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ORIGINAL INVESTIGATION

Web resource on available DNA variant tests for hereditary diseases and genetic predispositions in dogs and cats: An Update

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Abstract

Vast progress has been made in the clinical diagnosis and molecular basis of hereditary diseases and genetic predisposition in companion animals. The purpose of this report is to provide an update on the availability of DNA testing for hereditary diseases and genetic predispositions in dogs and cats utilizing the WSAVA-PennGen DNA Testing Database web resource (URL: http://research.vet.upenn.edu/WSAVA-LabSearch). Information on hereditary diseases, DNA tests, genetic testing laboratories and afflicted breeds added to the web-based WSAVA-PennGen DNA Testing Database was gathered. Following verification through original research and clinical studies, searching various databases on hereditary diseases in dogs and cats, and contacting laboratories offering DNA tests, the data were compared to the resource reported on in 2013. The number of molecularly defined Mendelian inherited diseases and variants in companion animals listed in the WSAVA-PennGen DNA Testing Database in 2020 drastically increased by 112% and 141%, respectively. The number of DNA variant tests offered by each laboratory has also doubled for dogs and cats. While the overall number of laboratories has only slightly increased from 43 to 47, the number of larger corporate laboratories increased, while academic laboratories have declined. In addition, there are now several laboratories that are offering breed-specific or all-breed panel tests rather than single-DNA tests for dogs and cats. This unique regularly updated searchable web-based database allows veterinary clinicians, breeders and pet owners to readily find available DNA tests, laboratories performing these DNA tests worldwide, and canine and feline breeds afflicted and also serves as a valuable resource for comparative geneticists.

Introduction

Hereditary disorders and genetic predispositions to disease occur frequently in dogs and cats (Giger et al. 2006; Bell et al. 2012; Slutsky et al. 2013; Giger 2019; Shaffer et al. 2019a), and a comprehensive listing is presented in the Online Mendelian Inheritance in Animals (Online Mendelian Inheritance in Animals [OMIA©] 2020) database. Some disorders are common to many canine or feline breeds due to their shared ancestry, while others are restricted to certain breeds or even a specific family of animals. Over the past 3 decades, a good proportion of these single gene defects in companion animals, commonly referred to as Mendelian inherited disorders, have been characterized by clinicopathological findings and inborn errors of metabolism and mapped to precise pathogenic DNA variants in specific genes (Giger et al. 2006; Lyons 2015; Mellersh 2016; Giger 2019; OMIA© 2020). Depending on the specific genetic defect, any organ system may be involved. In addition, depending on the genetic defect, clinical signs may appear at any time from birth to advanced age and can range from mild and static manifestations to progressive and life-threatening disease. Beyond palliative measures, specific clinically practical treatments are only available for a few inborn errors of metabolism, thus prevention of genetic disease by breeding healthy pets is of utmost importance (Giger et al. 2006; Bell et al. 2012; Giger 2019; OMIA© 2020).

It is undeniable that, as a group, hereditary diseases and genetic predispositions to disease in companion animals represent a major health problem in small animal clinical practice and is an important concern for breeders of dogs and cats as well. Since these naturally occurring disorders frequently recapitulate diseases in humans, they are also important to clinical scientists who are working toward

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a better understanding of the pathophysiology of genetic diseases and to undertake preclinical assessment of the safety and efficacy of novel therapies to benefit both veterinary and human patients (Bradbury et al. 2015; Casal and Haskins 2006; Mellersh 2012; Shaffer et al. 2019a, b) Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man [OMIM®] 2019; Valle et al. 2019; Switonski 2020).

A specific hereditary disease or genetic predisposition to disease in companion animals may be clinically suspected based upon breed and age predilection and characteristic clinical signs, imaging findings, and routine laboratory test abnormalities (Giger et al. 2006; Slutsky et al. 2013; Giger 2017). However, once the molecular genetic basis of a trait has been determined in a breed, documentation with a DNA test for the specific pathogenic variant (mutation) offers the most precise diagnosis, reflecting the trend toward precision medicine as in human medicine. Furthermore, DNA variant tests can be readily carried out on genomic DNA obtained from a variety of sample sources, e.g., cheek swabs and anticoagulated blood. If done correctly, DNA test methods are simple, precise, and inexpensive, if the costs for high-throughput equipment in large laboratories are excluded. Finally, DNA tests can identify animals at risk of developing disease before clinical signs are apparent and can also identify asymptomatic carrier animals for recessive traits before they are bred, thereby preventing the future production of affected pets (Giger et al. 2006; Slutsky et al. 2013; Lyons 2015; Mellersh 2016).

