# Pedigree Analysis and How Breeding Decisions Affect Genes

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To some breeders, determining which traits will appear in the offspring of a mating is like rolling the dice - a combination of luck and chance. For others, producing certain traits involves more skill than luck - the result of careful study and planning. As breeders, you must understand how matings manipulate genes within your breeding stock to produce the kinds of offspring you desire.

When evaluating your breeding program, remember that most traits you're seeking cannot be changed, fixed or created in a single generation. The more information you can obtain on how certain traits have been transmitted by your animal's ancestors, the better you can prioritize your breeding goals. Tens of thousands of genes interact to produce a single individual. All individuals inherit pairs of chromosomes; one from the mother, and one from the father. On the chromosomes are genes; so all genes come in pairs. If both genes in a gene pair are the same gene (for instance, “aa” or “AA”) the gene pair is called homozygous. If the two genes in a gene pair are unlike (for instance, “Aa”) the gene pair is called heterozygous. Fortunately, the gene pairs that make a cat a cat and not a dog are always homozygous. Similarly, the gene pairs that make a certain breed always breed true are also homozygous. Therefore, a large proportion of homozygous non-variable pairs - those that give a breed its specific standard - exist within each breed. It is the variable gene pairs, like those that control color, size and angulation that produce variations within a breed.

There are ways to measure the genetic diversity of a population. One method is to measure the average inbreeding coefficient (or Wright’s coefficient) for a breed. The inbreeding coefficient is a measurement of the genetic relatedness of the sire and dam. If an ancestor appears on both the sire and dam’s side of the pedigree, it increases the inbreeding coefficient. The inbreeding coefficient gives a measurement of the total percentage of variable gene pairs that are expected to be homozygous due to inheritance from ancestors common to the sire and dam. It also gives the chance that any single gene pair can be homozygous.

The types of matings that you choose for your breeding animals will manipulate their genes in the offspring, affecting their expression. Linebreeding is breeding individuals more closely related (a higher inbreeding coefficient) than the average of the breed. Outbreeding involves breeding individuals less related than the average of the breed. Linebreeding tends to increase homozygosity. Outbreeding tends to increase heterozygosity. Linebreeding and inbreeding can expose deleterious recessive genes through pairing-up, while outbreeding can hide these recessives, while propagating them in the carrier state.

Most outbreeding tends to produce more variation within a litter. An exception would be if the parents are so dissimilar that they create a uniformity of heterozygosity. This is what usually occurs in a mismating between two breeds, or a hybrid, like a Cockapoo. The resultant litter tends to be uniform, but demonstrates "half-way points" between the dissimilar traits of the parents. Such litters may be phenotypically uniform, but will rarely breed true due to the mix of dissimilar genes.

One reason to outbreed would be to bring in new traits that your breeding stock does not possess. While the parents may be genetically dissimilar, you should choose a mate that corrects your breeding animal's faults but complements its good traits. It is not unusual to produce an excellent quality individual from an outbred litter. The abundance of genetic variability can place all the right pieces in one individual. Many top-winning show animals are outbred. Consequently, however, they may have low inbreeding coefficients and may lack the ability to uniformly pass on their good traits to their offspring. After an outbreeding, breeders may want to breed back to individuals related to their original stock, to attempt to solidify newly acquired traits.

Linebreeding attempts to concentrate the genes of specific ancestors through their appearance multiple times in a pedigree. It is better for linebred ancestors to appear on both the sire's and the dam's sides of the pedigree. That way their genes have a better chance of pairing back up in the resultant offspring. Genes from common ancestors have a greater chance of expression when paired with each other than when paired with genes from other individuals, which may mask or alter their effects.

Linebreeding on an individual may not reproduce an outbred ancestor. If an ancestor is outbred and generally heterozygous (Aa), increasing homozygosity will produce more AA and aa. The way to reproduce an outbred ancestor is to mate two individuals that mimic the appearance and pedigree of the ancestor's parents.

Inbreeding significantly increases homozygosity, and increases the expression of both desirable and deleterious recessive genes through pairing up. If a recessive gene (a) is rare in the population, it will almost always be masked by a dominant gene (A). Through inbreeding, a rare recessive gene (a) can be passed from a heterozygous (Aa) common ancestor through both the sire and dam, creating a homozygous recessive (aa) offspring.

