Unnatural selection? Considerations in canine and feline genetic counseling

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Abstract

Molecular genetics and growing availability of molecular technologies are expanding exponentially, pushing boundaries of modern medicine. These bring continued challenges for veterinary genetic counseling which often falls behind human counterparts. There is an increasing need for veterinarians to not only understand this technology, but also to counsel clients to use it appropriately and be an informed voice in current political and socioeconomic debates. A basic understanding is important for veterinarians to use available technologies to control genetic diseases while maintaining genetic diversity in population. Veterinarians, particularly reproductive veterinarians, are in a unique position to bridge the knowledge gap between advancements in genetic science and clinical applications in small dog and cat breeding operations. Veterinarians can help breeders utilize tools such as estimated breeding values, inbreeding or heterozygosity estimates and mutation based genetic disease tests optimally in their breeding programs. There is a critical need to understand that mistakes of past should be replaced by exciting technological advances of future to implement breeding strategies that will more effectively reach small animal breeder's goals of producing dogs and cats that not only are what is desired for appearance, temperament, and workability, but also live long and healthy lives.

Keywords: Genetic counseling, genetic testing, estimated breeding values, population diversity, inbreeding coefficient, heterozygosity

Introduction

With recent advances in molecular genetics and growing availability of molecular technology, we witnessed emergence of genomics into our everyday lives. As we still struggle with bioethics, this technology is expanding at an exponential pace. We live not only in a world where we are constantly pushing boundaries of modern medicine, but also where this technology is readily available, even to public. This brings continued challenges for veterinary profession, which has often fallen behind human counterparts in veterinary genetic counseling. There is an increasing need for veterinarians to not only understand this technology, but to counsel our clients regarding implementation of this technology, as well as to have a voice in current political and socioeconomic debates.

Currently, there are > 700 known hereditary diseases in dogs and ~ half as many in cats, with a growing number of new diseases reported every year.[1] This led to development and growing need for incorporation of clinical genetics into veterinary practice, with small animal practitioners having an ever growing and vital role in both genetic counseling and detection of potentially new genetic diseases.

Hereditary disease is caused by a DNA mutation that can be passed from parent to offspring, whereas a congenital disease is present at birth. With this distinction, congenital diseases can be genetic, but not all congenital diseases are genetic.[2] For example, an autosomal recessive gene mutation in Portuguese water dogs results in early-age dilated cardiomyopathy and sudden death (Portuguese water dog juvenile dilated cardiomyopathy); however, perinatal infection with parvovirus can result in myocarditis with resultant myocardial damage, heart failure, and sudden death in young puppies as well.[3,4] Onset of clinical signs can vary for hereditary diseases. Some hereditary diseases may be apparent at early ages where most common presentations are embryonic/fetal death, stillbirth, or fading puppies/kittens. Unfortunately, many are undiagnosed as breeders and veterinarians may not pursue additional diagnostics in these prenatal and neonatal cases. Traditionally, hereditary disorder clinical signs may not be recognized until after weaning, as musculoskeletal, ocular, digestive and other anomalies may not be readily identifiable during neonatal phase of development. Some diseases may have a much later onset. One example is progressive retinal atrophy; affected animals suffer from retinal atrophy that leads to eventual blindness, with clinical signs rarely apparent before 3 - 5 years of age.[5]

Number and variety of genetic diseases is extremely large and many are very rare, with new diseases recognized at an exponential rate.[6] As such, it is important for a practicing veterinarian to consult reference sources (listed in Table) to obtain knowledge about a known genetic disorder, breed distributions, and distinguishing characteristics regarding diagnosis, treatment, and control. When previously undefined disorder is encountered, evidence of its genetic etiology should be ruled out.[7]

- Does the disorder occur in a greater frequency within a line or breed than in general population?
- Is the disease more common in animals with a higher degree of inbreeding (you need more than a typical 3 - 5 generation pedigree to reveal a more accurate degree of inbreeding)?
- Does the disease have a characteristic age of onset and clinical course, especially when seen in young animals?
- Is the same syndrome found in another species and is it known to be genetic?
- Is there a specific phenotypic defect or syndrome that is associated with a specific chromosomal abnormality?
- Can the disease process be related to a molecular defect such as a defect in an enzyme pathway, structural protein, or molecular receptor?