A decade ago, the WSAVA Hereditary Disease Committee engaged in the development of the first, and only comprehensive, web-based DNA-testing resource for hereditary diseases and genetic predispositions in dogs and cats, the afflicted breeds, and the laboratories worldwide offering such tests (Slutsky et al. 2013). This database differs from other online resources (Nicholas et al. 2011; Slutsky et al., 2013) by providing a listing of the laboratories worldwide that provide DNA testing for a given disease for cats and dogs and thereby complements OMIA. Since first reporting on this unique database in 2013, it has served veterinary clinicians, breeders, pet owners as well as scientists internationally. In addition, since its inception, this web-based DNA-testing resource for hereditary diseases and genetic predispositions in dogs and cats has been regularly updated by those at PennGen, University of Pennsylvania. While the database structure remains the same, we report here on updates on hereditary diseases in dogs and cats for which DNA-based tests are available and offered by laboratories worldwide and compare its current status (as of 2020) to that developed in 2010.

Methods

The web-based resource on hereditary diseases and genetic predispositions to disease of WSAVA and PennGen was developed as of 2010 with a Microsoft ASP.net program using a Microsoft SQL server and is hosted on the PennVet server of the University of Pennsylvania (URL: http://research.vet.upenn.edu/WSAVA-LabSearch). All information on the web-based DNA database was verified and updated, new DNA tests and new genetic testing laboratories were added, while others that no longer offer this service were deleted. All laboratories that provide updates and gave approval to be listed are included without exclusion, and there is no fee associated with being listed. The WSAVA, University of Pennsylvania, and PennGen do not exclude any DNA-testing laboratories, however, laboratories that were subsidiaries of larger testing providers or outsourced testing for genetic diseases were not included to avoid redundancies. In addition, laboratories which only perform comprehensive breed-specific or all-breed DNA panel testing (such as Embark, Laboklin, Wisdom Panel) are not contained in the database but are listed separately in this web resource as discussed below.

Data acquisition and content updating

To ensure the information of the originally listed laboratories was accurate and current, their web pages were reviewed, and the laboratories were directly contacted to assure up-to-date information. We also searched the internet for any additional laboratories now offering DNA testing outside of the original list. We searched the Association of American Veterinary Medical Colleges (Association of American Veterinary Medical Colleges [AAVMC] 2019), the American Kennel Club (American Kennel Club [AKC®] 2020), the Kennel Club (Kennel Club [KC©] 2020), Federation Cynologique Internationale (Federation Cynologique Internationale [FCI] 2020), Cat Fanciers' Association (Cat Fanciers' Association [CFA] 2020), the International Cat Association (The International Cat Association [TICA©] 2020), and associations involved with genetic research (AKC Canine Health Foundation© 2020; the Winn Feline Foundation© 2020; and Orthopedic Foundation for Animals [OFA©] 2020) for information on DNA testing for hereditary diseases and genetic predispositions to disease.

All laboratories were contacted by email (with email and phone call follow-ups as needed) and sent a spreadsheet for entry of each disease, gene affected, specific gene variants, species/breeds tested for, and also to verify all information that the WSAVA-PennGen DNA Testing Database already contained. The information received was compared to other sources (below), and any queries were resolved before

removing or adding new laboratories or updating data from previously listed laboratories. Laboratories are given the opportunity to contact the database at any time to provide updates.

In addition, regular database updates are performed either through the initiation and information requests performed on behalf of PennGen or through laboratory deposits of information; data are continuously added by members of the PennGen laboratories.

All disease-associated DNA variants and markers were gathered from OMIA© and scientific literature searches (PubMed®; Commonwealth Agricultural Bureau International [CABI©] abstracts; ResearchGate©; Google Scholar©) and reports from research groups; examples of keywords used in literature searches include the gene or disease name. Original literature sources and direct links are included in the database when available. Unpublished pathogenic variants (i.e., disease-associated mutations) were accepted when received from established research groups and laboratories. A few variants for which testing is offered have not been published and are, therefore, included when the information is provided by the investigators or testing laboratories. Variants are included without a peer-reviewed publication when conveyed by investigators or testing laboratories. Genetic variants were described using the standard nomenclature of Human Genome Variation Society (Human Genome Variation Society [HGVS©] 2020). Attempts were not made to identify patented variants or confirm licenses for specific DNA tests listed. Coat color and conformational DNA variants were not included in the WSAVA-PennGen DNA Testing Database unless associated with pathogenicity; for instance, embryonic lethal harlequin coat color variants in Great Danes (Clark et al. 2011), and skeletal deformities in Scottish folds (Takanosu et al. 2008; Gandolfi et al. 2016) were included.