The total inbreeding coefficient is the sum of the inbreeding from the close relatives (first cousin mating), and the background inbreeding from common ancestors deep in the pedigree. Such founding ancestors established the pedigree base for the breed.

Knowledge of the degree of inbreeding in a pedigree does not necessarily help you unless you know whose genes are being concentrated. The relationship coefficient, which can also be approximated by what is called the *percent blood* coefficient, represents the probable genetic likeness between the individual whose pedigree is being studied, and a particular ancestor. It is a measurement of the average percentage of genes the individual and the ancestor should have in common.

We know that a parent passes on an average of 50% of its genes, while a grandparent passes on 25%, a great-grandparent 12.5%, and so on. For every time the ancestor appears in the pedigree, its percentage of passed-on genes can be added up

and its "percentage of blood" estimated. In many breeds, an influential individual may not appear until later generations, but then will appear so many times that it necessarily contributes a large proportion of genes to the pedigree.

The average inbreeding coefficient of a breed is a measurement of its genetic diversity. When computing inbreeding coefficients, you have to look at a deep pedigree to get accurate numbers. An inbreeding coefficient based on 10-generation pedigrees is standardly used, but requires a computerized pedigree database to compute.

The average inbreeding coefficient for a breed will be based on the age and genetic background of the breed. A mating with an inbreeding coefficient of 14 percent based on a ten generation pedigree, would be considered moderate inbreeding for a Labrador Retriever (a popular breed with a low average inbreeding coefficient), but would be considered outbred for an Irish Water Spaniel (a rare breed with a higher average inbreeding coefficient).

Most breeds start from a small founding population, and consequently have a high average inbreeding coefficient. If the breed is healthy and prolific, the breadth of the gene pool increases, and the average inbreeding coefficient can go down over time. Some dog breeds were established on a working phenotype, and not on appearance. These breeds usually start with low inbreeding coefficients due to the dissimilar backgrounds of the founders. As certain individuals are linebred on to create a uniform physical phenotype, the average inbreeding coefficient can increase.

There is no specific level or percentage of inbreeding that causes impaired health or vigor. If there is no diversity (non-variable gene pairs for a breed) but the homozygote is not detrimental, there is no effect on breed health. The characteristics that make a breed reproduce true to its standard are based on non-variable gene pairs. There are pure-bred populations where smaller litter sizes, shorter life expectancies, increased immune-mediated disease, and breed-related genetic disease are plaguing the population. In these instances, prolific ancestors have passed on detrimental recessive genes that have increased in frequency and homozygosity. With this type of documented inbreeding depression, it is possible that an outbreeding scheme could stabilize the population. However, it is also probable that the breed will not thrive without an influx of new genes; either from a distantly related (imported) population, or crossbreeding.

Fortunately, most breeds do not find themselves in the position of this amount of limited diversity and inbreeding depression. However, the perceived problem of a limited gene pool has caused some breeders to advocate outbreeding of all individuals. Studies in genetic conservation and rare breeds have shown that this practice actually contributes to the loss of genetic diversity. By uniformly crossing all “lines” in a breed, you eliminate the differences between them, and therefore the diversity between individuals. Eventually, there will not be any “unrelated line” to be found. Everyone will have a mixture of everyone else’s genes. This practice in livestock breeding has significantly reduced diversity, and caused the loss of unique rare breeds.

A basic tenet of population genetics is that gene frequencies do not change from generation to generation. This will occur regardless of the homozygosity or heterozygosity of the parents, or whether the mating is an outbreeding, linebreeding, or inbreeding. This is the nature of genetic recombination. Selection, and not the types of matings used affect gene frequencies and breed genetic diversity.

If two parents are both heterozygous (both Aa) for a gene pair, on the average, they would produce 25% AA, 50% Aa, and 25% aa. (These are averages when many litters are combined. In reality, any variety of pairing up can occur in a single litter.) If a prolific male comes out of this litter, and he is homozygous aa, then the frequency of the “a” gene will increase in the population, and the frequency of the “A” gene will decrease. This is known as the popular sire syndrome. Of course, each individual has thousands of genes that vary in the breed, and everyone carries some deleterious recessive genes. The overuse of individual breeding animals contributes the most to decreased diversity (population bottlenecks), and the increased spread of deleterious recessive genes (the founders effect). Again, it is selection (use of this stud to the exception of others), and not the types of matings he is involved in that alters gene frequencies. Breeders should select the best individuals from all lines, so as to not create new genetic bottlenecks.

