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REVIEW

Empowering international canine inherited disorder management

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Abstract The mapping of the canine genome and the study of canine breed genomic architecture has revolutionized the discovery of genetic tests for inherited disorders in dogs. As the genetics underlying complex disorders are revealed, canine breeders and their registering organisations will be required to understand genetics in a much more sophisticated way. To facilitate the management of genetic disorders in the era of new complex information, we consider how best to apply the results of new research and analytical techniques to benefit the wider canine breeding community with the aims of improving canine health and maintaining benevolent genetic diversity. If this is not done, there is a serious risk that expensive and valuable genetic research will remain unused or be misused to the detriment of breeds. In this review, we make a case for the formation of an international organisation that will exist as a central repository for breed-based genetic analysis and information sharing. This organisation ("InterDog") could be modelled on a similar organisation that is monitoring genetic improvement of dairy cattle. The formation of such an organisation will require the collaboration of international kennel management organisations, researchers, and agencies offering genetic testing services.

Background

Selective breeding is the tool that breeders use to attain genetic improvement for their breeding objectives within closed purebred dog populations. In the process of selective breeding, animals with the greatest number of beneficial alleles are identified and used preferentially, while their peers with fewer beneficial alleles are used less, or not at all, for breeding. The desired result is increased frequency of beneficial alleles and decreased frequency of deleterious alleles. Selective breeding, therefore, relies on a targeted utilization of genetic variation or diversity. Thus, there is an inherent conflict between genetic improvement through selection and maintaining genetic diversity; however, unless there is an extreme reduction of effective population size during selection, benevolent genetic diversity (genetic variation not corresponding to disease risk) can, with care, be retained.

Traditionally, it has been desirable for animals to "breed true" for the breeder's objectives, including breed-type and an absence of disease traits. However, the weight of scientific evidence suggests that genetic conformity is not desirable. Genomic heterogeneity has been shown to correspond to improved fertility, production, and vitality in a variety of production animal species (e.g., Sorensen et al. 2008). It is possible for highly homozygous populations to be healthy, if all the alleles that have reached fixation correspond to a healthy state, such as in certain lines of inbred mice. However, the chance of a particular line reaching fixation for healthy alleles (and purging of unhealthy alleles) for every gene is so low as to be unattainable in acceptable dog breeding practice, and so genetic progress in health and welfare objectives must be balanced appropriately against retaining genetic diversity. Indeed, the risk of fixation for unhealthy alleles through genetic drift or close breeding may be higher than previously guessed. In humans, there is strong evidence that each individual is heterozygous for many tens of genetic disorder alleles (Altshuler et al. 2010). Excessive use of popular animals (e.g., those cleared of known genetic disorders for

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which marker tests exist) has the potential to increase the frequency of the specific deleterious alleles possessed by these individuals. Later close breeding practices among progeny of such animals can increase the chance of animals inheriting two copies of a disorder allele from any ancestor common to both parents. Therefore, even when selection is undertaken for health- and welfare-related goals (i.e., animals free of known disorders), care must be taken to ensure that the reduction in effective population size through the use of popular breeding animals does not cancel out the health and welfare gained by selection against disorders.

A major challenge in improving welfare for all dogs is to assist breeders in making balanced and informed breeding choices relating not only to recessive Mendelian disorders, but also to multifactorial genetic disorders such as hip dysplasia (Wilson et al. 2011), epilepsy (Casal et al. 2006; Ekenstedt et al. 2011), diabetes mellitus (Short et al. 2007), autoimmune disorders (Chase et al. 2006; Wilbe et al. 2010), and cancer, all of which affect both purebred and crossbred dogs. For purebred dogs, it is also desirable to maintain a breed-type that is consistent with health and welfare.

Thus far, the canine breeding community has been tantalized by the opportunities presented by new technologies to tackle existing disorders (e.g., Guo et al. 2011; Karlsson et al. 2007), but it has been given scant advice on how to incorporate information arising out of research into their breeding programs. Strategies to reduce the occurrence of single Mendelian disorders in a population are relatively well understood, but when the breeders must deal with multiple disorders, complex disorders, and other breeding objectives, strategic advice is hard to find.

Fortunately, new genetic technologies and statistical methods are available to facilitate desirable changes, maintain traits at desirable levels once they have been reached, and prevent loss of genetic diversity (Kinghorn 2011; Kinghorn et al. 2002). Our new challenge will be to manage not only phenotypic information such as radiographic scores, but genotyping and sequencing information ranging from results for single-locus tests to whole-genome marker scans. These data can then be incorporated into breeding-risk scores for complex disorder traits. The internationalization of dog breeding means that sufficient information for making knowledgeable choices must be available to breeders irrespective of the country in which they reside. The key to making this possible is internationally shared information (Hedhammar et al. 2011).