Only breeds recognized by the AKC, KC, and the FCI were included in the database. With respect to breeds, we did not accept "all breeds" as an option for the breeds for which a specific DNA test is offered. Moreover, laboratories that offer this option frequently do not state if they have found any homozygous or heterozygous animals in breeds other than those listed in the WSAVA-PennGen DNA Testing Database. It is, however, recognized that any DNA variant may potentially occur in any breed or in mixed breed dogs or domestic house cats due to interbreeding. Thus, information on mixed breed dogs was only included, if a DNA variant was not known to occur in any specific breed. Regarding domestic cats, breeds recognized by CFA and TICA as of 2020, and domestic shorthaired and longhaired cats where disease occurs have been listed.

Based upon technological advancements, the number of disease-associated DNA variants identified, and the many breeds affected, several commercial laboratories have developed high throughput platforms to offer breed-specific panels or testing for nearly all published DNA variants (comprehensive panels or all-breed panels). Since the programming of this current web resource for DNA testing was originally designed based upon individual variant diseases and breeds in 2010, genetic laboratories offering breed-specific and all-breed screening panels for dogs and/or cats are not contained within the database but are prominently featured (with corresponding links) on the homepage of the WSAVA-PennGen DNA Testing Database.

For some diseases and associated DNA variants, additional information is provided in the form of a PDF document. This includes a brief disease description, mode of inheritance, clinical signs, diagnostics, prognosis, and treatment options if any. While published data may be sparse, it also mentions how common a disease is in a certain breed (e.g., isolated case, family, widespread) and where the disease has been documented (regional vs worldwide) if known. The information is being gathered by the authors and from many colleagues with first-hand experience for specific diseases. Frequently, this included individuals who first discovered and/or characterized the DNA variant and disease. A questionnaire was created with Google© forms for the authors to complete with information about their DNA variants.

Statistical data analysis

Data pertaining to the number of laboratories, tests offered, as well as the number of variants and diseases was exported from the SQL system and analyzed to examine the difference between information compiled in the original and current database using MS Office and RStudio (version 3.6.2, RStudio Team 2020). Means and medians along with their corresponding standard deviations and interquartile ranges were computed. The Chi-square goodness of fit test was used to compare laboratory count data. For data where two percentages were compared, percentages were first converted into proportions before testing for statistical significance using the Chi-square test. A p value of < 0.05 was considered significant.

Results and discussion

Breadth of hereditary disease traits in companion animals

During the past decade, extensive progress has been made in the molecular genetic characterization of hereditary diseases and genetic predispositions in dogs and cats. Beside major advancements in clinical diagnostic approaches in veterinary medicine, the introduction of powerful molecular

genetic tools, such as genome wide association studies and whole genome or exome sequencing, led to detailed genomic information on hundreds of companion animals (Ostrander et al. 2017; Jagannathan et al. 2019; Longeri et al. 2019; OMIA© 2020). According to published lists of hereditary disorders (OMIA© 2020, Giger et al. 2006; Bell et al. 2012; Giger 2019), there are currently 775 hereditary diseases in dogs and 357 hereditary diseases in cats. For some diseases, the affected gene has been identified and sequenced and an increasing number of pathogenic DNA variants has been determined (Table 1). For instance, a single ancestral missense variant in the *F7* gene is responsible for the common mild coagulopathy (factor VII deficiency) in many dog breeds (Donner et al. 2016, 2019), while a half dozen disease-associated variants involving at least two genes (*SLC3A1* and *SLC7A9*) cause autosomal recessive, autosomal dominant, and androgen-dependent cystinuria in dogs (Brons et al. 2013). Similarly, in cats, erythrocytic pyruvate kinase deficiency causing intermittent hemolytic anemia has been associated with a single deletion in the *PKLR* gene in many different feline breeds and domestic house cats worldwide (Giger et al. 1997; Kushida et al. 2015), while several variants in two genes (*HMBS* and *UROS*) predominantly cause porphyria with erythrodontia and mild anemia as dominant or recessive traits in cats (Clavero et al. 2010, 2013). These examples from the authors' laboratory demonstrate the variety and complexity of hereditary diseases and genetic predispositions in dogs and cats, making it virtually impossible for any one individual to have a comprehensive knowledge of all hereditary disease traits, genetic variants, breed susceptibilities, and availability of genetic tests.

For the purpose of this database, with a similar trend in human medicine, and adopted in OMIA©, we define a single heritable disease as an illness with characteristic clinical signs and laboratory test and/or imaging abnormalities that occurs due to the presence of one or more genetic defects in one specific gene. Thus, a particular hereditary disorder can be caused by several different DNA variants in the same gene but are considered different diseases if different genes are involved. Different variants in the same gene may also cause different disease manifestations and varied modes of inheritance. Thereby, the anchoring of hereditary diseases and genetic predispositions by gene and then gene variants should avoid misunderstandings. There are also a few historical exceptions like von Willebrand disease type 1–3 in dogs based upon the different quantitative and qualitative effects of specific *vWF* gene variants (Brooks and Catalfamo 2010).