It is noteworthy that genetic diseases are not limited to purebred dogs and cats. Although mixed-breed dogs generally have a lower degree of inbreeding, many populations (e.g. local stray cats) may have a higher than expected degree of inbreeding. In general, autosomal recessive diseases are more likely to be expressed when there is a higher degree of inbreeding. However, dominant disease and polygenetic diseases may be just as likely in mixed breed populations as they are in more inbred populations, depending upon the disease and the population.[2]

Diagnostic approach to identifying genetic disorders

Clinical approach to identify genetic disease begins with a thorough history and physical examination. Additional queries regarding littermates and relatives as well as in some cases, a population medicine approach when dealing with kennels and catteries, will assist with collection of infectious disease, toxin, nutritional, and other important data to be considered in investigation of new diseases. Diagnostic tests generally are required to further support a genetic disorder in a diseased animal.[8] For example, radiology and other imaging techniques may reveal skeletal malformations, echocardiogram may reveal cardiac anomalies and ophthalmologic examination may further define an inherited eye disease. Routine tests such as a complete blood cell count, chemistry screen and urinalysis may suggest specific hematologic or metabolic disorders and may help rule out many acquired disorders. Based on these findings, additional clinical function testing may more clearly define a gastrointestinal, hepatic, renal, or endocrine problem.[10,11] Histopathology of a tissue biopsy or a necropsy evaluation from an affected animal are often required for a complete evaluation and definitive diagnosis for animals with a genetic defect. The latter is particularly important when faced with a fading neonatal puppy or kitten, as this may give information vital to surviving littermates as well as future planned breeding; however, this important diagnostic tool is often underused.

Few laboratories provide special diagnostic tests that allow for investigation into a possible inborn error of metabolism (Table). Inborn errors of metabolism include biochemical disorders due to a genetic defect in structure and/or function of a protein or receptor. For example, a deficiency in enzyme β - glucuronidase resulting in the lysosomal storage disorder Mucopolysaccharidosis VII has been reported in German shepherd dogs as well as a mixed-breed dog.[10] Most useful specimen to detect biochemical derangements is urine, as abnormal metabolites are filtered but not resorbed by kidneys.

Table. Some useful websites relating to canine and feline genetic diseases

Listings of available tests and testing center information:

- http://www.akcchf.org/
- https://embarkvet.com/
- https://www.optimal-selection.com
- https://www.betterbred.com/
- http://research.vet.upenn.edu/Default.aspx?alias=research.vet.upenn.edu/penngen
- http://www.vmdb.org/cerf.html
- ttp://www.vetgen.com/
- http://www.vgl.ucdavis.edu/
- http://www.vetdnacenter.com/
- http://www.caninegeneticdiseases.net/
- http://www.healthgene.com/
- http://www.labradorcnm.com/
- http://www.vdl.umn.edu/
- http://www.vetmed.wsu.edu/deptsVCGL/
- http://www.aht.org.uk/genetics.html
- http://vetmed.tamu.edu/labs/cytogenics-genomics
- http://www.babs.unsw.edu.au/canine_genetics_facility.php
- http://www.medigenomix.de/zuechterservice_hund.html
- http://www.catgenes.org/
- http://www.dogenes.com/
- http://www.animalsdna.com/

Databases and recommendations for health screening:

- http://omima.angis.org.au/
- http://sydney.edu.au/vetscience/lida/
- http://ic.upei.ca/cidd/
- http://www.vet.cam.ac.uk/idid/
- http://www.caninehealthinfo.org/
- http://www.gdcinstitute.org/
- http://www.rvc.ac.uk/VEctAR/

Metabolic screening laboratory:

- http://research.vet.upenn.edu/Default.aspx?alias=research.vet.upenn.edu/penngen

Karyotyping/Cytogenetic services:

- http://vetmed.tamu.edu/labs/cytogenics-genomics/karyotyping
- http://www.vgl.ucdavis.edu/services/index.php
- http://www.vet.upenn.edu/RyanVHUPforSmallAnimalPatients/SpecialtyCareServices/MedicalGenetics/ResearchFacilities/CytogenicsLab/tabid/708/Default.aspx

Selected parentage testing services:

