Genetic Research and The Future of Dog Breeding

Attending the 6th Annual Tufts Canine & Feline Breeding & Genetics Conference

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As a representative of The Basenji Health Endowment, I was privileged to be able to attend the 6th Annual Tufts Canine & Feline Breeding & Genetics Conference, organized by Dr. Jerrold Bell and the Tufts University Cummings School of Veterinary Medicine. Over two days 12 experts in the fields of canine and feline health research made wonderfully informative presentations on the subject of companion animal genetic health research.

The first day focused on the topic of genetic diversity and how to best maintain genetic diversity as more and more genetic and phenotypic health tests are becoming available. While opinions differed on how best to evaluate diversity in a domestic animal breed, all the experts agreed on a few important points.

1. Popular Sire Effects continue to be the biggest hindrance to maintaining genetic diversity in any breed.
2. Health testing should be an important component of any breeding program, but breeding decisions should not be solely based on the elimination of a disease causing allele from the population. Breeding decisions are complex decisions that should take many factors into account.
3. The populations of domestic breeds should not be evaluated in the same light as wild populations. All domestic breeds will have higher inbreeding coefficients than would be recommended for a wild species.

The second day focused on Hip Dysplasia. Although this is not a major health concern for our breed, there was a lot of useful information about how genetically complex diseases are currently being evaluated and what tools exist for making informed breeding decisions about genetically complex diseases in the future.

Although basenjis were not the primary focus of any of the studies presented at the conference, many issues that are important to basenji fanciers were discussed at length. I have attempted to break down all of this valuable information by topic.

Evaluating Breed Diversity

Managing Genetic Disease

Hip Dysplasia

Practical Steps

Evaluating Breed Diversity

Traditional measures of genetic diversity within a breed include pedigree analysis to calculate the overall coefficient of inbreeding (COI). None of the experts felt that this number was very important. All agreed that this overall number can only go up over time in any closed population, but what was more important was maintaining a low rate of increase in the coefficient of inbreeding for the breed overall over time. Dr. Bell was quick to say that this does not mean that all breedings should have the goal of a low COI. If every mating is a complete outcross, then eventually the population will be completely homogenous. His view, which I share, is that a diversity of breeding strategies and goals will translate into genetic diversity for the breed as a whole. This is trickier than it sounds. For example, stud X may have perfect health testing, great conformation with lots of wins in the BIS ring, and also have many performance titles. I for sure would want to breed my bitch to him! And so would everyone else. There goes our diversity. Popular sire effect is the biggest stumbling block to maintaining genetic diversity. A dramatic example was shown of a popular Quarter Horse sire, Impressive, who produced 2,250 foals in his lifetime, has over 50,000 descendants and later was shown to have been the source for a spontaneous mutation causing a disease called Hyperkalemic Periodic Paralysis.

Avoiding popular sire effect is so vitally important that in some countries the kennel clubs impose limits on the number of offspring allowed from any one sire. That is not about to happen through AKC, but stud owners should seriously consider limiting the number of pups that their individual dog produces, regardless of how worthy he is of being used.

On the first day of the conference Dr. Pam Weiner presented some of her work on unraveling genetic structure within breeds. As many breeders would intuitively suspect, evaluation of the genetics confirms that in many domestic breeds of companion animals as well as livestock, there are often discernable sub-populations. For example, genetic analysis shows clear genetic differences between Labrador Retrievers from the US versus their cousins in the UK. Also, there are discernable genetic differences between “field lines” and “show” lines. This shows some “hidden” diversity within breeds. It brought to mind for me Dr. Sponenberg’s talk at the 2012 BCOA National Specialty. He suggested that we think of the African sub-populations of basenjis as marbles in a bag. If we, as breeders, can maintain a diversity of approaches, we will be replicating that model, creating sub-populations that can interact periodically to maintain diversity.

<u>Effects of inbreeding</u>

Dr. Gregoire Leroy presented findings that show a quantifiable decrease in litter size and longevity in dogs with a COI above 6.25% versus those with a lower COI. He related that in many countries matings between close relatives (full or half-sibs for example) have been banned. Although, his was the strongest voice for avoiding matings with high COIs, even he pointed out that some inbreeding can theoretically have positive effects at the population level by exposing recessive deleterious alleles. Despite this theoretical benefit, his recommendation was to avoid high COI breedings as much as possible.

<u>Genetic Diversity in Companion Animals</u>

The organizer of this conference was Dr. Jerold Bell from Tufts Veterinary School. He is a breeder of Gordon Setters, as well as a veterinarian. His was the strongest voice in favor of the judicious use of inbreeding and linebreeding to maintain breed type. According to Dr. Bell, once a studbook is closed, genetic diversity within that breed will be reduced by approximately 35% while the breed

is undergoing selection for breed type. While this may not be completely applicable to basenjis, I would say that we should probably expect to see something of this effect once our stud book is closed again. Though this topic did not come up at this conference, I would suggest that our breed is in a unique situation. We have new founders and we can preserve these new bloodlines by freezing semen from new founders or their male progeny. I would encourage all owners of new founders to do this for the good of the breed. If representation of a specific founder dog disappears from the population in the future, it can be reintroduced via artificial insemination (AI).