Structure of WSAVA-PennGen DNA Testing Database

The WSAVA-PennGen DNA Testing Database for hereditary diseases and genetic predisposition in dogs and cats, developed a decade ago, provides information succinctly and has become a valuable clinical resource for providing precise diagnoses and for insuring the breeding of healthy pets. Any DNA-testing laboratory can be listed without any charge and the database is freely accessible. The database has three search options, by disease/test, by breed, and by laboratory, and also uses synonyms and related terms to identify variants, genes, diseases, as well as abbreviations (e.g., PK for pyruvate kinase deficiency). For ease of navigation, drop-down menus allow for further filtering of searches by species, breed, and variant. The WSAVA-PennGen search function generates a single result page, reducing unnecessary scrolling to find the variant of interest and laboratories offering it. It also contains further descriptions in a PDF format for some diseases. The search engine result returns laboratories offering the test; the laboratory that found the

Table 1 Genetic diseases and DNA variants in dogs and cats listed in the WSAVA-PennGen DNA Testing Database comparing 2013 to 2020

	Dogs (*n*)		Change (%)	Cats (*n*)		Change (%)	Total (*n*)		Change (%)
	2013	2020		2013	2020		2013	2020	
Genetic diseases with known DNA variant(s)	121[a]	247[a]	+104*	27[a]	60[a]	+107*	148	307	+107*
Genetic disease tests listed in WSAVA-PennGen	111	228	+106*	20	37	+112*	125	265	+112*
Known DNA variants listed for genetic diseases in OMIA	109[a]	281[a]	+158*	25[a]	65[a]	+158*	134	346	+70*
Total DNA variants listed for genetic diseases in WSAVA-PennGen	143	353	+147*	24	49	+141*	167	402	+141*
Single DNA variant for a disease	87	218	+151*	15	27	+140	102	245	+140*
Multiple DNA variants for a single disease	24	46	+92	5	9	+90	29	55	+90
Range of variants	2–6	2–8		2	2–4				
DNA variants known to affect a single breed	100	227	+127*	15	20	+115	115	247	+115*
DNA variants affecting multiple breeds	43	96	+123*	9	16	+77	52	112	+115*

[a]Reported and/or listed in OMIA

*The following figures were found to be statistically significant with a *p* value of 0.05

defect and offering the DNA test is listed first, the rest listed alphabetically.

Content and developing trends of WSAVA-PennGen DNA Testing Database

Advancements in genetic technologies and increased owner and breeder interests have fueled the growth of the genetic testing industry. Of the hereditary diseases and genetic predispositions to disease reported to have one or more pathogenic DNA variants in dogs and cats that are listed in OMIA©'s database, a large proportion can be tested for clinical diagnostic, screening, and breeding purposes. The verified information on currently available DNA tests for hereditary diseases and genetic predispositions in dogs and cats is displayed on the WSAVA-PennGen DNA Testing Database website. The homepage search display (Supp. Fig. 1) for disease, DNA test, and laboratory are part of a computer program which has only undergone slight modifications since 2010.

Compared to the original database, the number of diseases and variants currently being tested has more than doubled (Table 1). The number of hereditary disorders caused by multiple different variants has also grown but is still small (Table 1). In contrast to humans that may have many different variants in same gene that cause a particular hereditary disorder with identical or similar clinical manifestations (apart from a specific ethnic group or geographic region) (Stenson et al. 2017; NCBI ClinVar), the number of variants in dogs and cats is relatively small due to common inbreeding practices. Based upon the origin and development of canine and feline breeds, several variants can be seen in multiple breeds, due to common ancestry, breed admixture to another breed, and/or splitting of one breed into different but closely related breeds. Due to inbreeding, animals with autosomal recessive traits are typically homozygous for the same DNA variant (while in humans affected are frequently compound heterozygotes). Even with autosomal dominant traits, affected animals in the same breed generally have the same variant. For autosomal recessive erythrocytic pyruvate kinase deficiency in dogs, there are five breed-specific *PKLR* variants described (Skelly et al. 1999; Gultekin et al. 2012). In cats, porphyria due to *HMBS* defects [six variants (Clavero et al. 2010, 2013)] and gangliosidosis GM2 due to *HEXB* deficiency [four variants (Muldoon et al.1994; Martin et al. 2004; Kanae et al. 2007; Bradbury et al. 2009)] are hereditary diseases with a large number of DNA variants. Noteworthy, there are also at least six different *CMAH* variants resulting in blood type AB (C) and B instead of the wild-type A in cats, and the associated naturally occurring alloantibodies are responsible for acute hemolytic transfusion reactions and neonatal isoerythrolysis (Kehl et al. 2019).