- http://www.vgl.ucdavis.edu/services/index.php
- http://www.vetgen.com/canine-profiling-parentage.html
- http://www.vetdnacenter.com/canine-parentage-test.html
- http://www.dnares.in/canine-veterinary-genetic-dna-parentage-testing-kits-laboratory.php
- http://www.uq.edu.au/vetschool/agl
- https://www.pawprintgenetics.com/parentage/product-select/
- https://dnaproofofparentage.com/
- https://www.happydogdna.com/proof-parentage/
- https://www.homednadirect.com/animal-dna-tests/

Selected DNA storage services:

- https://www.ofa.org/about/dna-repository
- http://www.animalsdna.com/www.animalsdna.com/web/page/canine/dna_banking/index.html
- https://www.vetgen.com/services-other.html
- https://www.antagene.com/en/antagene/dna-storage-service

In breeding/Heterozygosity evaluations

- https://embarkvet.com/
- https://www.optimal-selection.com
- https://www.betterbred.com/

Once identified, defect can be further investigated with more specific protein assays. Section of Medical Genetics at University of Pennsylvania School of Veterinary Medicine is one of few places that perform such tests to diagnose as well as to discover novel hereditary disorders www.vet.upenn.edu/penngen.[9]

In addition, few laboratories offer cytogenetic studies to evaluate for potential abnormalities in chromosomes (Table). Any cell capable of dividing can be used for this purpose; however, most commonly, blood lymphocytes or skin fibroblasts are used. For lymphocyte culture, blood is collected into sodium heparin, cultured in media and stimulated to divide. Cells are arrested in mitosis during metaphase where chromosomes are compacted. Chromosomes can then be stained to yield a typical banding pattern of chromosomes used in traditional karyotyping, or fluorescent probes can be used in a technique known as fluorescence *in situ* hybridization.

A thorough investigation into the family history of a patient with a suspected genetic disease is also important to determine a potential mode of inheritance. Knowing how a disease is passed from generation to generation is critical to plan a breeding program to manage genetic diseases, as well as starting investigation into a genetic cause of a new disease presentation. Inheritance patterns reported in veterinary medicine include autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant and complex (polygenetic) diseases.[2] Recessive diseases account for a majority of diseases for which a known inheritance pattern and a genetic defect are not identified.[12] However, with continued advances in molecular biology and technology, this is also becoming true for complex (polygenetic) disorders.

Types of genetic disorders

Autosomal recessive diseases are identified most commonly at presentation of affected animals with both sexes equally represented born to clinically normal parents. Typically, clinically normal parents have a common ancestor. These animals that are phenotypically normal are referred to as carriers (heterozygous for the disease-causing allele).[2] Common theories for increased prevalence of expression of autosomal diseases in purebred dog and cat populations include higher degree of inbreeding related to popular sire effects, selective inbreeding, and bottlenecks in their populations.

Autosomal dominant diseases are often seen with an affected individual produced from at least one affected parent, since carrying either one (heterozygous) or both (homozygous) copies of mutant allele will result in disease. However, not uncommonly, new mutations can occur which result in an affected animal that is produced by 2 clinically normal parents.[2] In some cases, diseases are referred to as being incompletely dominant. Traditionally, incomplete dominance occurs when expression of disease with a heterozygous genotype (one copy of the mutant allele) is an intermediate or has variable disease expression. In these cases, parents with the disease-causing allele may not exhibit any clinical signs and appear normal, yet they may pass that disease causing allele to their offspring. Some theorize that interactions with other modifying genes and in some cases, environment, affect disease expression and severity, making some believe that a proportion of these incompletely dominant diseases may have inheritance patterns more similar to complex modes of inheritance.