Sources of information on breed predispositions

A number of national groups already provide information for use in breeding programs, including test results for Mendelian inherited disorders and radiographic scoring results (Federation Cynologique Internationale 2011; Keller et al. 2011). However, the comparison of results from tests between individuals from different countries or even individuals within countries may be hampered by the use of different scoring strategies and assessment methods (Powers et al. 2010). As yet, research linking genetic disease evaluations derived from differing systems of analysis is scant. Also, as submission of genetic evaluations into many breeding programs is either formally voluntary or effectively voluntary, a submission bias may lead to favourable results being overrepresented in such a breeding program's core data (Paster et al. 2005). Ideally, a welfare-based breeding strategy requires all test results to be incorporated into scores that can be used by breeders to make maximally informed breeding decisions while still respecting owner confidentiality. This might be achieved by a requirement that all results be submitted to the analysing institution(s) but that the publication of individual dog results could be at the discretion of the dog's owner.

Data relating to registered breeds will represent only a portion of the wider dog population. In Australia, registered pedigreed dogs comprise less than 20% of the national canine population (Shariflou et al. 2011). Accordingly, there is a vast wealth of breed disorder information available (but largely untapped at this time) in the population of pet dogs. Information regarding the occurrence of diseases and disorders in the general dog population can be accessed through pet insurers (Hedhammar et al. 2011) or proposed veterinary surveillance strategies such as VEctAR (Veterinary Electronic Animal Record) Animal Surveillance (O'Neill et al. 2011). Scientific literature can also provide insights into disorder prevalence (Gough and Thomas 2010) and the genetic basis of disorders (Nicholas et al. 2011).

Impact assessment and priorities in canine disorder management

Most, if not all, breeds of dogs are predisposed to more than one disorder that seriously affects health and welfare. Consequently, for each breed there will be multiple health and welfare breeding objectives (Asher et al. 2009; Summers et al. 2010), in addition to conformational and behavioural objectives for the breed and the unique breeding objectives of individual breeders. It is likely that there will be few breeding candidates that are exemplary with respect to all health and welfare objectives (even setting aside the other breeding objectives). Accordingly, as the number of objectives and the threshold for breeding acceptability rise, the pool of potential breeding candidates shrinks. This creates a bottleneck that raises both genetic

concerns and practical concerns for breeders. The available selection pressure, in the sense of limiting the pool of breeding candidates, becomes a limited resource. Each time a new breeding objective is added to an existing breeding program, current selection pressure must be reallocated toward the new trait. This can either shrink the pool of acceptable sires and dams or result in less effective selection for all traits in the breeding program. If we assume that the financial resources available to breeders for genetic and other screening tests are limited, fewer animals will be able to be measured with expensive genetic testing procedures.

Because selection pressure is a limited resource, it should be budgeted carefully. Consequently, breeding objectives must be carefully considered and prioritized. Health and welfare objectives aim primarily to improve the subjective experience of the dog, although they should also benefit the subjective experiences of breeders and nonbreeding owners, the finances of breeders and nonbreeding owners, and, ideally, the professional success of breeders. Choosing and prioritizing health and welfare breeding objectives based on their impact on the canine subjective experience is challenging.

The Generic Index Severity Index in Dogs (GISID) is an attempt by veterinarians and animal welfare scientists to adapt human disease severity indices (Asher et al. 2009; Collins et al. 2011) to objectively quantify the impact of health and welfare concerns in dogs. It considers the disturbance caused by the disease state to normal behaviours, the likely duration of the impairment, the potential for complications, and the likely impact of the required treatment. Each of these four aspects is scored ordinally and the resulting four scores are summed together for a total composite score. This prioritization tool has been enhanced, first by the inclusion of prevalence (Collins et al. 2010) and, most recently, by also incorporating the proportion of life affected, to provide an estimate of the welfare impact on a breed: the breed-disorder welfare impact score (BDWIS) (Collins et al. 2011). At the very least, these methods offer a starting point in the development of complex breeding objectives.

