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An International Genetic Survey of Breed-Specific Diseases in Working Dogs from the United States, Israel, and Poland

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Abstract
Genetic diseases occur in breeds used for law enforcement. As important team members, dogs are expected to operate at peak performance for several years and are significant investments for both the initial purchase and extensive, specialized training. Previous studies have not focused on causes for retirement or euthanasia as genetic (inherited) versus acquired (environmental). We performed direct mutational analysis for breed-specific conditions on samples from 304 dogs including 267 law enforcement (122 US, 87 Israeli, and 58 Polish) and 37 search and rescue dogs. Genetic testing identified 29% (n = 89) of the dogs tested to be carriers of a genetic mutation and 6% (n = 19) to be at risk for a debilitating inherited condition that may eventually impair the dog's ability to work. At-risk dogs included Labrador Retrievers (n = 4) with exercise-induced collapse, Bloodhounds (n = 2) with degenerative myelopathy (DM), and German Shepherd dogs with DM (n = 12) or leukocyte adhesion deficiency, type III (n = 1). A substantial number of working dogs were shown to be at risk for genetic conditions that may shorten the dog's career. The loss of dogs, due to early retirement or euthanasia, as a result of preventable genetic conditions has an emotional cost to handlers and financial cost to service organizations that can be avoided with genetic screening prior to breeding, buying, or training.

Genetic diseases are known to occur in dog breeds commonly used for law enforcement and military service such as German Shepherd dogs (GSD), Belgian Malinois and Labrador Retrievers, among others. As important members of their teams, these dogs are expected to operate at peak performance for several years. Law enforce-

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ment and military working dogs are a significant investment considering the initial cost of purchase and the extensive, specialized field or combat training they require. Previous studies investigating reasons for discharge or euthanasia of working dogs have focused on general categories of disease [Dutton and Moore, 1987; Moore et al., 2001; Evans et al., 2007; Takara and Harrell, 2014]. None of these studies have utilized specific diagnostic criteria to narrow the cause for discharge or euthanasia to a genetic (inherited) versus acquired (environmental) basis. Advancements in molecular genetic technologies now allow for direct mutational analysis to identify working dogs at risk for debilitating inherited conditions that may eventually impair the dog's ability to work. The purpose of the study reported here was to identify known breed-specific genetic mutations associated with disease among law enforcement and search and rescue (SAR) dogs, with the goal of providing evidence-based justification for implementing programs to identify working dogs with at-risk genotypes prior to buying or training and to identify carrier dogs prior to breeding to avoid carrier to carrier matings that may result in at-risk dogs.

Table 1. Study dogs by breed and service capacity

Breed	US police	US search and rescue	Israeli police	Polish police	Total
German Shepherd	77	6	20	47	150
Belgian Malinois	20		47	11	78
Dutch Shepherd	5	4	4		13
Labrador Retriever	9	4	15		28
Other	11	23	1		35
Total	122	37	87	58	304

Other breeds included Bloodhound (6), English Springer Spaniel (1), Australian Shepherd (1), Belgian Sheepdog (2), Border Collie (3), Catahoula Leopard Dog (2), Czechoslovakian Vlcak (1), Golden Retriever (4), Standard Poodle (1), and mixed-breed (14)

Methods

Genetic Testing

Law enforcement agencies and SAR organizations in the US were contacted for sample collection on dogs in training, active duty, or retired to investigate for possible known inherited disease risks. In order to understand if differences might exist between dogs sourced from other populations, law enforcement working dogs were also ascertained from Israel and Poland (Table 1). In total, we performed molecular genetic testing on 304 dogs including 267 law enforcement dogs (122 US, 87 Israeli, and 58 Polish) and 37 SAR dogs (US only). Dogs were screened for 1–14 known genetic mutations depending on their breed (Table 2). Mixed-breed dogs were tested for breed-specific disease mutations according to the breed origin as identified by the handler.

Samples included 3 buccal swabs collected by the handlers for US dogs or whole blood collected in EDTA during routine examination by the attending veterinarians for dogs from Israel and Poland. Verbal and written informed consent was obtained prior to or at the time of collection from the superior officers and each handler.