X-linked recessive diseases are distinguished mainly by males being predominantly affected. Females are far less likely to be affected based on the presence of 2 X chromosomes and requirement for an affected male to survive long enough to reproduce with a carrier female in order to produce an affected female offspring.[8] First canine mutation discovered was X-linked recessive disease, Hemophilia B.[13] X-linked dominant diseases are extremely rare, e.g. X-linked Alport syndrome in Samoyed dogs.[14]

Y-linked disorders are caused by Y chromosome mutations. Since males inherit a Y chromosome from their fathers, every son of an affected father will be affected. However, since females only inherit an X chromosome from fathers, female offspring of affected fathers are always normal with Y-linked disorders. Since Y chromosome is relatively small and contains very few genes, there are relatively few Y-linked disorders and none reported in small animals. Another rare mode of inheritance in veterinary medicine is mitochondrial inheritance. This type of inheritance, also known as maternal inheritance,

applies to mutations of genes in mitochondrial DNA. Since only oocytes contribute mitochondria to the developing embryo, only mothers can pass on mitochondrial conditions to their offspring.[8]

Complex disorders are more difficult to identify as they result from combination of effects of multiple genes (polygenetic) as well as environmental influences that result in an expressed phenotype. Although complex disorders often cluster in breed or family lines, they do not have a clear-cut pattern of inheritance as seen with single-gene disorders.[2] This non-Mendelian inheritance pattern, as is often used to describe complex disorders, makes it difficult to determine an animal's risk of inheriting or passing on these diseases. Complex disorders are also more difficult to study and identify all factors leading to expression of disease. However, common veterinary diseases are increasingly recognized as having a genetic, heritable component. In fact, some common diseases recognized in veterinary medicine meet these criteria, including hip dysplasia, hypothyroidism, cancer and atopy.[15] Some argue that everything has a genetic component and it is how these genes are expressed by a multitude of factors that determines rate of disease. With increasing knowledge of gene involvement in disease, clinical veterinary genetics becomes increasingly important in diagnosis, management and prevention of disease in our patients.

Identification of unknown genetic diseases: genetic tests advantages and limitations

Veterinarians are part of an important team involved in identification and control of genetic diseases. Breeders, pet owners, primary care veterinarians, veterinary specialists, veterinary researchers, genetic databases and research funding institutions comprise vital pieces of this team. When a new genetic disease is suspected, team members need to work together to compile information and resources required to determine gene defect(s) involved. Sometimes this is not straightforward and easy. In general, researchers often modify and combine multiple techniques in uncovering a genetic mutation process, most common being genome-wide association study and candidate gene approach.

Genome-wide association studies compare DNA of 2 groups of participants: affected animals and similar animals without disease (normal controls). DNA is collected from these individuals and gene chips along with computer technology are used to read millions of DNA sequences. However, rather than reading entire DNA sequence, single nucleotide polymorphisms (SNPs) are used. SNPs are variations in a single nucleotide of a DNA sequence, used as markers for evidence of DNA variation. Different variations are then identified along with their association with different traits. If genetic variations are more frequent in diseased animals as compared to normal controls, variations are considered associated with the disease. Associated genetic variations are then considered linked-markers to the region of the genome where the disease-causing problem is likely to reside. Most SNP variations associated with disease are not in DNA region that codes for a protein. Instead, they are usually in large noncoding regions on the chromosome between genes that are edited out of the DNA sequence when proteins are processed. However, once these markers are linked to a disease, further molecular techniques can be utilized to narrow down the region and sequence potential genes, thus identifying mutations.[16]

Another method utilized in genetic mutation investigation is candidate gene approach. This approach requires researchers to investigate validity of an educated guess about genetic basis of a disorder, as opposed to genome-wide association studies that are predicated on an unbiased search of entire genome without preconceptions about role of a certain gene. Similar to genome-wide association studies, candidate gene approach involves comparison of affected individuals with normal controls; however, since 1 gene is the focus, large populations are not required for an association with disease to be detected. Major difficulty with this approach is that to choose a potential candidate gene, researchers must already have an understanding of disease pathophysiology and potential genes that may influence the mechanism of that specific disease, e.g. gene mutation known to cause same disease in another species.[17,18]

Often, linkage to a disease is known before mutation is identified. Linked marker testing can then be utilized to assist breeders in breeding choices before a mutation-based test is established. It is important for veterinarians and breeders to understand advantages and limitations for a particular genetic test to achieve their goals of controlling genetic diseases while maintaining genetic diversity in population as a whole. Several types of inherited disease screening and genetic tests are described in veterinary

medicine, including phenotypic testing, linked-marker testing and mutation-based tests. In short, not all genetic tests are created equally and understanding various types of tests along with mode of inheritance of a disease is vital to use tests appropriately. For example, linked marker testing may have 2 potentials for errors. First error can occur from a recombination event where the marker is no longer linked to mutant allele, resulting in either a false positive or false negative test.[2] In general, closer the marker is to mutant allele, more likely they will remain together, or linked, and less likely recombination will result in their separation. Another error occurs if the marker is not linked to mutant allele, but is present in a high enough frequency in the population that it may initially appear linked, resulting in a false positive test.[2] Although caution must be used when interpreting test results, it is important to recognize that a linked marker test is extremely useful when dealing with a disease for which the mutation is not yet known.