The relative importance of breeding objectives and canine health and welfare is also relevant to the very important question of when genetic "improvement" in a health or welfare objective should cease. While reduction of hip laxity is desirable in a breed with hip dysplasia, it does not follow that the association between improved welfare and a tighter hip continues indefinitely: a point at which further reduction in laxity would result in a plateau or decline in welfare is almost certain. Similarly, when reducing the frequency of a single-locus disorder, once the frequency is very low, it becomes increasingly difficult to achieve further reductions in frequency, and consequent improvements in health and welfare may not justify the selection resources devoted to the task. This concern has been addressed and incorporated into the BDWIS. It is important to recognize when any new breeding objective is first included that there is a natural end point to its occurrence in the breeding program and that its relative importance compared to other breeding objectives (and therefore the share of selection resources to which it is entitled) may be in constant flux.

Ultimately the importance of each health and welfare objective will depend, at any given moment, on the prevalence of the problem that it addresses and the prevalence and severity of the other health and welfare objectives with which it is in competition for selection resources. Integrated information and feedback from clinical outcome-based epidemiological information can be linked directly with schemes such as in VEctAR (Nicholas et al. 2011), and screening-test-based genetic trends can be linked into regularly updated BDWIS-based rankings of all genetic disorders extant in the breed. The situation for every breeding population is likely to be unique, and so the breed club level, with appropriate interaction with their within-breed international counterparts, seems to be the ideal level at which the breeding objectives should be set, with appropriate expert support using evidence-based data.

"Inter-Dog": a model for an international integrated breeding scheme

Systems, such as VEctAR, that provide evidence-based estimates of genetic disease prevalence, and BDWIS, which uses these evidence-based estimates of genetic disease to help objectively weigh breeding priorities, are of inestimable importance in effective, scientifically based breeding schemes. However, the conversion of breeding objectives into improved health and welfare outcomes requires that genetic evaluations of any sort be developed, collected, and processed according to scientifically rigorous standards, and that breeders (and other end users) are empowered with the knowledge and resources required to use the genetic evaluations optimally. Expenditure on high-quality genetic evaluations can be optimized by sharing the burden internationally. This makes the most efficient use of resources and minimizes the cost burden on stakeholders.

In the 1980 s, the international dairy industry faced precisely the same challenges as those outlined above, and the resolution of this need was to create the genetic evaluation organisation "Interbull" (Sorensen et al. 2008). We propose that a similarly designed organisation could be of enormous value in the breeding of dogs. An "Inter-Dog" organisation would compile and maintain the international pedigree resource, maintain records for individual dogs for

all available DNA tests and phenotypic assessments, and conduct regular (perhaps twice yearly) genetic evaluation calculations on the compiled data for each breed and each identified trait of interest. Summary results could be broken down to report Breed-by-Country interactions and these could be used to monitor disorder trends on a national level.

The key to the success of an international genetic evaluation system lies in the availability of pedigrees and the representation of common sires and dams across borders. As the custodians of pedigrees, the kennel registries would be key players in empowering their constituents to initiate a change for the better. The publication of genetic evaluation scores for traits of interest would create an atmosphere of transparency in the management of canine genetic disorders, whether they are simple or complex. Ideally, there would be links between the central genetic evaluation resource and others, such as those relating to genetic disorder surveillance. Further value would be gained through the active input of organisations that report on genetic test outcomes.

Data would be directly uploaded by genotyping organisations and phenotyping organisations or it could be compiled and submitted by the relevant kennel club to the central evaluation organisation ("Inter-Dog"). Release of evaluation results could be negotiated on a breed-by-breed basis within each country, and guidelines could be suggested or enforced by national breed-registering organisations. The central organisation could be accountable to contributing organisations and evaluations could include both traditional and minor breed registries, although the ability to provide common evaluations for breeds represented in more than one registry would rely on the use of common bloodlines across registries. The central organisation must be truly representative of the world canine breeding community, must be impartial with respect to breed and country, and all evaluations must be evidence-based.

During its establishment, the central body could be funded from research grants. A period of research would be required to establish the appropriate weightings for different sources of information and to identify the genetic relationships between traits with measurements available. Once established, the central organisation could be funded by subscription to access information and by industry-based levies on dog registrations or phenotyping procedures.

Making the most of information on Mendelian traits

Even when considering genetic tests for single-locus disorders, it is difficult for the layperson to efficiently evaluate the quality of tests on offer. It is not always clear whether the test is a mutation-based test of high quality, or a marker-based test that may be subject to some degree of error. Also, apparently similar disorder phenotypes might be generated by different mutations in different breeds, so the utilities of genetic tests need to be validated in each breed. Additionally, while a disorder phenotype might be controlled predominantly by major risk loci, the lethality or age of expression of the disorder may be controlled by other loci which are not assessed in the genetic test.

