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Update on WSAVA's work on hereditary diseases

Urs Giger

Section of Medical Genetics, School of Veterinary Medicine, University of Pennsylvania, 3900 Delancey St, Philadelphia, PA 19104-6010, USA

Taking a look at the WSAVA Hereditary Diseases Committee

The World Small Animal Veterinary Association's (WSAVA's) Hereditary Diseases Committee (HDC) was formed to offer small animal clinicians around the world clinically relevant information on the diagnosis and management of hereditary diseases and genetic predispositions to disease in dogs and cats. Its key achievement so far is the creation of an online DNA database on hereditary diseases which is accessible free of charge to practitioners wherever they are working. Committee members also offer educational seminars to improve the genetic health of companion animals worldwide. Committee chair Professor Urs Giger from the University of Pennsylvania offers this update on its work.

Where are we now?

Incredible progress has been made in understanding hereditary diseases and the genetic predisposition to disease in dogs and cats which have become recognized as a key clinical issue in small animal practice worldwide. Hereditary diseases are seen both in purebred animals and in mixed-breed dogs and domestic cats, but in-breeding practices certainly favour the more frequent occurrence of specific hereditary defects in specific breeds (e.g. anaemia caused by PK deficiency in West Highland White terriers and Abyssinian cats but also others). Some are present at birth; others become evident as puppies and kittens grow while yet others cause disease only in adult animals. Genetic defects can affect any organ system and include malformations, inborn errors of metabolism and genetic predispositions to infections, immune diseases, drug reactions, cancer, and degenerative diseases.

We don't know the exact number of hereditary diseases affecting dogs and cats because some disorders are poorly defined, while others are caused by different mutations in the same or different genes. Progressive retinal atrophy, for instance, is based upon clinical onset and progression, as well as pathological and molecular studies a very heterogeneous group of blinding disorders. Similarly, epilepsy is expected to be caused by different gene defects, but little is known as of today about the molecular basis. Overall, the latest thinking suggest that cats may be affected by few hundred hereditary diseases while around one thousand are likely to affect dogs.

Most of the hereditary diseases which are clearly defined are known to be inherited by an autosomal recessive trait. This means affected animals are homozygous for a specific gene mutation. Its parents appear clinically unaffected but are carriers. Less common are those with an x-chromosomal or dominant mode of inheritance. Some of the common predispositions to disease are being recognised to have a complex inheritance pattern; this means more than one mutation is responsible (polygenic) and that disease expression is further influenced by the environment. Examples include hip and elbow dysplasia, immune-mediated disorders, and cancer predispositions.

The completion of the canine and feline whole genome sequences and the development of more sophisticated and affordable genetic laboratory tools have led to rapid progress in our understanding of health and disease at the molecular genetic level. Currently more than two hundred disease-causing mutations have been identified in dogs and approximately three dozen mutations in cats. More discoveries are imminent. These are typically breed-specific, but some are ancestral, causing disease in many different breeds. In general, DNA mutation tests for established diseases in specific breeds are the most accurate and precise diagnostic tests available in clinical practice. In addition, DNA marker tests referring to a genetic single nucleotide polymorphism (SNP) near the disease-causing mutation can be helpful. For others, characteristic clinical signs, routine and special laboratory test abnormalities may support a diagnosis.

Treatment and Control of Hereditary Diseases

Treatment for hereditary diseases and genetic predisposition is often limited clinically but some diseases can be cured or well controlled. For instance, hereditary cobalamin malabsorption seen in several canine breeds can be treated with cobalamin injections every two-four weeks. Bleeding due to von Willebrand disease, haemophilia and other coagulopathies can be treated with plasma transfusions. A type of cystinuria seen in many breeds, including Mastiff-types, Scottish Deerhounds and Irish terriers, can be cured by castration. However, many diseases can only be managed with supportive care and are still progressive.

This makes the key issue the genetic control of these hereditary diseases in future generations. While it is simple to stop breeding affected animals and carriers, this can result in a further reduction in the narrow gene pool of a breed and it is important to remember that carriers with excellent breed characteristics can be safely used when DNA tests are available so long as they are bred to clear/normal animals and offspring considered in future breedings are tested.

How the WSAVA Hereditary Disease Committee Helps

For the small animal clinician, keeping up with the immense recent progress can be overwhelming as the information available on clinical genetics and the spectrum of disorders and genetic predispositions continues to accumulate. It can be a daunting task to diagnose and manage patients with hereditary diseases in each breed and to engage constructively with breeders. The WSAVA Hereditary Disease Committee aims to help by providing

readily accessible and comprehensive resources in various forms on hereditary disease testing and management in small animals.

In 2012, we launched a web search tool and database, allowing clinicians to search for information on the DNA tests which exist for specific hereditary diseases, breeds, and the labs that test for them. This database, which is constantly updated, is one of the most frequently accessed resources on the WSAVA website. It is based at the University of Pennsylvania with access free to veterinarians, breeders and pet owners. You can check out the resources on the WSAVA Hereditary Diseases here: <http://www.WSAVA.org/HereditaryDefects.htm>

The Emerging Issues related to Hereditary Disease

Several emerging issues are posing new challenges and changing our approach to hereditary diseases.