Mendelian disease traits in WSAVA-PennGen DNA Testing Database

The diseases included in this database are caused by genetic defects with simple Mendelian inheritance, and not those with complex inheritance. As highlighted in this DNA-testing database, the majority of genetic diseases represent autosomal recessive traits followed by autosomal dominant traits and X-linked recessive traits. These modes of inheritance were found at similar proportions in the past and 2021, and none of the changes was found to be statistically different (Table 2). For X-linked recessive traits, variants are frequently restricted to a particular family and individual variants are rarely seen in multiple families in companion animals like in humans, and thus do not affect larger breed populations [e.g., eight *F9* gene variants with two in the same canine breed (Airedale terrier) (Evans et al. 1989; Mauser et al. 1996; Gu et al. 1999; Brooks et al. 2003; Mischke et al. 2011a, b; Brenig et al. 2019)]. A nephritis in Samoyeds [*COL4A5* missense (Zheng et al. 1994)] and congenital cornification disorder in Labrador retrievers and Chihuahuas [*NSDHL* deletion (Bauer et al. 2017; Leuthard

Table 2 Modes of inheritance for canine and feline hereditary diseases in the WSAVA-PennGen DNA Testing Database comparing 2013 and 2020

Mode of inheritance	Dogs, %		Cats, %		Total, %	
	2013 ($n=130$)[b]	2020 ($n=229$)[b]	2013 ($n=25$)	2020 ($n=35$)	2013 ($n=146$)[b]	2020 ($n=246$)[b]
Autosomal recessive	82.3[a]	84.7	76.0[a]	77.1	86.3[a]	89.8
Autosomal dominant	10.0[a]	10.9	16.0[a]	17.1	11.6[a]	12.6
X-chromosomal-linked recessive or dominant[c]	6.2[a]	3.9	8.0[a]	5.7	6.8[a]	4.5

None of the values was found to be statistically different with a p value > 0.05

[a]FromSlutsky et al. (2013)

[b]One mitochondrial disorder included in total

[c]One and two X-chromosomal dominant traits in 2013 and 2020, respectively

et al. 2019)] are the only two known X-linked dominant traits (Table 2). Of course, the effects of a specific pathogenic variant of any Mendelian trait can be influenced by modifying genes, epigenetics, and environment, most of which still need to be elucidated in companion animals and other species (Lustgarten et al. 2020). It is also recognized that due to these influences, a DNA variant may be associated with more or less severe clinical manifestations in certain breeds or individuals. Despite great hope based upon the European Lupa project, complex disease traits are still not well defined at the molecular genetic level in companion animals and human patients (Lequarré et al. 2011). Therefore, DNA screening for complex hereditary diseases and genetic predispositions in dogs and cats is not yet established.

A concern that needs to be addressed with DNA testing is the correlation between DNA-testing results and disease manifestation and progression, i.e., genotype to phenotype correlation. Animals that test positive for a pathogenic variant may remain asymptomatic or may only occasionally develop clinical signs, as exemplified by variants causing a genetic predisposition to bleeding [such as factor VII deficiency in beagles (Donner et al. 2016)], cancer, and infection and other gene variants that are only mildly contributory to disease. Some individuals within a breed may show incomplete penetrance as had been observed with exercise induced collapse in Labrador retrievers [*DNM1* c.767G>T (Minor et al. 2011)], hyperuricosuria in Weimaraners [*SLC2A9*, c.616G>T (Karmi et al. 2010)], and degenerative myelopathy in Pembroke Welsh corgis [*SOD1*, c.52A>T (Awano et al. 2009; Ogawa et al. 2011)]. In addition, some variants have been identified to occur in other apparently non-related breeds, and clinical validity must still be established through genotype–phenotype correlations in these breeds.

While the main focus of the WSAVA-PennGen DNA Testing Database is to provide a comprehensive current searchable web resource to quickly find hereditary diseases, DNA tests, and laboratories offering DNA tests for genetic disease traits in dogs and cats, we have added PDF files with additional information for clinicians, breeders and pet owners for each hereditary disease in both species for some diseases (Supp. Figure 2). This includes the information on the web-search display, as well as clinical disease descriptions, onset of disease, typical clinical signs, mode of inheritance, diagnostic tests, prognosis, and recommendations regarding DNA testing. While the PDFs of several hereditary diseases have been completed, we are still in the process of adding others. Similarly, the OMIA© disease number retrieved with the disease name using the search engine for any disease one can directly access those documents by following the OMIA© link.

