

AT A CROSSROADS

THE IMPACT OF GENETIC TESTING ON BREED DIVERSITY

“Big Red,” a popular Disney movie from 1962, made the Irish Setter a Top 10 breed in American Kennel Club registrations, a lofty ranking that came with a price, says Anne Marie Kubacz, of Jackson, New Jersey.

“By the early ’70s, there was an explosion of progressive retinal atrophy (PRA), which began as night blindness in the breed. Breeders unknowingly produced puppies that showed signs around 6 weeks of age and became blind by 1 to 2 years old,” says Kubacz, health chair of the Irish Setter Club of America (ISCA) Foundation. “It was an emotionally charged disease, and everyone wanted to do the right thing.”

Seeking answers, the parent club began working with Gustavo Aguirre, VMD, PhD, professor of medical genetics and ophthalmology at the University of Pennsylvania School of Veterinary Medicine. With Dr. Aguirre’s guidance, Irish Setter breeders knowingly test bred dogs to help advance research to determine the inheritance and causative mutation for the early-onset disease. At the time, test breeding was the only way a breeder could know if a sire or dam was genetically clear of *rcd-1* PRA and would not produce blind puppies.

Dr. Aguirre found that rod-cone dysplasia type 1-PRA in young Irish Setters was caused by a nonsense mutation in the cGMP phosphodiesterase β -subunit gene (*PDE6B*). Identifying that cGMP was critically involved in the disease was based on a study published in September 1978 in *Science*. Once the gene and mutation were identified in 1994, a direct DNA test empowered breeders to selectively breed carriers, the dogs most responsible for disseminating the unwanted gene, to genetically

normal dogs, and select genetically clear offspring for use in future breeding.

“Because of *rcd-1*, our club has always been a proponent of supporting research to help advance the health of our breed as well as that of all dogs,” says Kubacz, one of eight ISCA representatives — more than any other club — who attended the 2019 AKC Canine Health Foundation National Parent Club Canine Health Conference sponsored by Purina.

“Although our club usually sends two or three people, our board members felt it was important for more of us to attend this year,” Kubacz says. “They felt it was important to learn about the outcomes of the Canine Health Foundation work we support and to help sort out the currently

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Jerold Bell, DVM, adjunct professor of genetics at the Cummings School of Veterinary Medicine, Tufts University

available genetic testing for *rcd-1* and other diseases. We really are at a crossroads.”

Parent clubs determine the breed-specific genetic and health screening tests for their respective Orthopedic Foundation for Animals’ Canine Health Information Center (CHIC) program. A dog receives CHIC certification if it has been screened for all the required tests designated by the parent club and if those results are publicly available in the database. The intent is to help improve the overall health of the breed and allow breeders to make informed breeding decisions. As an example, health screenings for hip dysplasia, autoimmune thyroiditis and PRA are required for Irish Setters to earn CHIC numbers.

Historically, every year at the Jane Gavin Health Clinic held during the ISCA National Specialty, health screenings are performed along with the collection of blood samples for *rcd-1* evaluation by a genetic testing lab. Until this year, blood samples were sent to a

ROOTED IN TRADITION

The 12th biennial AKC Canine Health Foundation National Parent Club Canine Health Conference held in August 2019 in St. Louis followed tradition in educating and enlightening nearly 300 attendees about a broad swath of topics. Insights into canine health and genetic research that is part of the Foundation's active grants portfolio of 135 studies totaling more than \$10.8 million provided key learnings and triggered robust, heartfelt interactive panel discussions. Talks by researchers centered on the impact of nutrition on diseases, autoimmunity and vector-borne diseases, infectious diseases and cancer, and genetics and dog breeding. The leading funder worldwide of exclusively canine health research, the Foundation has provided over \$52.9 million for more than 970 grants since 1995. These studies have resulted in more than 760 scientific articles and have been cited more than 26,000 times in peer-reviewed journals. Purina is proud to be the charter sponsor since 1997 of this important parent club canine health conference.



Eight members of the Irish Setter Club of America – more than any other club – attended the AKC Canine Health Foundation National Parent Club Canine Health Conference. They are, front row, from left, Kelli Aitken and Jeanine Wilson, and back row, from left, Dr. Diane Brown, CEO of the Foundation, Anne Marie Kubacz, Carolyn Dison, Karolynne McAteer, Dr. Cheryl Stiehl, Dr. Linda Kalmar, and Mary Lamphier.

lab that performed a bundle test of three autosomal recessive conditions in Irish Setters: *rcd-1*; *rcd-4*, a late-onset form of PRA; and canine leukocyte adhesion deficiency (CLAD), a blood disorder that can cause abnormal blood clotting and immune dysfunction.