After this initial genetic bottleneck which he describes at the foundation of any breed, the overall COI of the breed as a whole can only go up. Dr. Bell recommends evaluating a ten generation aggregate COI based on decade of birth for every decade of the existence of the breed. In this way, by comparing the 10 generation COI for each decade, one can assess whether inbreeding is increasing rapidly from decade to decade. He feels this is an important tool for evaluating the overall genetic diversity within a breed. He has published such evaluations for Cavalier King Charles Spaniels and Birman cats.

He again emphasized the catastrophic effects of popular sire syndrome in destroying genetic diversity within a breed, noting that often a popular sire is followed by another popular sire, which in many cases is his son or close relative, making the problem even worse.

His conclusions:

-The effects of inbreeding (homozygosity, large haplotype blocks, and increased linkage disequilibrium) are a natural consequence of breed formation.

-Healthy breed gene pools require expanding, or large stable populations.

-Breed health should be measured based on regular surveys of health and reproduction.

- Genetic selection for breed characteristics should avoid disease related phenotypes.

- Genetic selection for breed health should be directed against specific disease liability genes and phenotypes.

- Breeders should avoid the overuse of popular sires- the most significant factor in limiting breed genetic diversity.

Managing Genetic Disease

While many specific studies of canine and feline genetic disease were presented, there was no simple set of rules laid out for breeders to follow when trying to maintain a breeding program while avoiding producing progeny affected by genetic disease. Many researchers emphasized that as our research tools become more sophisticated, breeders will be faced with more polygenetic diseases, environmentally influenced diseases, and some diseases that may have variable expression in carriers. There will not be any one size fits all solution for any one breed or any one disease.

It was mentioned that there is an estimate that every human being carries ~1,000 deleterious mutations. All purebred dogs will carry some “bad” genes. Our job as breeders is to balance breed type, genetic diversity, and health.

Examples of Complex Genetic Diseases

On Saturday afternoon there were a few presentations on the management of specific genetic diseases in dogs and cats. Dr. Paula Henthorn presented her work on Canine Cystinurea. It is an example of the kinds of complex diseases that researchers are beginning to unravel. There appear to be four different types that have been discovered in dogs to date, none of which is a simple autosomal recessive trait. Interestingly, it has been discovered that the form found in Mastiffs, Scottish Deerhounds, and Irish Terriers is androgen-dependent and occurs only in intact males.

Dr. Kate Meurs presented her research on heart disease in cats and dogs. Seeing some of the huge problems in some breeds of cats and dogs, I was happy that this is not a significant problem in our breed.

Dr. Elizabeth McNeil gave a presentation on her ongoing study of gastric cancer in dogs using SNP chip analysis.

The discussion following these presentations focused on how to manage genetic disorders without sacrificing genetic diversity. I felt this was a timely discussion for the BCOA and BHE since we have managed to obtain DNA tests for both Fanconi disease and one form of PRA in the recent past. The discussion reflected the policies already in place by our club. Don't throw the baby out with the bathwater!

The panel was unanimous in their opinion that:

a. Breeders should test for health problems and make the results public.
b. Breeders should not be afraid to produce carriers of recessive traits, either by breeding an affected to a clear or a carrier to a clear. If you breed your carrier to a normal and the best puppy is a carrier, keep it.
c. If you can avoid producing affected animals, you should do so, but in some breeds the incidence for certain traits is so high that avoidance of producing affected animals is not possible to do without sacrificing genetic diversity. Breeders need to make an educated judgment.
d. There should be breed specific goals at the breed club level for example:
    -maintain genetic diversity
    -maintain certain breed characteristics
    -educate breeders/puppy buyers
    -promote research/ health testing
    -perform periodic breed health surveys

Hip Dysplasia

Day two of the conference was dominated by presentations on Hip Dysplasia (HD). Hip Dysplasia is present to some extent in all breeds of dogs and also in wolves. We are fortunate that basenjis have a relatively low incidence of Hip Dysplasia, with an incidence of just 3.6% per OFA's 2012 stats. Still it does exist in our breed, so it was interesting to hear about the history of the disease, as well as some of the more recent research on the subject. I also learned about some statistical tools being used by breeders in Europe that are useful for limiting incidence of HD, but might also be useful in evaluating other complex traits.