Laboratories contained in WSAVA-PennGen DNA Testing Database

The DNA-testing laboratories worldwide listed in the WSAVA-PennGen DNA Testing Database have only slightly increased from 43 to 47 currently (Table 3). During this period, there were 11 new DNA-testing laboratories added, and 7 were removed because of closures or mergers with other laboratories. Geographically, most DNA-testing laboratories are in North America and Europe with only isolated laboratories on other continents.

There are now more commercial and fewer academic laboratories compared to the past. The academic laboratories represent most often the investigators' laboratories in which the variants were originally identified. Since their focus is on research, and the daily operation of a diagnostic DNA-testing laboratory is time-consuming (from sample receiving to reporting results), and disruptive for research, it is understandable and appropriate that investigators leave the diagnostic screening to specialized diagnostic laboratories. This change, together with the freely accessible knowledge of DNA variants (abandoned patenting and licensing) and advancements in diagnostic technologies has led to a shift in testing primarily by academic laboratories to corporate laboratories. Accordingly, these laboratories are considerably larger and offer far more tests with automated processing. The average number of diseases and associated DNA

Table 3 Characteristics of DNA-testing laboratories for hereditary diseases and genetic predispositions in the dog and cat contained in the WSAVA-PennGen DNA Testing Database comparing 2013[a] to 2020

Parameter	2013	2020	% Change
Total, *n*	43	47	+9.3
Corporate/non-for-profit, *n* (%)	21/22 (49/51)	26/21 (55/45)	+23.8/ -4.5
Continents North America/Europe/others[a]	22/19/2	21/22/4	− 4.5/+15.8/+100
Genetic disease tested per laboratory			
Corporate/non-profit, mean (SD)	20.0 (NA)/5.0 (NA)	53.1 (46.3)/19.7(39)	+165.5/+294
Median (IQR)	15/2 (NA)	39 (14.5–82)/7.5 (1.5–20.8)	–
Range	1–67/1–27	1–162/1–176	–

[a]From Slutsky et al. (2013)

[a]Australia and Japan each one in 2013; Australia (2), Japan, and South Africa in 2020

variants that one DNA testing laboratory, independent of whether academic or corporate, is offering has, therefore, drastically increased (Table 3).

Multidrug Resistance 1 (*ABCB1*, c.295_298del) is the most common genetic predisposition test offered for dogs, occurring in several breeds, but other diseases such as von Willebrand disease type 1 (*vWF*, c.7437G>A), primary lens luxation (*ADAMTS17*, c.1473+1G>A), hereditary cataracts (*HSF4*, g.85286582_3insC), and canine degenerative myelopathy (*SOD1*, c.118G>A) are also offered by close to a dozen laboratories, with the majority being the corporate and/or panel testing laboratories. In cats, pyruvate kinase deficiency (*PKLR*, c.693+304G>A), polycystic kidney disease (*PKD1*, C.10063C>A), and AB blood grouping (*CMAH*, six variants) are the most common DNA tests offered. A few DNA variants are still patented and exclusively offered or only offered by few laboratories due to mutations and gene still being unpublished [for example, predisposition to avian tuberculosis in Miniature Schnauzers (Ghielmetti and Giger 2020) and hereditary necrotizing myelopathy in Kooiker hounds].

Testing for single trait versus breed-specific or all-breed screening

When the WSAVA-PennGen DNA Testing Database was developed a decade ago, only single tests were offered by laboratories. In addition, while each canine and feline breed is typically afflicted by a single variant for a specific hereditary disease exhibiting similar clinicopathological manifestations, several hereditary diseases and genetic predispositions are now recognized at the molecular level in several breeds. Thus, more DNA tests may become available for any breed. The largest number of DNA tests offered for any breed in the WSAVA-PennGen DNA Testing Database is for Labrador retrievers and domestic shorthair cats with 26 and 22 disease traits, respectively (Fig. 1).

Since the development of the WSAVA-PennGen DNA Testing Database for companion animals, technologies have advanced, and multiplex testing has become available and affordable. Therefore, a few DNA-testing laboratories specialize in panel tests, either for specific breeds or for all, or most available, hereditary diseases and genetic predispositions in either dogs or cats. To accomplish this, they use automated high throughput equipment with fast and precise testing abilities and integrated analyses and reporting. When performed in large numbers, these tests reduce the cost per DNA test drastically, meaning that a panel test for a breed or a species costs nearly the same as a single-DNA variant test. Several laboratories are now offering 'breed-specific' or 'all-breed' DNA test panels for either dogs or cats with currently three exclusively testing cats and five exclusively dogs (Tables 3, 4). The number of specific tests per breed reported in the WSAVA-PennGen DNA Testing Database is very similar to those offered in these panel tests by several laboratories and reported on by Donner et al. (2016, 2019) and Hayward et al. (2016). While many more DNA tests are now offered by these testing laboratories, no single laboratory offers all tests due to unpublished variants, patent or license restrictions, and/or lack of demand for testing.