Decisions to linebreed, inbreed or outbreed should be made based on the knowledge of an individual's traits and those of its ancestors. Inbreeding will quickly identify the good and bad recessive genes the parents share, based on their expression in the offspring. Unless you have prior knowledge of what the offspring of milder linebreedings on the common ancestors were like, you may be exposing your litters (and buyers) to extraordinary risk of genetic defects. In your matings, the inbreeding coefficient should only increase because you are specifically linebreeding (increasing the percentage of blood) to selected ancestors.

Don't set too many goals in each generation, or your selective pressure for each goal will necessarily become weaker. Genetically complex or dominant traits should be addressed early in a long-range breeding plan, as they may take several generations to fix. Traits with major dominant genes become fixed more slowly, as the heterozygous (Aa) individuals in a breed will not be readily differentiated from the homozygous-dominant (AA) individuals. Desirable recessive traits can be fixed in one generation because individuals that show such characteristics are homozygous for the recessive genes. Individuals that pass on desirable traits for numerous matings and generations should be preferentially selected for breeding stock. This prepotency is due to homozygosity of dominant (AA) and recessive (aa) genes. However, these individuals should not be overused, to avoid the popular sire syndrome.

Breeders should plan their matings based on selecting toward a breed standard, based on the ideal temperament, performance, and conformation, and should select against the significant breed related health issues. Using progeny and sib-based information to select for desirable traits, and against detrimental traits will allow greater control.

# The Effects of Genetic Testing: Constructive or Destructive?

By Jerold S. Bell, DVM, Tufts Cummings School of Veterinary Medicine
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Every breed has genetic disorders. Finding tests that identify carriers of the genes which cause these disorders is a goal in all breeds. Once a genetic test is found, however, it is a double-edged sword: Its use can enable breeders to improve a breed or devastate it.

Without genetic tests, the number of dogs that can be identified as carriers is low, even though many dogs may be suspected of being carriers because they have relatives that are known to be affected. Without tests, though, genetic-disease control involves breeding higher-risk dogs to lower-risk dogs. Dog breeds have closed gene pools; in other words, the diversity of genes in a given breed is fixed. The number of dogs removed from consideration for breeding based on concerns regarding a specific genetic disease is usually low, and therefore does not greatly alter the breed's gene pool, or diversity.

A genetic test that should be used to help maintain breed diversity should not result in limiting it.

However, once a genetic test is developed that allows breeders to positively determine if a dog is a carrier of a defective gene, many owners are likely to remove carrier dogs from their breeding stock. Although doing so is human nature, this temptation must be overcome. Any quality dog that you would have bred if it had tested normal should still be bred if it tests as a carrier.

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In such circumstances, carriers should be bred to normal-testing dogs. This ensures that affected offspring will not be produced. Carrier breeding stock should be subsequently replaced with normal-testing offspring that exceeds it in quality. If the only quality offspring is also a carrier, then use that offspring to replace your original carrier. You have improved the quality of your breeding stock, even though the defective gene remains in this generation. It is certainly true, though, that the health of the breed does depend on diminishing the carrier frequency and not increasing it. You should therefore limit the number of carrier-testing offspring that you place in breeding homes. This does not mean, however, that you should prevent all of them from being bred. It is important to carry on lines. A genetic test that should be used to help maintain breed diversity should not result in limiting it.

## Consider All Aspects

We know that most dogs carry some unfavorable recessive genes. The more genetic tests that are developed, the greater chance there is of identifying an undesirable gene in your dog. Remember, however, that your dog is not a single gene, an eye, a hip, or a heart. Your dog carries tens of thousands of genes, and each dog is a part of the breed's gene pool. When considering a breeding, you must

consider all aspects of the dog - such as health issues, conformation, temperament and performance - and weigh the pros and cons. When a good-quality dog is found to carry a testable defective gene, there is a better option than removing that dog from your breeding program. That option is to breed it, so that you can keep its good qualities in the gene pool, and then replace it in your program with a normal-testing dog.