Once a gene mutation is identified, it is important to note that these mutations are very specific. Small animals within same or a closely related breed may likely have same disease-causing mutation for a particular disease. However, small animals of other breeds, particularly unrelated breeds, with same disorder, may also have different mutations that may not be detected with a mutation-based test.[8] There may also be > 1 genetic mutation within a breed that may result in similar clinical signs and in these cases, all mutations need to be evaluated.

DNA tests have several advantages. Test can be performed at any age and long before clinical signs become apparent, detecting affected, normal and carrier animals. DNA can be extracted from any nucleated cell, such as white blood cells, cheek cells, hair follicles, semen and even formalinized tissue. Cheek swabs should be used very cautiously or avoided in nursing animals due to potential contamination of oral cavity with maternal nucleated cells.[8] Since DNA is very stable and small quantities are required, it can be banked for long-term storage and utilized in future genetic studies. There are several veterinary DNA storage facilities for this purpose. Key factor in usefulness of DNA for future studies is determined by complete and thorough records on that animal. An animal suffering from an inherited disease needs to have an accurate diagnosis of the cause of that disease in order to prevent false associations when utilizing that animal's DNA for a potential gene mutation study. For example, a cat with suspected liver disease due to amyloidosis needs to have histopathological conformation of that disorder, or there is a risk that an animal with hepatic adenocarcinoma may confuse and invalidate future genetic studies.

Although identifying genes causing disease is of valuable assistance, that alone is insufficient. Understanding how to implement testing and educating clients to responsible use of these technologies is vital. So, knowledge of molecular genetics and current biotechnology is only 1 piece of the puzzle.

Genetic diversity

Development of pedigree animals are due to selection for a particular set of physical and/or behavioral characteristics. This can be considered both a "blessing and a curse", because the result has been obtained from inbreeding within close family lines resulting in both preservation of desired features as well as undesirable genetic traits becoming fixed within breeds.[19,24] Closed populations, such as purebred animals, with high levels of selection pressure, suffer from a loss of genetic diversity. For example, in dogs, 2 major events resulted in a significant loss in genetic diversity which only continues in these closed populations. These 2 major events include domestication and development of breeds. In managed populations, genetic diversity can be maintained by careful selection in order to maximize optimal contributions of each breeding animal.[20.26] However, in most purebred organizations, e.g. dog breed clubs, there is no single organization to assist with directing breeding strategies.[24] This is why veterinary genetic counseling is so vital to the future of dog breeding. Individual breeders should have insight into population genetics and methods to preserve as much genetic diversity in these closed breeds as possible.[23] Veterinarians offer a great way to improve that insight and bridge the knowledge gap.

Evaluating genetic diversity

One of the oldest observations of population genetics is that inbreeding reduces fitness in offspring compared to offspring of unrelated individuals. Consequently, most human populations prohibit marriage of related individuals and many animal breeders discuss measures of inbreeding. Inbred

individuals have a lower degree of genome wide diversity or heterozygosity because a fraction of their genome is identical by descent inherited by a common ancestor. All measures of inbreeding attempt to predict the proportion of the genome that is identical by descent.[21,22] Classical measure of this is the pedigree in breeding coefficient.[28,29] Calculated inbreeding coefficient predicts proportion of the genome that is inherited by descent due to known common ancestor of parents and the assumption that the pedigree founders are unrelated and not inbred. While traditionally, the coefficient of inbreeding has been considered the best measure for an individual's inbreeding, it has been suggested to be imprecise due to several factors, including inability to account for inbreeding caused by distant ancestors not included in the pedigree. With development of molecular technologies, genetic evaluations of inbreeding have been replacing traditional probability calculations.[27]

Several techniques have been described to evaluate genetic diversity being reported as an evaluation of heterozygosity rather than the traditionally reported inbreeding coefficient designed by probability calculations of pedigrees.[25,26] There are 3 main companies offering genetic testing services that includes an evaluation of heterozygosity. These companies are utilizing either short tandem repeats (STRs) or single nucleotide polymorphisms (SNPs).