“Owners now get results from a panel DNA test that includes more than 170 health conditions,” Kubacz says. “All these years, we have been used to getting results that provide information about diseases that are meaningful to our breeding programs. We’ve started telling members they are getting bonus information and not to be concerned about diseases that have not been reported and are not a problem in our breed. On one hand, breeders and owners want to do what is right and test for conditions that are pertinent to their breed, and on the other hand, there’s confusion about how to interpret the results when there are so many additional tests.”

Genetic testing for canine diseases, including new panel DNA testing and how these tests impact breed diversity and the health of dog breeds, was a featured topic at the AKC Canine Health Foundation National Parent Club Canine Health Conference. In the wake of concerns about preserving rare dog breeds and an overall decline in purebred dog breeding — the once Top 10-ranked Irish Setter is now 77th in AKC breed registrations — these topics are becoming increasingly important to parent clubs and breeders.

“The AKC Canine Health Foundation is committed to advancing the health of dogs through sound scientific research while also providing educational outreach for breeders, veterinarians

and other dog professionals,” says Dr. Diane Brown, CEO of the Foundation. “Thanks to our partnership with Purina, we are able to hold the canine health conference every other year to bring these groups together with canine health researchers, including geneticists, to share and discuss complex matters such as DNA testing and breed diversity.”

RELEVANT GENETIC TESTING

Deciphering a genetic soup of panel DNA health test results to determine what is relevant to an individual breed and individual breeding program can be overwhelming. Likewise, so can the selection of appropriate genetic testing labs for parent clubs.

“Inappropriate genetic tests limit your ability to pay attention to what is meaningful,” Jerold Bell, DVM, adjunct professor of genetics at the Cummings School of Veterinary Medicine at Tufts University and a genetic advisor to national parent breed clubs, told conference attendees during his talk on understanding dog breeds as populations.

Leigh Anne Clark, PhD, associate professor of genetics at Clemson University, advised in her talk on genetic risk assessment, “If a disease is not a problem in your breed, don’t make it a problem. Then, more dogs can be used for breeding. Breeders have free will to decide what is most important to them in their breeding and health programs.”

Along with choosing genetic health tests for their breeds, parent clubs weigh in on the best testing labs to perform health screenings. The myriad of choices and lack of standardization among genetic testing labs in the U.S. and worldwide led to the

development of the Harmonization of Genetic Testing for Dogs (HGTD) initiative in April 2017.

Brenda Bonnett, DVM, PhD, CEO of the International Partnership For Dogs (IPFD) and a veterinary epidemiologist, told attendees in her talk on harmonization of genetic testing and breed-specific resources, “Five years ago, there were too many DNA testing labs focusing on single-gene tests and lots of questions about which tests were reliable. Gaps in understanding DNA test reliability, lab quality assurance, balanced breeding, and test advice for individual breeds led to IPFD’s HGTD initiative. We plan to create comprehensive breed-specific packages that describe the health picture for breeds nationally and internationally and that include breed-specific recommendations for health testing.”

Funding support from the Orthopedic Foundation for Animals, American Kennel Club, AKC Canine Health Foundation, Leadership Sponsors including genetic test providers, and IPFD founding members gave rise to IPFD’s HGTD initiative (<https://dogwellnet.com/ctp/>). A two-year research grant from the AKC Canine Health Foundation, with sponsorship from several parent clubs, is helping move the effort forward.

“The idea is to improve standardization and access to robust genetic testing that will support health improvements and sustain a healthy future for dogs,” Dr. Bonnett explains. “We want to support best practices in the discovery, communication and application of genetic testing to maximize the opportunity to positively impact the health of individual dogs and breeds and to ensure a sustainable future for healthy dogs.”