There are breeders who contend that no more than 10 percent of carrier dogs should be removed from breeding in each generation. Otherwise, they say, the net loss to the gene pool would be too great. In fact, *less than 10 percent of all dogs in a breed are ever used for breeding*. Dog breeds do not propagate according to what is known as the Hardy-Weinberg equilibrium, where all members of a group reproduce and pass on their genes to the next generation. Breeders already place tremendous pressure on their gene pools through selective breeding decisions. Indeed, breeders who focus their selective pressure on the more elusive traits in their dogs, rather than on testable and predictable single-gene conditions, are right to do so.

**The Dangers**

It is important that breed clubs educate their owners on how genetic tests should be properly interpreted and used. History has shown that breeders can be successful in reducing breed-wide genetic disease through testing and making informed breeding choices. You should remember, however, that there are also examples of breeds that have actually experienced more problems as a result of unwarranted culling and restriction of their gene pools.

These problems include: reducing the incidence of one disease and increasing the incidence of another by repeated use of stud dogs known to be clear of the gene that causes the first condition; creating bottlenecks and diminishing diversity by eliminating all carriers of a gene from the pool, instead of breeding and replacing them; and concentrating on the presence or absence of a single gene and not the quality of the whole dog.

Breeders are the custodians of their breed's past and future. "Above all, do no harm" is a primary oath of all medical professionals. Genetic tests are powerful tools, and their use can cause significant positive or negative changes. Breeders should be counseled on how to utilize test results for the best interests of the breed.

# Removing the stigma of genetic disease

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(Adapted from an article published in the "Healthy Dog" section of the October, 2003 *AKC Gazette*)

An inevitable consequence of breeding is the occurrence of genetic problems. No one wants to produce affected dogs, yet some breeders and owners are quick to assign blame. There are no perfect dogs, and all dogs carry some detrimental genes.

The emotional reaction to producing a dog with a genetic disorder often follows what is called the grief cycle:

* Denial: This isn't genetic. It was caused by something else.
* Anger: This isn't right! Why is this happening to my dogs?
* Bargaining: My dog sired more than 100 other dogs that are healthy. So this one doesn't really count, right?
* Depression: My kennel name is ruined. No one will breed to my dogs.
* And, finally, acceptance: My dog was dealt a bad genetic hand.

There are ways to manage genetic disorders, breed away from this, and work toward a healthier breed.

**Getting beyond denial**

Unfortunately, many breeders can't get beyond the denial stage. Some will hold to increasingly improbable excuses, rather than accept that a condition is genetic. They will falsely blame relatively rare disorders on common viruses, bacteria, or medications. The fact that these organisms or drugs are common to millions of dogs annually who do *not* have these disorders is not considered.

Reducing the stigma of genetic disease involves raising the level of conversation from gossip to constructive communication. Dealing with genetic disorders is a community effort.

Some owners state that their veterinarian recommended not sending in a hip radiograph to the Orthopedic Foundation for Animals (OFA) because the dog would probably be diagnosed with hip dysplasia. Then these owners lull themselves into believing that since the dog wasn't evaluated, it does not have hip dysplasia. The fact that a dog does not have an official diagnosis does not mean the dog has normal hips, "not affected" with hip dysplasia.

It is important to confirm diagnoses of genetic disorders with blood tests, radiographs, or pathology specimens. However, the primary concern should always be for the individual dog. If an affected dog is not suffering, it *should not* be euthanized simply to obtain a pathological diagnosis. The increased availability of non-invasive techniques has made diagnoses easier to obtain.

Once confirmation of a genetic disorder is made, denial sometimes becomes deception, which is not acceptable. There are breeders who actively seek to prevent diagnoses and later necropsies, but who eventually realize those actions are detrimental to the breed, and in the long run to themselves.

**Working together to improve our breeds**

Reducing the stigma of genetic disease involves raising the level of conversation from gossip to constructive communication. Dealing with genetic disorders is a

community effort. Each breeder and owner will have a different level of risk or involvement for a disorder. We do not get to choose the problems with which we have to deal. Breeders should be supportive of others who are making a conscientious effort to continue breeding their dogs while decreasing the risk of passing on defective genes.

Breeders should follow up on the puppies they have placed. Breeders should periodically contact their puppy buyers and ask about the health of the dogs. Some breeders fear they will be castigated if a dog they placed develops a problem. However, the vast majority of owners of affected dogs are *pleased* that their breeder is interested in their dog, and in improving the health of the breed so that other affected dogs are not produced.