Given the multitude of competing breeding objectives, the accuracy with which a genetic test result truly corresponds to a genetic disease must be considered when allocating selection resources to a test outcome. Inter-Dog could provide an independent source of expert information for breed societies on the likely utility of available genetic tests. Additionally, the colocation of disorder phenotype and genotype information could provide a means to automatically update information on breed penetrance and efficiency of DNA-based testing regardless of whether it is mutation- or marker-based. If submitted epidemiological data were to include linked unique dog identifiers, then broader disease outcomes could be linked directly back to genotype frequencies within country and breed. These could better inform risk values for potential sires and dams.

Making the most of information on complex (multifactorial) disorder traits

Complex traits present even greater challenges for breeding management. As we begin to ascertain the genetics underlying complex traits, we will need to be able to consider all available information, assess its quality, and understand the relationship between the measurements made to assess one complex trait with other traits of value to the breed. In the first instance, it is imperative that information for complex traits measured by different methods and in different countries be able to be combined so that breeders, armed with optimal information, can make good breeding decisions that benefit canine welfare. Use of sophisticated analyses of collective international data sources to provide results specific to breed and country of origin, along with the education on how these results can best be used, will provide significant opportunities for breeders to tackle issues of relevance to their breed.

For multifactorial traits, high-quality genetic evaluations are typically conducted by scoring one or more appropriate phenotypes and calculating Estimated Breeding Values (EBVs) for the disorder (Lewis et al. 2010; Thomson et al. 2010; Wilson et al. 2011). An evaluated animal's EBV represents the superiority of the animal's genes that affect the breeding objective relative to the complement of genes

of the "average" animal in the breed or in a cohort. All available information about the animal's value as a breeding animal is combined, with appropriate statistical weighting techniques, into the EBV.

When considering disease phenotypes, the information from the candidate itself, its relatives, marker genotypes related to the phenotype from either the individual of concern or its relatives, and phenotypes or marker genotypes for genetically correlated traits (traits controlled by common genetic loci) can be incorporated into the evaluation process. The quality of the information provided by each information source in consideration of the breeding objective affects the importance accorded this information in the final EBV calculation.

Existing methods used to calculate EBVs also allow the calculation of the accuracy with which an EBV is known. Statistical techniques for the estimation of breeding values and the accuracies of the breeding values have been used in the livestock industries for decades. In dairy cattle there is considerable excitement about the future of EBVs derived almost entirely from genomic tests, so-called genomic EBVs (gEBVs) (Hayes et al. 2009). These may provide a considerable advantage if the EBV of the animal can be determined with a high degree of accuracy before any phenotypic information on that animal becomes available. In theory, this could offer substantive advantages for dog breeders (Guo et al. 2011), who are frequently faced with the task of selecting breeding replacements at ages as young as 8 weeks when the decision is made to send the pup to a breeding or a pet home. Even when selection is possible on older dogs, it may not be possible to attain an accurate measurement from a breeding candidate for a substantial amount of time (e.g., skeletal maturity at least for hip dysplasia and often later for immunological diseases or cancers).

It should be recognized that the population structures of dairy cattle and pedigree dogs are very different, particularly in terms of the number of offspring produced by parents (particularly sires). Because in dog populations relatively few progeny are derived from any given parent, it may not be possible to evaluate entirely genomic EBVs for dogs with great accuracy (Hayes and Goddard 2010) and so the collection, storage, cleaning, and processing of phenotype and pedigree information will remain necessary for the foreseeable future.

Inter-Dog could facilitate the calculation of high-quality EBVs/gEBVs. As an international organisation, the members will have access to pedigree information relating to international populations of the same breed. International EBVs (with methodologically appropriate adjustments for country-specific factors) are advantageous in facilitating the international movement of breeding dogs and genetic material, as breeders in the destination country can more easily appraise the superiority of the genes. Such international movement facilitates genetic diversity and could potentially advantage numerically small or more genetically homogenous breeds. An additional advantage to international EBVs is that they may allow the inclusion of information from genetic evaluation of relatives in other countries, increasing the accuracy of an individual animal's EBV, again advantaging numerically small breeds where lower EBV accuracies are most likely. By facilitating international evaluation and movement of genetics, international EBVs made possible by Inter-Dog would advantage breeders and canine health, especially in numerically small populations, which can be particularly at risk of genetic disease.

Making the most of information from genetic research

There is considerable current research activity toward understanding the genes responsible for single-locus genetic disorders and the genes that contribute in a large way to complex genetic disorders. This research is vital for understanding the aetiology and pathogenesis of these disorders, providing a foundation for future development of treatments and therapies, understanding the diseases as a potential model for analogous human disease and the development of genetic tests for these genes (or markers of these genes) to potentially aid control through selective breeding. Generally, it is the last of these aims, genetic tests, which has the greatest potential for immediate improvement of canine welfare.