Among the tools and resources that the HGTD initiative is developing to help dog breeders understand genetic testing for their breed are:

- A portal at *DogWellNet.com* to provide information on genetic testing providers, genetic tests and breed-specific tests
- A Quality Testing Database with 40 major genetic test providers (GTPs) participating and 36 others listed, searchable by their status as a commercial, nonprofit, academic, test developer, or non-test developer lab and with quality information on participating GTPs
- Information on over 300 tests for more than 400 breeds
- A Health Strategies Database for Dogs (HSDD) to include all conditions in which health testing (DNA and other) is required, recommended or on the radar of kennel clubs, breed clubs or veterinary organizations
- An Expert Panel to provide genetic counseling resources

Kubacz, of the ISCA Foundation, laments about what can happen when breeders and owners rely on unapproved genetic testing labs. “As a club, we are always battling misinformation on the internet about genetic tests for our breed and reliable testing labs,” she says. “About 20 years ago, a few members were using a less costly lab that was not approved for *rcd-1* testing. Dogs were reported as clear, but in time the owners realized

they were carriers when two supposedly clear dogs produced a blind puppy.”

ADDRESSING GENETIC DIVERSITY

Dog breeds were produced by inbreeding or linebreeding on a small group of founding canine ancestors. Breeders selected for purposefully bred litters based on phenotype, form and function. In some breeds, deleterious mutated genes, primarily recessive genes, accumulated in the background of their gene pool, resulting in conditions such as *rcd-1* in Irish Setters.

As Dr. Bell points out, dog breed survival relies on maintaining the breadth of genetic diversity and quality traits. “Breed genetic diversity has to do with maintaining unique lines, not on measurements of homozygosity or heterozygosity,” he says.

“The most common genetic diseases seen by veterinarians every day in their practices are due to ancient liability genes that originated in ancestors that preceded the separation of breeds,” says Dr. Bell. “These include allergies, hip dysplasia, heart diseases, cataracts, cruciate ligament disease, hereditary cancers, and others. They occur in purebred and mixed-breed dogs.”

About 65 percent of heritable diseases are autosomal recessive conditions compared with polygenic or genetically complex diseases, notes Dr. Clark. “To help maintain genetic diversity, breeders should consider reducing the number of times a sire or dam is bred,” she says. “You also have to look at the impact of environmental factors, such as stress, toxins, hormones, activity level, diet, and even ultraviolet exposure, on disease conditions.”

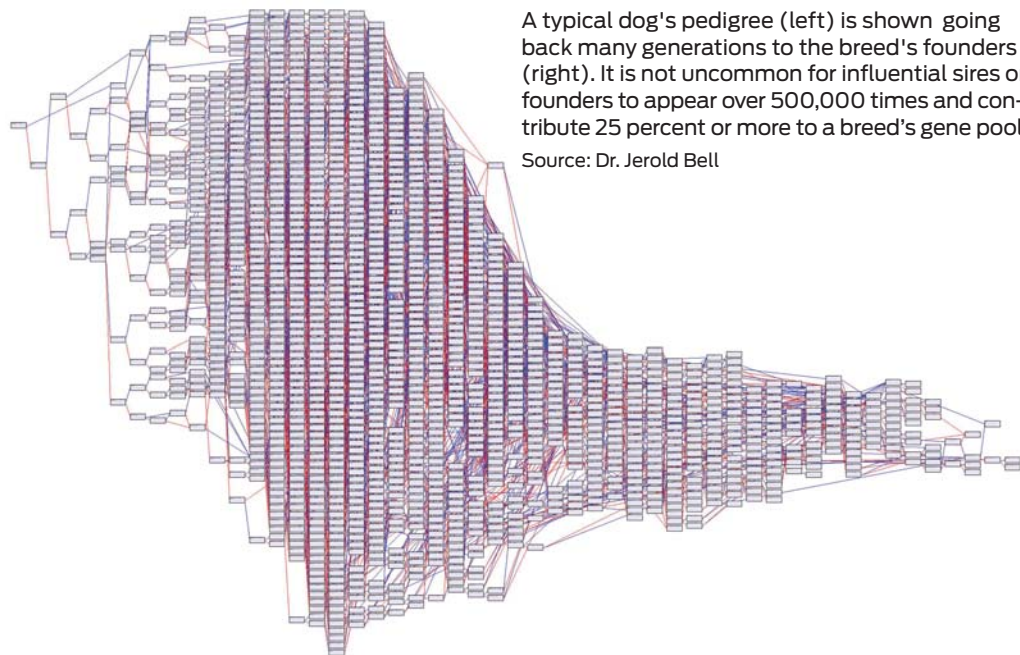
Dr. Bell agrees, adding that “the majority of the 65 percent of recessive mutations are rare diseases, while the most frequently seen genetic diseases are complexly inherited.”