Table 2. Disease loci studied by breed

Breed[a]	Disease	Gene	Reference
German Shepherd, Belgian Malinois, Dutch Shepherd	anhidrotic ectodermal dysplasia	*EDA*	Casal et al., 2005
	degenerative myelopathy	*SOD1*	Awano et al., 2009
	hemophilia A	*F8*	Christopherson et al., 2014
	hyperuricosuria	*SLC2A9*	Bannasch et al., 2008
	leukocyte adhesion deficiency, type III	*FERMT3*	Boudreaux et al., 2010
	mucopolysaccharidosis VII	*GUSB*	Ray et al., 1998
	multidrug resistance 1	*ABCB1*	Mealey et al., 2001
	renal cystadenocarcinoma and nodular dermatofibrosis	*FLCN*	Lingaas et al., 2003
Labrador Retriever	centronuclear myopathy	*PTPLA*	Pelé et al., 2005
	degenerative myelopathy	*SOD1*	Awano et al., 2009
	exercise-induced collapse	*DNM1*	Patterson et al., 2008
	hereditary nasal parakeratosis	*SUV39H2*	Jagannathan et al, 2013
	progressive retinal atrophy, progressive rod cone dystrophy	*PRCD*	Zangerl et al., 2006
	retinal dysplasia/oculoskeletal dysplasia 1	*COL9A3*	Goldstein et al., 2010
	skeletal dysplasia 2	*COL11A2*	Frischknecht et al., 2013

[a] Dogs were screened with breed-specific disease tests. Mixed-breed dogs were screened with breed-specific disease tests according to breed origin as identified by the handler. Breed-specific tests are available at https://www.pawprintgenetics.com/products/breed/. Eight additional Labrador Retriever disease tests are available at https://www.pawprintgenetics.com/products/breeds/76/.

DNA was extracted using routine standard methods. Mutation regions were investigated using a variety of methods depending on the specific mutation, as previously described [Shaffer et al., 2015, 2016]. Results of testing were provided to handlers or superior officers upon request.

Relatedness Analyses

To better understand any biases in our ascertainment of carrier or at-risk animals, we performed relatedness analyses. To assess the relatedness among dogs identified to be carriers or at risk for degenerative myelopathy (DM), a population analysis was performed on a subset of 46 dogs including individuals from 3 subpopulations based on the dog's location: US, Poland, and Israel. Each individual was genetically characterized using 12 short tandem repeats based on Wictum et al. [2013]. Analysis of molecular variance was conducted to calculate fixation index (Fst) values [Excoffier et al., 1992; Huff et al., 1993; Peakall et al., 1995; Michalakis and Excoffier, 1996] as well as a pairwise relatedness analysis [Lynch and Ritland, 1999] using commercially available software [Peakall and Smouse, 2006]. The regression of the parameters was calculated in the pairwise population analysis using commercially available software [Brown, 2001].

Results

Genetic Analysis

Among the dogs tested, we found that 29% (n = 89) were heterozygous carriers of a disease mutation and 6% (n = 19) were homozygous, at risk for a disease mutation (Table 3). At-risk dogs included Labradors Retrievers with exercise-induced collapse (EIC) (n = 4), GSD at risk for DM (n = 12) or leukocyte adhesion deficiency, type III (LADIII) (n = 1), and Bloodhounds at risk for DM (n = 2) (Table 4). Because of the small dataset, we did not attempt to understand whether any statistical differences existed between geographic locations. Dogs were surveyed to simply identify at-risk and carrier dogs for the conditions tested.

Relatedness

The loci studied were polymorphic with an average number of 9.25 alleles per locus (range of 6–12) (Table 5). The genetic analysis indicated that there are likely 3 subpopulations/bloodlines among the subset of the 46 GSD studied. The Fst values showed more associations between the US and Polish subpopulations (0.040), and when compared to the Israeli subpopulation, the Fst values were higher indicating less gene flow between the US and Israeli or Polish and Israeli populations (0.095 and 0.122, respectively).