However, the aim of developing a genetic test may not be the most pressing of concerns for the research team in question, and opportunities for development of genetic tests with the potential to improve canine welfare may be inadvertently missed. Missed opportunities may be especially common when considering tests for genes that affect complex disorders, as a genetic test may not be commercial on its own, despite potentially being of considerable value for gEBVs. Inter-Dog would have the capability to advocate the potential that research findings may have for affecting short- and medium-term genetic improvement in dogs. They could be particularly important as assistance to breeders and breed societies who have contributed financial and genetic resources to the research but who do not have sufficient specialist knowledge to make use of the research to improve the welfare of their animals without assistance.

Education and empowerment of stakeholders

As noted above, there is a regrettable scarcity of information available to breeders and breed societies about how

to go about the complex process of managing multiple and complex genetic diseases simultaneously. Experience in production species shows that animal breeders can, with the right support structures in place, become highly adept at using selection indexes and EBVs/gEBVs. An important role for Inter-Dog would be to empower breeders and breed societies to use similar evidence-based techniques to improve canine health and welfare in concert with other breeding objectives. This would be achieved in part by offering access to educational resources on the genetic evaluations that Inter-Dog would produce, a structure for contact between breed organisations and academics and researchers to discuss breeding concerns, and integrated up-to-date tracking of phenotypic and genetic trends allowing feedback and, if needed, troubleshooting advice from specialists.

Educational resources should also be made available to animal welfare organisations and the nonbreeding public. This group includes current and potential owners of pedigree dogs as pets, organisations from which they might seek advice, and other persons concerned with animal welfare. Advising the public directly (and indirectly through animal welfare organisations) about the complexity involved in managing complex and multiple genetic disorders in breeds and increasing awareness about the varying efficacy of genetic tests may encourage them to support breeds and breeders who, by participating in Inter-Dog, are taking evidence-based steps for improving canine health and welfare. Understanding the solid scientific underpinning of Inter-Dog's techniques and the record of success which evidence-based selective breeding has had in other species may increase public confidence in the ability of breeders to improve pedigree dog welfare, forestall unhelpful future legislative requirements, and help remove any unfair stigma that has become attached to conscientious breeders as public concern about pedigree dogs has risen.

Potential for the future

An important feature in the design of Inter-Dog will be that it be sufficiently flexible to incorporate future directions in canine breeding. Single-locus disorders arise due to DNA mutations and the occurrence of new genetic disorders will always remain a possibility. Inter-Dog potentially could be expanded to have a role in the timely investigation and management of newly emergent potentially genetic disorders. The complex disorders for which Inter-Dog produces EBVs/gEBVs could be expanded as the needs of dog breeders change. While an initial focus on complex disorders such as hip dysplasia, elbow dysplasia, and multifactorial cancers seems prudent, EBVs could be formulated for any desirable heritable trait. EBVs for suitable temperament, skill as assistance dogs, and desirable litter sizes may all have the potential to improve canine welfare and canine utility to breeders and owners.

Conclusions

The recent implementation of the VEctAR system for detecting and monitoring genetic diseases in dogs and tools such as BDWIS for quantifying each disease's impact on canine health and welfare have created the possibility of genuine evidence-based health and welfare breeding objectives in pedigree breeds. Breeders of pedigree dogs are charged with the task of improving canine welfare by achieving effective selection upon these objectives. However, there is little information available to breeders to help them select against multiple simple and complex genetic disorders simultaneously. Breeders are in need of resources to help them engage with the ever-increasing cohort of available screening and diagnostic tests (both genetic and phenotypic) and the growing body of genomic research to enable them to select for health and welfare breeding objectives as effectively as possible.

To achieve these aims we propose the establishment of an international body to be called Inter-Dog, modelled on the very successful organisation Interbull. Such a body would be able to (1) provide advice about the efficacy of diagnostic tests for particular diseases in particular populations, (2) create international EBVs and gEBVs for complex disorders, thus facilitating increased accuracy through the inclusion of international information and facilitating international travel of breeding animals and genomic material, (3) seek to ensure that new genomic research is used for the direct short- and medium-term benefit of canine health and welfare in instances where these applications may have been overlooked, and (4) empower breeders to manage multiple and complex genetic disorders by providing the necessarily technological and educational resources and access to specialist knowledge.

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