Statistics from OFA

Dr. Greg Keller was present representing the OFA (The Orthopedic Foundation for Animals). He gave a nice discussion of the history of OFA. He also addressed his views on trying to make OFA evaluations more uniform by encouraging breeders and veterinarians to use chemical restraint (sedation) for taking OFA films. He admitted that an argument could be made that all sedation exposes the animal to risk and that OFA films are an elective procedure, but feels that evaluations are more accurate under sedation.

For the balance of his talk, he presented statistics that he has gleaned from the OFA database showing that the overall incidence of HD is going down gradually over time. One of the most interesting charts from his talk showed the percentage of affected dogs (those scored as dysplastic) from every possible mating (excellent x excellent, excellent x fair, etc). It showed a clear correlation between parental combined scores and % affected offspring. In the chart below each parent is assigned a numerical score 1=excellent, 2= good, 3=fair, 4=borderline, 5=mildly dysplastic, 6= moderately dysplastic, and 7= severely dysplasic. Parental scores were then added together and the % dysplastic progeny calculated for each score. So, excellent x excellent = 2 and the chart shows a 3.58% incidence of dysplasia in progeny of excellent x excellent breedings from the OFA database.

This chart represents hip phenotype data on 490,966 progeny in the OFA database for which the hip phenotype for both parents are known. It reprinted here from Dr. Keller's talk with the permission of OFA.

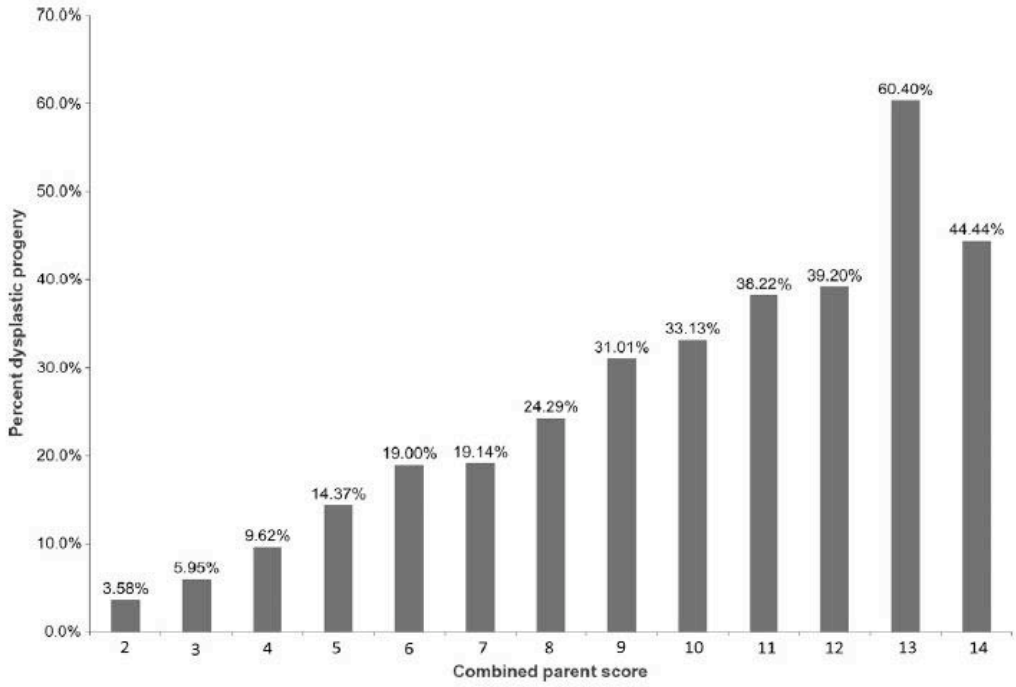

Fig. 1. Relationship of Combined Parent Score to percentage of hip dysplastic progeny.

This chart clearly shows how important it is to evaluate the hips of breeding animals. According to this chart, if you were to breed your bitch with Good hips to a mildly dysplastic male, each pup

would have a 19.14% chance of being dysplastic. Incidence of dysplasia in basenjis is, as previously referenced, low (3.6%), but it does exist and this chart emphasizes how important it is to know the status of both parents even in a breed with low incidence of HD.

Dr. Keller was clear in saying that OFA does not know the clinical status of any dog that they evaluate, so it is very possible, and he has heard anecdotally that many dogs evaluated by OFA as dysplastic are asymptomatic. On the other hand, he also stated that it is his opinion that OFA stats are slightly skewed to be better than reality because many x-rays of severely dysplastic dogs will be pre-screened by the veterinarian taking the x-ray and the owner or breeder will then refrain from spending the money to have those x-rays evaluated by OFA.

I was also interested to see some other statistics which he presented about HD prevalence in the 44 breeds with over 5,000 hip evaluations to date in the OFA database. Basenjis were not included. Incidence rates ranged from a low of 1.8% in Siberian Huskies to a high of 24.4% in Newfoundlands. In general HD is related to weight with heavier breeds being more likely to be affected. Also, HD status is generally related to elbow status.