In order to assess the relatedness within and between these subpopulations, we performed a pairwise relatedness analysis [Lynch and Ritland, 1999]. The results demonstrated that out of 1,035 tests, 7.8% of comparisons showed relatedness. The remaining dogs (92.2%) were unrelated at the level of parent-offspring, full siblings, and half siblings. Among the 7.8% related individuals, most of their relatedness fell between the half siblings and parent-offspring with only a few with relatedness between parent-offspring and full siblings and only one above full siblings, which were 2 dogs from the US subpopulation (Fig. 1).

Discussion

Results of the present study indicate that dogs that have been put into service, either as a law enforcement dog or a SAR dog, have a substantial risk of being a carrier or at risk for a breed-specific genetic disease. After substantial investment in cost and training, working dogs at risk for disease would reasonably be expected to have a shortened career due to their eventual disability. In previous publications examining the reasons for retirement or euthanasia in working dogs, authors cite degenerative

Table 3. Summary of working dogs' results

Breed	United States			Israel			Poland			All locations		
	total	carrier	at risk	total	carrier	at risk	total	carrier	at risk	total	carrier	at risk
German Shepherd	83	35 (42%)	10 (12%)	20	5 (25%)	1 (5%)	47	13 (28%)	2 (4%)	150	53 (35%)	13 (9%)
Belgian Malinois	20	1 (5%)	0	47	5 (11%)	0	11	4 (36%)	0	78	10 (13%)	0
Dutch Shepherd	9	0	0	4	0	0	–	–	–	13	0	0
Labrador Retriever	13	5 (38%)	1 (8%)	15	14 (93%)	3 (20%)	–	–	–	28	19 (68%)	4 (14%)
Other	34	7 (20%)	2 (6%)	1	0	0	–	–	–	35	7 (20%)	2 (6%)
Total	159	48 (30%)	13 (8%)	87	24 (28%)	4 (5%)	58	17 (29%)	2 (3%)	304	89 (29%)	19 (6%)

Other breeds included Bloodhound (6), English Springer Spaniel (1), Australian Shepherd (1), Belgian Sheepdog (2), Border Collie (3), Catahoula Leopard dog (2), Czechoslovakian Vlcak (1), Golden Retriever (4), Standard Poodle (1), and mixed-breed (14).

