torsion or Gastric Dilation.

Dilated cardiomyopathy has been recognized in the breed, but a genetic basis has not been determined.

Neurological problems include a peculiar laryngeal paralysis in older dogs, which can lead to stridorous and difficult breathing. St. Bernard are also susceptible to epilepsy, a condition that appears to be increasing in frequency in many pure breeds of dogs. Epilepsy usually manifests at around 6 months to 5 years of age.

Autoimmune disease and allergies occur in St. Bernard, as they do in many other pure breeds and even mongrels. Autoimmune conditions include thyroiditis and hypothyroidism, autoimmune hemolytic anemia, Addison's disease, myasthenia gravis. Allergic dermatitis and eczyma are problems in the breed and often predispose to otitis externa.

2. Disease traits involving Mendelian inheritance

A deletion mutation in the *ARHGEF10* gene has been found to be highly associated with an inherited polyneuropathy in Leonberger and Saint Bernard Dogs [18]. The age of onset is usually before 4 years of age. Although not sex-linked, affected males outnumber females by about 2 to 1. A random sampling of 383 St. Bernard found 1.8% to be heterozygous for the mutation and 98.2% homozygous for the normal gene [18]. If the carrier rate is correct, 2.6% of St. Bernard would be affected.

Degenerative myelopathy occurs in St Bernard dogs, as it does in many other breeds. The incidence of heterozygous carriers for the SOD1a mutation in St Bernard is around 15% with 3% of dogs being homozygous for the mutation and at high risk for degenerative myelopathy and 78% homozygous normal [19].

Type 1 von Willebrand's disease occurs in the breed as an autosomal recessive disorder, but abnormal bleeding is uncommon and most likely to occur during routine or elective surgeries or from wounds in younger dogs.

DNA tests are available for DM and vWD 1.

C. Recommended health checks [10]

1. Hip Dysplasia - OFA or PennHIP evaluation at a minimum age of 24 Months

2. Elbow Dysplasia - OFA evaluation at a minimum age of 24 Months

3. Eye Examination by a certified veterinary ophthalmologist at a minimum age of 22 Months

4. Cardiac Evaluation - Advanced cardiac exam by Boarded Veterinary Cardiologist at a minimum age of 24 months. The St. Bernard Club of America also recommends a cardiac ultrasound at four years of age or after to monitor cardiac health

5. Degenerative Myelopathy - DNA test for SOD1a mutation by an approved lab

6. Autoimmune thyroiditis (Optional)- Thyroglobulin antibody test

IV. What does DNA-based genetic testing tell us about St Bernard

The 30 St. Bernard that were tested constituted a single breed based on allele and allele frequencies for the 33 autosomal STR loci and PCoA. The breed has retained about one-third of all existing canid genetic diversity. This is similar to many smaller breeds but is only about half that found within large and popular breeds such as the Golden and Labrador Retrievers and the various types of Poodles. More diversity is likely to be discovered as more dogs are tested, but this extra diversity is unlikely to significantly alter these figures. Although retained genetic diversity is average, St. Bernard breeders have done a very good job in maintaining this diversity in a relatively random state. However, similar to most other dog breeds, there are small groups of dogs within the population that are much more inbred or outbred than the population average. These more heavily inbred and outbred dogs tend to cancel each other and give the impression that all puppies are products of the least possibly related parents, which is not the case. Therefore, DNA testing will be helpful in identifying least related parents to decrease IR scores in their puppies.

It is interesting find how well the results of DNA testing correlated with breed history. DNA-based testing indicates that a small number of founders or founder line played a large role in the breed's evolution. A single allele at three different autosomal STR loci was found in 82-92% of the dogs tested. One third of all St. Bernard inherited a unique DLA 1096/2023 haplotype. It would be tempting to postulate that these lineages were inherited by descent from dogs bred in the Great St Bernard Hospice, and among them, even Barry. However, there is also strong evidence that many other lineages were involved in creating the modern St. Bernard. In fact, the St. Bernard (and Havanese) appear to be the most mixed breeds studied to date by the VGL. Significantly, the numerous breeds that have genetic signals in the St. Bernard are almost exclusively from the UK, which is consistent with the breed's history. The most notable contributors are a number of hunting breeds, among the most significant being Labrador and Golden retrievers and Poodle. One would expect that Molasser type breeds would also be in the mix, but their contributions appear to be small and did not show up in PCoA graphs. However, a pattern of unique DLA haplotypes sharing was observed between St. Bernard, English Mastiff and Mastiff suggesting a more ancient or distant ancestry with Mastiff-type dogs. Although the St. Bernard may have started in Switzerland, their subsequent evolution appears to be mainly in the British Isles.

A lack of genetic diversity is not in itself bad, providing the founder population was relatively free of deleterious genetic traits and breeders have been judicious in avoiding a loss or imbalance in the original diversity. The St. Bernard is surprisingly clear of simple (Mendelian) breed-specific heritable disease traits. The health problems that exist are of a complex genetic basis and are common to many dog breeds and even mongrels [20]. Many complex disease conditions are an inadvertent result of significant changes to the structure of axial or appendicular skeleton or head, or to function. Many of these form and function changes have occurred over the thousands of years that humans have used artificial selection to mold dogs to their needs. Therefore, many

complex heritable traits found in dog breeds have a much more ancient origin and pre-existed in the foundation stock of a breed

The biggest problem facing pure breeders of dogs are the disease traits that are of Mendelian origin. Three hundred thirty-two disorders that follow simple Mendelian inheritance have been identified in dogs to date, of which 266 have known causal mutations [23]. Mendelian traits are usually autosomal recessive in nature and frequently in linkage with a region of the genome that has been subjected to strong positive selection for a phenotype that is deemed desirable in the show ring or for some specific performance. A lack of genetic diversity has two effects on Mendelian disease traits. The less diversity that is present in a breed, the more likely that bouts of artificial selection for certain desired traits (form or function) will lead to the appearance of simple genetic diseases. The second problem with low genetic diversity involves how the appearance of a simple genetic trait will be handled. Elimination of such deleterious mutations may result in loss of genetic diversity, especially when diversity is already limited [22]. In such cases, breeders must not eliminate the trait, but rather must breed around it by selecting parents that will not produce affected puppies. Therefore, breeds that lack genetic diversity must be managed much more closely to avoid further loss of genetic diversity (to minimize Mendelian disorders) and use more caution when dealing with how they are managed [21, 22]. Fortunately, St. Bernard breeders have comparatively few deleterious Mendelian traits to deal with compared to many other breeds. Type 1 von Willebrand's and degenerative myelopathy are present in many breeds and most likely were introduced in the founders. The clinical manifestation of these disorders is often inapparent, mild, or delayed, causing them to be ignored in many cases. Juvenile polyneuropathy appears in both St. Bernard and Leonberger [18], suggesting that it is a more ancient mutation that was captured from a common founder or founder line.

Lack of genetic diversity in the DLA region is another problem that many pure breeds have to deal with. Loss of genetic diversity in the DLA region is commonly associated with an increase in the incidence and manifestations of autoimmune disorders, allergic conditions, and increased susceptibility to specific infectious agents. There is even question whether disorders of unknown etiology, such as epilepsy and cardiomyopathy, may also be forms of autoimmunity. At present, St. Bernard do not appear to suffer any more greatly from autoimmune disorders, allergies, and specific infectious diseases than many other breeds and even mongrels. However, there is wisdom in retaining as much diversity (heterogeneity) in the DLA region as in other parts of the genome and to avoid homozygosity. Imbalances in DLA types can also be addressed by concentrating whenever possible on using dogs for breeding that have rarer types.

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