In 2013, the only panel test available was through Genoscoper (later named MyDogDNA®, which is now owned by Mars®). As of 2021, there are currently eight DNA testing laboratories offering panel tests worldwide (Table 4).

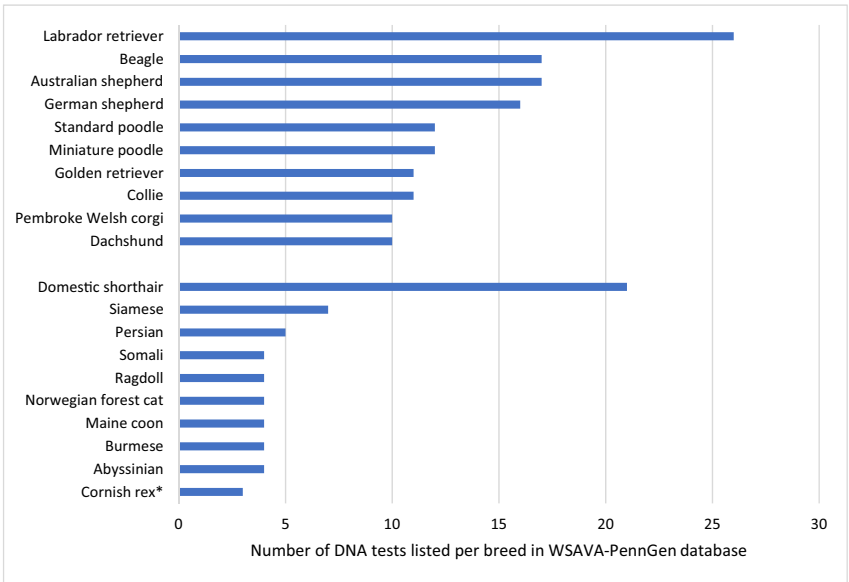

Fig. 1 Top 10 canine (a) and feline breeds (b) with largest number of DNA tests for hereditary diseases and genetic predispositions in the WSAVA-PennGen Testing Database in 2020

* These breeds all have the same three tests available: British longhair/shorthair, Cornish rex, Devon rex, domestic longhair, LaPerm, sacred Birman, Savannah, Scottish fold, Siberian, Singapura, Sphynx, oriental shorthair

Table 4 Panel all-breed or breed-specific panel DNA testing laboratories for health and breed-related disease-associated variants (alphabetically)

Laboratories	Location	Website	Canine (C) feline (F)	Breed-specific disease panel tests	Overall all-breed disease panel tests
Basepaws	Torrance, CA, USA	https://basepaws.com/	F		✓
Embark	Boston, MA, USA	https://mbarkvet.com	C		✓
Laboklin	Bad Kissing, Germany	https://laboklin.com	C/F	✓	
Mars/Wisdom Panel	Vancouver, WA, USA	https://www.mars.com/ https://www.wisdompanel.com/	C		✓
MyDogDNA		https://mydogdna.com	C		✓
Optimal Selection		https://optimal-selection.com	C/F		✓
MyCatDNA		https://mycatdna.com	F		✓
Orivet	Hartford, CT, USA St. Kilda, Australia	https://www.orivet.com/	C/F	✓	✓
Paw Print Genetics	Spokane, WA, USA	https://www.pawprintgenetics.com	C	✓	
Canine HealthCheck		https://www.caninehealthcheck.com	C		✓
My CatScan		https://www.mycatscan.com	F		✓
The Pet Genetics Lab	Isle of Man, UK	https://www.petgeneticslab.co.uk/	C/F	✓[a]	✓[b]
Veterinary Genetics Laboratory	Davis, CA, USA	https://vgl.ucdavis.edu	C/F	✓	

[a]Breed-specific tests offered only for dogs, not cats

[b]Overall all-breed tests offered only for cats, not dogs

Furthermore, of these panel laboratories identified, one company (Mars®) owns three of them (i.e., is the parent company), while Paw Print Genetics® has three different brands, two of which are panels for dogs and cats. Since these DNA panels are not breed and disease specific, laboratories offering these panels are not included in the database but are instead listed on the front page of the WSAVA-PennGen search engine with their hyperlinked URLs.