In reality, only a small number of dogs are used to produce the next generation, Dr. Bell says. “Influential ancestors are different from popular sires. For example, in today’s Cardigan

DOG GENETICS 101

- Dog breeds were created by inbreeding dogs with the same phenotype, essentially creating partial clones
- All purebreds as well as mixed breeds have deleterious mutations — disease-causing genes — that accumulated in the background of their gene pool
- Breed survival depends on maintaining genetic diversity and quality traits
- Outcrossing to a mate that phenotypically complements your dog’s good traits will help introduce new traits to your bloodline, though it is important to breed back to dogs related to the original breeding stock to solidify new traits
- Linebreeding concentrates genes of a particular ancestor(s) multiple times in both the sire’s and dam’s side of the pedigree





A typical dog's pedigree (left) is shown going back many generations to the breed's founders (right). It is not uncommon for influential sires or founders to appear over 500,000 times and contribute 25 percent or more to a breed's gene pool.

Source: Dr. Jerold Bell

Welsh Corgis, Withybrook Brock born in 1941 does not appear usually until the 14th generation, but he appears on average over 500,000 times contributing approximately 25 percent of the genes to all Cardigans. With popular sires, males are bred without the benefit of an evaluation over time, resulting in the loss of other quality male lines and potentially contributing to deleterious genes.

“Breed-specific genetic disorders are due to recent mutations and result from the expression of specific deleterious genes,” Dr. Bell says. “An increase of breed-related diseases is due to homozygosity of deleterious recessive or additive liability genes that have accumulated primarily because they are not expressed by the carriers in the heterozygous state. An unaffected carrier can perpetuate the spread of deleterious genes, which can increase in frequency if linked to positively selected genes, or through genetic drift, which is the random accumulation of disease liability genes in the absence of selection.”

For many genetic disorders, genetic tests are available to identify carriers. Dr. Bell advises breeders to breed quality carriers to non-carrier dogs and replace the carrier parent with a quality non-carrier offspring. “In this way breeding lines — and breed genetic diversity — are not abandoned, and testable disease liability genes can be lost in one generation,” he says.

Meanwhile, for other disorders genetic screening and medical history help to differentiate normal from affected dogs. “The selection against disease-causing genes is the only way to reduce the transmission of genetic diseases. Ensuring that the parents are healthy is key to the health of the offspring. If all breeders include pre-breeding genetic screening in their mate selection, then dogs will be healthier,” Dr. Bell says.

A pre-breeding veterinary examination should include:

- Phenotypic examination of a dog's musculoskeletal, cardiac,

ophthalmologic, gastrointestinal, pulmonary, and dermatologic systems, as well as screening for behavioral abnormalities

- Medical history for inherited diseases such as allergies, seizures, bloat, bladder stones, cruciate ligament disease, and others that cannot be identified during an examination

Breeding healthy dogs is an ongoing effort. Parent clubs conduct breed health surveys to learn about conditions and diseases that could be increasing and may warrant investigation. The Irish Setter parent club regularly conducts health surveys and includes owners who are not members to gather the most valid information. The OFA website maintains online, real-time breed health surveys designed by parent breed clubs.

As Dr. Bonnett pointed out in her talk, “Parent club and health committee representatives indicate that they sometimes have challenges educating their members and achieving compliance with even straightforward recommendations. Successful application of scientific information requires more effective communication strategies to achieve appropriate application of health testing recommendations.”

Cheryl Stiehl, DVM, of Woodbine, Maryland, a member of the ISCA health committee and a first-time attendee of the AKC Canine Health Foundation National Parent Club Canine Health Conference says, “I loved the conference from a dog breeder's and veterinarian's perspective. You can never be done learning. The focus should be on science-based information, which is what this conference is all about.”

Reflecting on the progress the Irish Setter club has made since the *rcd-1* mutation discovery by Dr. Aguirre, Kubacz says, “Nearly 30 years later, we still get blindness in some dogs, showing there are unscrupulous breeders who are not using the test. This is why breed health education is so important and why our club supports AKC Canine Health Foundation research.”

From 2001 to 2019, the Irish Setter Club of America Foundation provided funding of \$538,000 to support several Foundation studies, including the Tick-Borne Disease Initiative, degenerative myelopathy, cancer, and bloat. In 2019, the club is providing funding of \$200,000 for research of hemangiosarcoma, lymphoma, epilepsy treatment, and others.

“Knowing more makes a difference in all our animals' lives,” says Kubacz, the 2013 AKC Sporting Breeder of the Year. “We are at a crossroads. Being knowledgeable about genetic testing and the best ways to breed healthy dogs has never been more important.” ■