A short tandem repeat (STR) in DNA occurs when a pattern of 2 or more nucleotides is repeated and repeated sequences are directly adjacent to each other. An STR is also known as a microsatellite. Pattern can range from 2 - 6 base pairs and is typically in a noncoding region of DNA. As noted above, single nucleotide polymorphisms (SNPs) are genome regions in which 2 strains differ by a single base pair. Both methods of genome scanning have application-dependent advantages and disadvantages.

Microsatellies can arise through replication slippage, unequal crossing over, or mutations extending or interrupting a series of repeats, whereas SNPs generally arise via point mutations. As a result, new microsatellite variations arise more frequently than new SNP variations. However, the absolute number of SNP differences is about a thousand-fold higher than microsatellite differences. Thus, SNP and microsatellite analyses can provide complementary information, with each is better suited for some tasks than others.[28]

Microsatellites have been the genetic markers of choice for > 2 decades. They are informative and interspersed throughout the entire genome. However, microsatellites can be more time consuming for trained personnel to analyze, even with appropriate software or automated methods. Recent advances in high-throughput DNA sequencing, computer software and bioinformatics have increased popularity of SNPs. They have promising advantages, including greater abundance, genetic stability, simpler nomenclature and suitability to automated analysis and data interpretation. Furthermore, SNPs have been used in discovery of quantitative trait loci (QTL), the association of phenotypic traits and genetic markers allowing for evaluation of specific productive traits and identification of individuals and breeds.[23]

Consolidation of tests: current trends

Currently, there is a move toward consolidation of many available genetic tests from small businesses and universities to larger companies offering analysis of genetic diversity (based on SNPs or microsatellites to evaluate in-breeding). Sudden availability of large amounts of genetic data for breeders is frequently misinterpreted and is an opportunity for veterinarians to bridge the knowledge gap. Some of these companies include Embark, Optimal Selection and BetterBred. Optimal Selection currently offers similar testing for cats. Embark and Optimal Selection are utilizing SNPs, whereas BetterBred, which is partnered with the University of California Davis Veterinary Genetics Laboratory, utilizes microsatellites and is available only for certain breeds. In addition to offering tools for evaluating in-breeding of individual dogs, both Optimal Selection and Embark have begun offering a "match making tool" that compares genetic diversity information between individuals of a proposed mating.

Estimated breeding values

Currently, the vast majority of genetic tests available are for single-gene disorders. Many dog and cat breeders continue to rely solely on phenotypic data when dealing with complex disorders such as hip dysplasia. They are mostly screening prospective breeding animals and selecting breeding pairs with this

limited information; their goal is to reduce disease incidence, but the approach has flaws and progress is slow. In this area, we can learn more from large-animal producers who have utilized estimated breeding values (EBV) for decades to manage diseases with more complex inheritance and improve production parameters. Estimated breeding values (EBVs) are the value of an individual as a genetic parent. They utilize all that is known about a trait, in an effort to predict the potential that the trait will be expressed in the offspring. The more that is known about the trait, including the environmental conditions associated with individuals as well as heritability percentage, the greater accuracy.[30] Large-animal producers have used EBVs to do everything from increase volume, butterfat and protein in milk to improve production of lean meat from beef animals, to increase feed efficiency and improve reproduction.[30]

In US beef industry, various breed associations are responsible for calculating EBV's. Most associations, however, contract with a university that specializes in advancing technology for doing the (inherently complex) EBV calculations.[30] Major universities where contract computing is done include Iowa State University, Cornell University, Colorado State University and University of Georgia. Computing EBV's for dairy industry is performed by Animal Improvement Programs Laboratory, Beltsville Agricultural Research Center, Agriculture Research Service, US Department of Agriculture where staff work year-round to improve and implement process of calculating EBV's for dairy cattle.[30]