A discernment should be made between breed-specific DNA test panels for known DNA variants causing disease in the particular breed or 'all-breed' panel comprehensive DNA-screening panels. The latter assumes more of a 'one size fits all' testing kit, i.e., the panel offers screening for many diseases, some of which are relevant to a specific breed, while others may not be. In some cases, these comprehensive all-breed disease-screening kits specify which variants are relevant to a specific breed.

Additional considerations when testing for hereditary disease traits in companion animals

Compared to most other diagnostic tests used in clinical practice, genomic DNA tests identifying specific genomic variants have become the most accurate and precise diagnostic tests in clinical diagnostic laboratories. Mistakes with genomic testing for pathogenic DNA variant can be due to animal and sample misidentification and other human errors. Contamination is readily minimized by adhering to cleanliness protocols and avoiding cheek swabs immediately after puppies and kittens have nursed. Laboratories use robotics and unidirectional workflows to avoid any contaminations. In addition, allelic dropout continues to be an issue that can be difficult to avoid with most technologies; precautions can be taken to minimize this from happening (Shaffer et al. 2019a). However, the WSAVA-PennGen Database did not assess the quality of the laboratories listed. In human medicine, laboratories are assessed and approved to run only very specific DNA variant tests through a process that is rigorous. Currently, there are no official specific quality control assessments offered for genomic DNA testing in companion animals except regarding general good laboratory practice. Shaffer and her associates have published on the current situation in canine genomic DNA testing in companion animals and provided comprehensive proposals for improved practices, with standards and guidelines for quality assurance which should be followed (Shaffer et al. 2019a, b). When adding information to the database, if a website is found providing inaccurate information (for example, the wrong gene or mutation is listed for a test), we will contact that laboratory and refrain depositing that information into the database until the laboratories either clarifies or corrects the misinformation.

While the WSAVA-PennGen DNA Testing Database offers current information on DNA testing for variants associated with known hereditary diseases and genetic predispositions in dogs and cats, it does not address the need for genetic counselling. In human medicine, genetic

disease testing is typically tightly connected with medical genetic counselling. There is an urgent need to not only counsel the pet owner, but also the primary veterinary care clinicians, specialists, and breeders. Various laboratories offer additional information or even a veterinary consult service along with the test results, but additional counselling is clearly required, whether the animal is a pet or intended for breeding.

Unfortunately, very few veterinarians, geneticists, and breeders have specialized in or received training in genetic counselling. In addition, as revealed in OMIA© and the WSAVA-PennGen DNA Testing Database, there are so many different hereditary diseases and genetic predispositions in dogs and cats that one person cannot be knowledgeable in all of them. Instead, genetic counselling requires a concerted effort to share information between pet owners, clinicians, geneticists, and breed organizations as well as scientists. In the future, the diagnosis and management of complex traits with more than one major genetic variant, which is not addressed in this database, will make the situation even more daunting. This is certainly an area that needs to be rapidly developed to gain the most from the vast testing abilities currently available and which will likely expand rapidly in the near future.

Conclusions

The WSAVA-PennGen DNA Testing Database was the first and remains unique in that (1) it includes both feline and canine hereditary diseases, and (2) there is no charge for genetic testing providers to be listed in the database. It provides easily accessible information on DNA tests, afflicted breeds, and DNA testing laboratories for hereditary diseases and genetic predispositions in dogs and cats. While the structure has remained the same for the past decade, its content has been continuously updated and now contains more than twice as many variants and genetic diseases for which DNA testing is available. This searchable web resource will likely continue to be helpful to veterinary clinicians, pet owners, and breeders in their quest to diagnose and prevent hereditary diseases in dogs and cats.

It complements the most complete companion animal genetic database OMIA©, another free web-based resource, which does not have the practical search tools for laboratories, tests, and breeds. Very recently, International Partnership for Dogs (International Partnership for Dogs [IPFD] 2020) established a similar searchable database as WSAVA-PennGen DNA Testing Database, except it does not list information for laboratories not paying to be listed and does not list cats. The OFA provides a database of available tests through their partnership with the University of Missouri as well as providing a listing of other genetic testing laboratories but requires the user to navigate to these individual laboratories webpages to search for available tests (if not offered at University of Missouri) (OFA© 2020). Several previous online resources are no longer available or have not been updated regularly (Nicholas et al. 2011; Slutsky et al. 2013).

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Compliance with ethical standards

Conflict of interest The authors are or were associated with the academic PennGen Laboratories which offer DNA, metabolic, and hematological testing for certain hereditary diseases in dogs and cats.

Data availability statement The datasets generated and analyzed are available upon request from the authors.

Animal use approval Not applicable as neither animals nor tissue samples were used in this study.

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