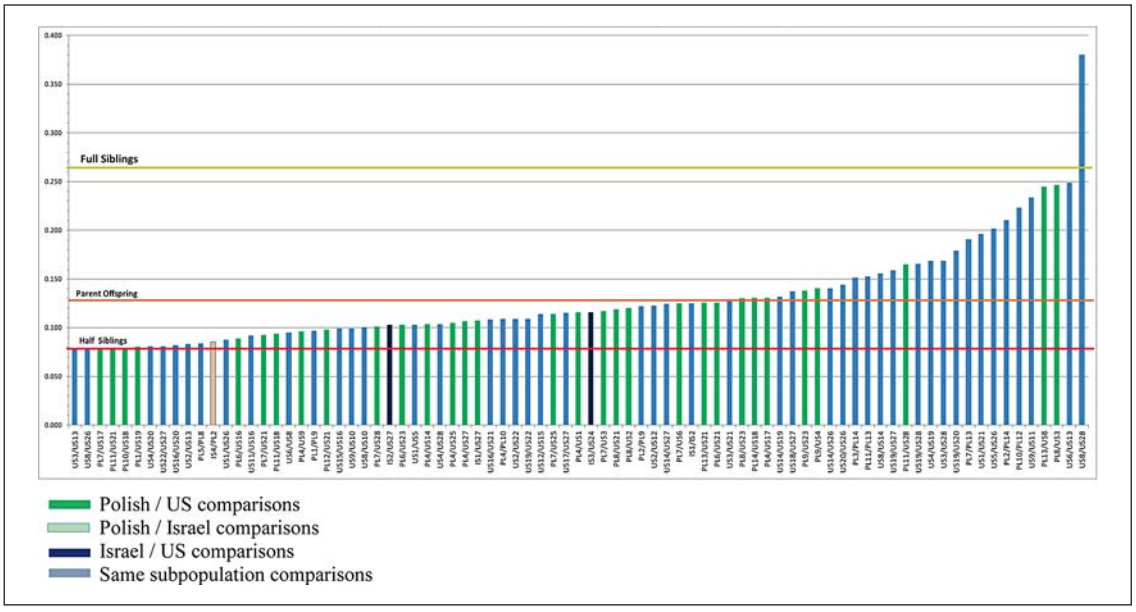

Fig. 1. Pairwise relatedness of positive comparisons. The *x* axis represents the names of the individuals that were compared; the *y* axis represents the statistical value associated to their relatedness analysis. The horizontal lines represent the relatedness values calculated for half siblings (red), parent-offspring (orange), and full siblings (yellow).

diseases [Evans et al., 2007], spinal cord disease [Moore et al., 2001; Evans et al., 2007], or musculoskeletal disease [Takara and Harrell, 2014], leading to the speculation of possible DM in these dogs [Dutton and Moore, 1987; Moore et al., 2001]. In our study, DM was the most common finding among the dogs investigated. To emphasize, the dogs identified as carriers or at risk for DM were randomly selected from dogs being trained, actively working, or recently retired. No dogs showed any symptoms of disease at the time of sampling. In our cohort, 12 GSD were identified to have the at-risk genotype for DM, 9 dogs of 77 studied from the US, 1 of 20 from Israel and 2 of 47 from Poland. Our relatedness studies indicated that the majority of DM carrier or at-risk dogs were not related to a close degree.

The average age of onset for dogs with DM is approximately 9 years of age [Awano et al., 2009]. This autosomal recessive disease affects the white matter tissue of the spinal cord and is considered the canine equivalent to amyotrophic lateral sclerosis (Lou Gehrig disease) found in humans [Awano et al., 2009]. Affected dogs usually present in adulthood with gradual muscle atrophy and loss of coordination typically beginning in the hind limbs due to degeneration of the nerves. The condition is not typically painful for the dog, but will progress until the dog is no longer able to walk. The prevalence of this mutation in the GSD population has been estimated to be about 0.37, with about 22% of dogs studied found to be homozygous [Holder et al., 2014; Zeng et al., 2014]. Although DM is considered an autosomal recessive disease with incomplete penetrance, one study showed high penetrance with dogs showing signs of disease in all dogs at risk over the age of 8 [Holder et al., 2014]. Thus, DM may be a significant challenge for older law enforcement GSD, given that carrier and at-risk dogs were identified from all 3 countries (20% of GSD studied from Israel, 25% from Poland, and 38% from US). Additionally, of the 4 Bloodhounds tested from the US, 2 had the at-risk genotype for DM and 2 were carriers. Nine Belgian Malinois (4 from Poland and 5 from Israel) were also identified as carriers for DM.

A number of other carriers and at-risk dogs for various diseases were identified in this study (Table 4). Four Labrador Retrievers were identified as at risk for EIC (1 from US and 3 from Israel). EIC is an autosomal recessive neuromuscular disorder and presents as exercise intolerance in otherwise apparently healthy dogs [Patterson et al., 2008]. Affected dogs are usually diagnosed before 2 years of age and appear normal during low to moderately strenuous activity. However, shortly after 5–20 min of strenuous exercise, affected dogs will begin to walk with a wobbly, uncoordinated gait that often only affects the hind limbs. These episodes typically last 5–10 min, and most

Table 4. Mutations identified by breed

Breed/Mutation	Carrier	At risk
German Shepherd		
Degenerative myelopathy	46	12
Leukocyte adhesion deficiency, type III	7	1
Belgian Malinois		
Degenerative myelopathy	9	
Mucopolysaccharidosis VII	1	
Labrador Retriever		
Exercise-induced collapse	12	4
Progressive retinal atrophy, progressive rod cone dystrophy	6	
Hereditary nasal parakeratosis	1	
Bloodhound		
Degenerative myelopathy	2	2
Australian Shepherd		
Multidrug resistance 1	1	
Catahoula Leopard		
Degenerative myelopathy	1	
Mixed breed		
Degenerative myelopathy	4	

Table 5. Regression results for relatedness in specific trend lines

R^2	Power	Exponential	Linear	Log	Polymorphic
Non relatives	0.9977	0.9022	0.5013	0.7523	0.9265
Half siblings	0.9912	0.8728	0.5632	0.8052	0.9443
Full siblings	0.9269	0.733	0.5897	0.8263	0.9497

dogs will recover within 15–30 minutes. In working dogs that are affected, episodes would likely be stressful for the handler and could jeopardize both the dog and handler in certain situations.