Estimated breeding values change, as data used to calculate them is constantly evolving. Understanding their use in breeding programs for those unfamiliar with genetics can be overwhelming. For the large-animal industry, the Cooperative Extension Service was very successful in educating farmers on the use of EBVs. One of the most successful tools for teaching beef cattle breeders how to use EBV's was the computer cow game.[30] This created real-world scenarios where producers would make breeding choices based on EBVs. Typical of the real-world, a certain percentage of cows in every herd would fail to conceive, calves would die and other calamities would strike. Out of all this mayhem and information, however, emerged new calves with new records that became the basis for a new round of EBV's.[30] Selection decisions could be made and the process repeated. Cattle breeders enjoyed competing with each other to see who could produce the greatest genetic improvement in their herd in 5 generations of selection. Such a tool was suggested by prominent canine geneticist, Dr. Elton Leighton, specifically written for dog breeding and implemented online, could be used to teach dog breeders about EBV's.[30]

Dr. Leighton and the team at the Seeing Eye, have been utilizing estimated breeding values for years to improve genetic selection for dogs to succeed in their program as well as to improve dogs' health, in particular, hip health. They continue to publish successful demonstrations of their research showing how dog breeders can incorporate these techniques to improve selection for these more complex inherited diseases.[31]

The task of calculating EBV's is generally complex and relies on diverse sharing of a large amounts of data, with accuracy of the EBV's based on accuracy of information reported, or lack thereof. To be successfully implemented with dogs, groups of dog breeders, e.g. national parent clubs or the American Kennel Club, need to decide that routinely computing EBV's is an important task to be undertaken. Any of these dog breeder organizations can turn to U.S. beef or dairy industries or Seeing Eye for examples of how to organize data collection and calculation processes. Recent advances in computing algorithms and computer software to implement these algorithms now facilitate simultaneously calculating EBV's on several traits measured on thousands of dogs.[30]

Conclusion

With growing advancements in molecular genetics and genetic tests being developed at an exponential rate, it is important for veterinarians and breeders to have a basic understanding of how to utilize these techniques in order to control genetic diseases while maintaining genetic diversity of the population as a whole. Emergence of genomics into clinical veterinary practice has led to the need for development of a team-based approach to control and identify genetic disorders in small animals.[8] Hard work and cooperation among breeders, pet owners, primary-care veterinarians, veterinary specialists, veterinary researchers, genetic databases and funding institutions has resulted in development of nearly 200 genetic tests.[6] This research has not only benefited the lives of our small animal patients and their

families, but has also increased understanding of genetic diseases in other species, including humans. Going forward, we all need to continue our vital roles in this process so that we can further unlock mysteries behind some very common diseases in veterinary medicine. Veterinarians, particularly reproductive veterinarians, are in a unique position to bridge the knowledge gap between advancements in genetic science and clinical application in small dog and cat breeding operations. We can assist breeders in understanding current genetic status of their own breed so they can work to preserve population size of their breed. We can help breeders utilize tools such as estimated breeding values, inbreeding or heterozygosity estimates, and mutation-based genetic disease tests optimally in their breeding programs. We can help them to understand that the mistakes of past should be replaced by exciting technological advances of future to implement breeding strategies that will more effectively reach their goal of producing dogs and cats that not only are what is desired for appearance, temperament and workability, but also live long, healthy lives.

Conflict of interest

There are no conflicts of interest to declare.