HD is an example of a complex trait for which there will not ever be one responsible gene identified that breeders can screen for, but OFA is showing that the old adage of “Breed the best to the best and hope for the best” can still be useful, we just need to identify who the “best.”

Of course, hip score is only one trait and breeders need to take the whole dog, their whole breeding program, and the good of the breed a whole into account when making breeding decisions. All the presenters reiterated this concept. No one factor should be the overriding consideration in making breeding decisions.

HD management in the UK

The next speaker, Dr. Tom Lewis was from the Animal Health Trust in the UK. It was very interesting to get a European perspective on the problem of HD. In the UK and many European countries they are using estimated breeding values (EBVs) to help breeders make well-informed decisions. I have to admit that I had no idea what an EBV was. EBVs have been in use in livestock breeding for many years. EBVs are a statistical tool that can predict, based on pedigree analysis, what level of a quantifiable trait (for example milk production) an individual will produce. A bull can be evaluated for milk production by assigning him an EBV based on milk production of his maternal ancestors and his female progeny. An EBV for this trait can be calculated for a whole breed or a herd and then the farmer can choose to use a bull that has a higher EBV for milk production than the average bull. This has been widely used in livestock for such traits as egg production, milk production, wool production. Any trait that is quantifiable can be selected for by using EBVs to guide breeding decisions.

Hip scores make HD a quantifiable trait, so Dr. Lewis and his colleagues have been working with The Kennel Club in the UK to establish public COIs for every recognized breed and is working on establishing EBVs for HD for all those breeds. The Kennel Club has used this info to establish a free online tool for all breeders in the UK called Mate Select. Any UK breeder can see the average COI for their breed (basenjis are listed at 5%) and what COI their hypothetical breeding will produce. Eventually, this tool will include HD EBVs for all breeds and the breeder can see which breedings have an EBV that is better than the breed average and which are worse. This tool can be found here: http://www.thekennelclub.org.uk/services/public/mateselect/genetic-diversity.aspx .

Dr. Lewis found that selection using EBVs is on average of 1.16 times more accurate than using hip scores across 16 breeds. The use of EBVs is dependent on good data. The more dogs in a pedigree that have hip scores, including those sold as pets, the more useful the EBV.

I was very excited to learn more about this tool. The next speaker, Dr. Rory Todhunter from Cornell vet school spoke about pedigree analysis he has done for US Labrador Retriever's and his creation of a tool similar to the UK Kennel Club's Mate Select. It became public in 2010 and can be found here: http://www.vet.cornell.edu/research/bvhip/ You must register to look at the database, but registration is free.

There were a lot of questions about EBVs in the panel discussion that followed. The panel agreed that it was very unlikely that AKC would follow the UK Kennel Club's lead and provide this kind of public statistical tool, but Dr. Keller from OFA said that it was something that OFA was at least considering offering in the future. Dr. Todhunter indicated that as long as there is a good pedigree database available for a breed that EBVs and COIs could be calculated for any breed. There are no commercial services available for this kind of analysis, but Dr. Todhunter hinted that researchers might be willing to collaborate with breed clubs who are willing to cover the cost of such an analysis.

Practical Steps

Now that we have all this information, what can we as breed club and as individual breeders/ fanciers do? Here's some food for thought.

BCOA/BHE

1. Consider establishing a limit on the number of pups/ litters that should be produced by any individual animal. Could this be included in our Code of Ethics?
2. Consider changing awards for top producing animals to reward a higher percentage of titled offspring versus a higher number of titled offspring.
3. Think about funding research to determine the COI of American basenjis and perhaps EBV tool for HD in basenjis. Maybe have a ten year COI evaluation done for the past few decades?
4. Is there something we can do to encourage owners of male founders to freeze semen from their males? Should this be subsidized?
5. What can we do to encourage public posting of health results? The public database shows a less than 1% incidence of HD in basenjis, but using hidden results, the OFA stat jumps to 3.6%. Obviously, a lot of dysplastic results are not being published.
6. Perform a breed health survey through OFA. We need to know what our real health priorities should be.

Individual Breeders

1. Limit the use of any one individual for breeding. Think about using a less popular stud dog.
2. Know the COI for your proposed breeding. Most pedigree programs can do the calculation for you.
3. Do health testing and publish your health results.
4. Don't breed to a dog whose full health data is not published.
5. Have clear goals.

6. Think of the good of the breed in terms of type, temperament, health, and genetic diversity whenever you breed a litter.

The above are my suggestions of ways that the BCOA, the BHE, and individual breeders can use the information from the conference. I tried to summarize the highlights of this very informative meeting, but if you want to see more, the written materials can be found here: www.vin.com/tufts/2013/