Finally, one GSD puppy that was in the process of training was identified to have LADIII. This puppy showed signs of illness at the time he was entered into the study. The trainer initially reported diarrhea at 6 weeks of age which resolved with antibiotics. After the course of antibiotics ended, the pup developed severe joint swelling, which also resolved with antibiotics. After the second course of antibiotics ended, he developed pneumonia. Additionally, the dog had persistently high neutrophil counts. LADIII is an autosomal recessive blood disorder affecting GSD [Boudreaux et al., 2010]. Affected dogs have abnormal platelet and white blood cell activity resulting in abnormal blood clotting and immune system dysfunction. Dogs may present with lameness, prolonged bleeding, and recurrent chronic infections often accompanied by fever. Dogs can have a normal lifespan with this condition, although they are susceptible to life-threatening bleeding after injury or surgical procedures.

Many of the canine genetic diseases that have tests available for screening have a recessive mode of inheritance. Thus, although carriers are not at an increased risk of developing the condition, carriers should be identified to prevent carrier to carrier breedings. These diseases can be controlled during breeding by pairing a carrier with a known normal (noncarrier) dog. Thus, it is not necessary to eliminate carrier dogs from the breeding pool, and this is actually discouraged to help maintain diversity within a breed. But controlled breeding of known genotypes can effectively eliminate these recessive diseases from future generations.

Based on our relatedness analysis for carriers and at-risk dogs for DM, there was no correlation based on the country from which the samples were derived, although the Fst results indicated a separation of the Israeli subpopulation from the US and Polish subpopulations. This might be explained by a common origin of these dogs; about 85% of US military dogs are purchased from Eastern Europe [Burns, 2016], and it would be reasonable to assume a similar origin for law enforcement dogs since many of these dogs come from the same breeders as military dogs. However, Israel is also known to buy some of its breeding dogs from European countries; thus, the relatedness results cannot be completely explained. With the increasing costs of importing dogs, many countries are starting their own breeding programs [Lanoue, 2012]. Historically, DM was thought to be specific to the GSD, as it has been referred to as German Shepherd dog myelopathy [Braund and Vandevelde, 1978]. However, DM is now recognized as a common genetic condition in a large number of breeds [Zeng et al., 2014], and as such, should be screened for before importing or breeding any working dogs.

Given the expense in acquiring, training, and maintaining these highly skilled working dogs, care should be taken to ensure their overall health [Jones et al., 2004; Stojsih et al., 2014]. According to Takara and Harrell [2014], the procurement process for military working dogs is aimed at reducing the frequency of genetic and developmental diseases. However, radiography and routine hematologic and biochemical screenings are not adequate to identify underlying genetic conditions. We advocate that genetic health should be included in the assessment of service dogs prior to training or purchasing.

Genetic diseases that have known mutations with established diagnostic testing can be easily avoided through careful breeding programs. Although our study was conducted on law enforcement and SAR dogs, it would be reasonable to apply these findings and recommendations to all working dogs including service, assistance, and military dogs. The loss of dogs due to early retirement or euthanasia as a result of preventable genetic conditions has an emotional cost to handlers and financial cost to service organizations that can be avoided with genetic screening prior to breeding, buying, or training any working dogs.

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Statement of Ethics

Informed consent was obtained from all of the dogs' handlers and/or superior officers. Samples from dogs in the US were obtained from the handlers using noninvasive buccal swabs. Blood samples from dogs in Israel and Poland were obtained using venipuncture by a licensed veterinarian overseeing the care of the dogs.

Disclosure Statement

L.G.S. is the owner of Genetic Veterinary Sciences, Inc. The remaining authors have no conflicts of interest to declare.

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