References

1. Nicholas FW: Online Mendelian inheritance in animals (OMIA): a comparative knowledgebase of genetic disorders and other familial traits in non-laboratory animals. Nucleic Acids Res 31:275-277 (http://omima.angis.org.au/).
2. Traas AM, Casal M, Haskins M, et al: Genetic counseling in the era of molecular diagnostics. Theriogenology 2006;66:599-605.
3. Werner P, Raducha MG, Prociuk U, et al: A novel locus for dilated cardiomyopathy maps to canine chromosome 8. Genomics. 2008;6:517-521.
4. Van Vleet JF, Ferrans VJ: Myocardial diseases of animals. Am J Pathol 1986;124;98-178.
5. Ackerman, L: The genetic connection: a guide to health problems in purebred dogs. AAHA Press, 2000.
6. Giger U. Clinical tools to diagnose hereditary disorders. Proceedings of the 34th World Small Animal Veterinary Congress 2009 - São Paulo, Brazil.
7. Patterson DF, Aguirre GA, Fyfe JC, et al: Is this a genetic disease? J Small Animal Pract 1989;30:127-139.
8. Giger U: Clinical Genetics. In Textbook of Veterinary Internal Medicine. Ettinger S, Feldman E. Saunders, Philadelphia, 2005.
9. Giger U, Jezyk PF: Diagnosis of inborn errors of metabolism in small animals. In: Current Veterinary Therapy XI. Kirk RW, Editor. WB Saunders; Philadelphia: 1992. p. 18-22.
10. Giger U. New insights into hereditary diseases and genetic predisposition to disease in dogs. Proceedings of the 34th World Small Animal Veterinary Congress 2009 - São Paulo, Brazil.
11. Giger U. Peculiarities of feline hereditary disorders. Proceedings of the 34th World Small Animal Veterinary Congress 2009 - São Paulo, Brazil.
12. Meyers-Wallen VN: Ethics and genetic selection in purebred dogs. Reprod Domest Anim 2003;38:73-76.
13. Evans JP, Brinkhouse KM, Brayer GD, et al: Canine hemophilia B resulting from a point mutation with unusual consequences. Proc Natl Acad Sci USA 1989;86:10095-10099.
14. Cox ML, Lees GE, Kashtan CE, et al: Genetic cause of X-linked Alport syndrome in a family of domestic dogs. Mamm Genome 2003;14:396-403.
15. Suter NB, Ostrander EA: Dog star rising: the canine genetic system. Nat Rev Genet 2004;5:900-910.
16. Pearson TA, Manolio TA: How to Interpret a Genome-wide Association Study J Amer Vet Assoc 2008;299: 1335-1344.
17. Aguirre GD, Ray K, Acland GM: Candidate gene studies in canine progressive retinal atrophy. Digital J Ophthalmol 1998;4:3 www.djo.harvard.edu/site.php?url=/physicians/oa/381logy
18. Kwon JM, Goate AM: The Candidate Gene Approach. Alcohol Research & Health 2000;24:164-168.
19. Farrell LL, Schoenbeck JJ, Wiener P, et al: The challenges of pedigree dog health: approaches to combating inherited disease. Canine Genet Epidemiol 2:3.doi: 10.1186/s40575-015-0014-9.eCollection 2015
20. Leroy G, Abitbol M: Breeding strategies against genetic disorders in dog breeds. Anim Genet 2009;23:323-332.
21. Mellersh C: DNA testing and domestic dogs. Mamm Genome 2012;23:109-123.
22. Ostrander EA: Both ends of the leash - the human links to good dogs with bad genes. N Engl J Med 2012;367: 636-646.
23. Padgett GA: Control of canine genetic diseases. Howell Book House, NY.1998.
24. Rooney N, Sargan D: Pedigree dog breeding in the UK: a major welfare concern? A report commissioned by the Royal Society for the Prevention of Cruelty to Animals. 2009.
25. Ives AR, Whitlock MC: Inbreeding and metapopulations. Science 2002;295:454-455.

26. Allendorf FW, Hohenlohe PA, Luikart G., Genomics and the future of conservation genetics. Nat Rev Genet 2010;11: 697-709.
27. Balloux F, Amos W, Coulson T: Does heterozygosity estimate inbreeding in real populations? Mol Ecol 2004;13: 3021-3031.
28. Keller MC, Visscher PM, Goddard ME: Quantification of inbreeding due to distant ancestors and its detection using dense single nucleotide polymorphism data. Genetics 2011;189:237-249.
29. Wright S: Coefficients of inbreeding and relationship. Am Nat 1922;56:330-338.
30. Leighton, EA: Using Estimated Breeding Values to Reduce the Incidence of Genetic Diseases in Dogs. Presented at a Meeting of the International Elbow Working Group. 1999.
31. Leighton EA, Holle D, Biery DN, et al: Genetic improvement of hip-extended scores in 3 breeds of guide dogs using estimated breeding values: Notable progress but more improvement is needed. *PLoS One*. 2019;14(2):e0212544. Published 2019 Feb 22. doi:10.1371/journal.pone.0212544.