Genetic disease counselling

Clinicians should play a crucial role in guiding their clients – pet owners and breeders - on the diagnosis, management and control of hereditary diseases. Quantitative objective measures as to the tests to be considered for the wellness screening of puppies and kittens need to be developed. As the onset and severity of the disease, diagnostic test, options to treat, and mode of inheritance vary, specific recommendations are needed. Sound recommendations are particularly challenging to formulate for complex disease traits. These diseases are currently being actively investigated to provide a better understanding and sound guidelines. There is no animal completely free of any deleterious genes.

Breed club recommendations and laws

Several countries have animal welfare laws preventing the breeding of affected animals. A number of national breed clubs and associations have also implemented strict guidelines for breeding. Informed responsible breeding should be implemented for the welfare of animals. We welcome these developments and encourage that clinicians utilize these sources and specific guidelines in their region?

Laboratories offering specific DNA tests

There has been an increase in laboratories offering DNA tests for specific hereditary diseases and other genetic traits. DNA tests specific for a particular mutation are generally robust but there are no accreditation processes currently in place to assure quality in each laboratory. We aim to set standards for laboratories which may restrict testing to laboratories using the best techniques as well as appropriate controls. The move toward new affordable chip and other technologies will further change testing from single disease tests to panel testing which likely will be restricted to larger laboratories.

Prevalence of diseases and registries

Until now, it has been difficult to get reliable assessment of the frequency of diseases in a breed and region. Samples submitted to laboratories are biased and often driven by the

discovery of affected and carrier animals and breeder participation. Furthermore, laboratories do not necessarily post or share the number of animals tested and screening results. With a good test and follow through by breeders, the disease and carrier prevalence may rapidly decline and even become eradicated. The frequency may also vary between countries based upon their participation in screening programs and popular sires used in breeding. Registries such as OFA are a good source, but they are based on voluntary disclosures. CERF and PennHIP are two examples of registries containing every tested animal.

Patents for DNA tests

Until recently DNA mutations could be patented which limited the availability of tests to certain laboratories receiving a license – and thereby also made them more expensive. However, as these are naturally occurring mutations and not innovations and their discoveries are supported by federal funds, they can no longer be patented in the USA and DNA tests are now becoming more readily available after peer-reviewed publication.

Panel screening in breeds and species

Mixed-breed and purebred tests have been available for a few years. They are based on chip technology and assess multiple alterations in the genome (SNPs - single nucleotide polymorphism). This and other technologies have been recently applied to hereditary disease mutations. In fact, it is now possible and more affordable to even obtain a whole genome sequence of an animal which could reveal all deleterious traits known at the molecular level. Panel screening can make testing simpler but interpreting the vast data information is more complicated. No animal will be found to be perfect, particularly if its entire genome is sequenced and analysed. It is also a concern that a certain disease-causing mutation in a particular breed may not clinically manifest the same way in another breed as modifying genes may be improve or worsen the condition as much as environmental influences.

Distribution of updated information

It is a major task to collate and keep up-to-date the ever-growing resource of information on hereditary diseases and genetic predispositions. This is particularly challenging as molecular genetics is not (yet) the regular vocabulary of clinicians, therapeutic opportunities are limited, genetic counselling is different for each disease and can be time consuming and breeders may not follow through with recommendations for healthy breeding. Thus, it will also be important to educate breeders and show judges to improve the genetic health of animals.

To help increase the supply of information and to update small animal clinicians globally, the theme for this year's WSAVA World Congress 2017 is Hereditary Diseases. During Congress, global experts including members of the WSAVA Hereditary Disease Committee will update delegates on important developments and practical tips on hereditary diseases and discuss the topic with a broad perspectives.

WSAVA World Congress takes place from September 25–28, 2017 in Copenhagen. Early bird booking rates end in May 2017. Further information is available here: www.wsava2017.com.

What is the WSAVA?

The WSAVA aims to enhance the quality of veterinary care for companion animals and to create a global community of veterinarians, working together for the benefit of both animals and people. Its members and affiliates comprise 101 veterinary organisations from around the world, including the BSAVA. Between them, they represent around 200,000 individual veterinary clinicians. The BSAVA is one of the WSAVA's strongest supporters, and many of our members have held or are holding offices in the Association, with a number active on its working parties and committees. As a BSAVA member, you are automatically a member of the WSAVA.

Who sits on the WSAVA Hereditary Diseases Committee?

Professor Urs Giger, University of Pennsylvania (chair)

Adjunct Professor Jerold Bell, Tufts University and private practitioner

Dr Neale Fretwell, Mars Veterinary

Professor Ake Hedhammar, Swedish University of Agricultural Sciences

Dr Cathryn Mellersh, Animal Health Trust

Professor Claire Wade, University of Sydney

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