A breeder cannot predict or prevent every health problem. If an owner's dog is discovered to have a problem, show your concern.

Breeders and breed clubs should be cooperative and supportive of researchers studying genetic disorders in their breed. Through research funded by breed clubs and by the AKC Canine Health Foundation (CHF), new genetic tests for carriers of defective genes are continually being developed.

The Canine Health Information Center (CHIC; www.caninehealthinfo.org) was established by the CHF and the Orthopedic Foundation for Animals (www.offa.org). CHIC is an online registry that works with the breed parent clubs to establish a panel of testable genetic disorders that should be screened for in each breed. The beauty of the CHIC concept is that dogs achieve CHIC certification by completing the health-checks. Passing each health test is not a requirement for certification. CHIC is about being health conscious, not about being faultless.

My hope for each breed is that there will eventually be so many tests for defective genes that it will not be possible for any dog to be considered "perfect." Then we can put emotions aside and all work together on improving our breeds.

Breeders must lead the way to remove the stigma of genetic disorders. The applications for both the OFA and CHIC health registries include options that allow for open disclosure of all health-test results or semi-open disclosure listing only normal results. It is up to breeders to show that they are ready to move genetic disorders out of the shadows and check off the boxes for full disclosure.

More and more national clubs are having health seminars and health screening clinics at their specialties. This shows those breed clubs and breeders care about the genetic health of their breeds, and are working toward a healthier future.

# Breeding Strategies for Managing Genetic Traits

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With each new generation of dogs, breeders ask, "How can I continue my line and improve it?" Aside from selecting for conformation, behavior and ability, breeders must consider how they are going to reduce the incidence of whichever genetic disorders are present in their breed. There are no answers that will fit every situation. There are, however, guidelines you can follow to preserve breeding lines and genetic diversity while reducing the risk of producing dogs that carry defective genes, or are affected with genetic defects.

**Autosomal Recessive Disorders**

In the case of a simple autosomal recessive disorder for which a test for carriers is available, the recommendation is to test your breeding-quality stock, and breed carriers to normal-testing dogs. The aim is to replace the carrier breeding-animal with a normal-testing offspring that equals or exceeds it in quality. You don't want to diminish breed diversity by eliminating quality dogs from the gene pool because they are carriers. As each breeder tests and replaces carrier dogs with normal-testing dogs, the problem for the breed as a whole diminishes.

For some disorders there are tests known as linkage-based carrier tests, which can generate a small percentage of false positive and negative results. When using these tests to make breeding decisions, it's advisable to first determine whether the results correlate with the test results and known genotypes of relatives.

When dealing with a simple autosomal recessive disorder for which no carrier test exists, breeders must assess whether each individual dog in their breeding program is at high risk of being a carrier. This requires knowledge of the carrier or affected status of close relatives in the pedigree. An open health registry that is supported by the parent club makes it easier for breeders to objectively assess these matters. By determining the average carrier-risk for the breeding population, breeders can select matings that have a projected risk which is lower than the breed average.

If breeding a dog that is at high risk of being a carrier, the best advice is to breed to a dog that has a low risk. This will significantly diminish the likelihood that affected dogs will be produced, and can reduce by up to half the risk that there will be carriers among the offspring. Using relative-risk assessment as a tool, breeders should replace higher-risk breeding dogs with lower-risk offspring that are equal to or better than their parents in quality. Relative-risk assessment allows for the continuation of lines that might otherwise be abandoned due to high carrier risk.

Breeding a dog only once and replacing it with an offspring allows breeders to improve their chances of moving away from defective genes and also limits the dissemination of defective genes. When dealing with disorders for which carriers cannot be identified, the number of offspring placed in breeding homes should be kept to a minimum.

**Autosomal Dominant Disorders**

Autosomal dominant genetic disorders are usually easy to manage. Each affected dog has at least one affected parent, but it can be expected that half of the offspring of an affected dog will be free of the defective gene. With disorders that cause death or discomfort, the recommendation is to not breed affected dogs. To produce the next generation of a line, a normal full sibling of an affected dog can be used, or the parent that is normal can be used.

A problem with some autosomal dominant disorders is incomplete penetrance. In other words, some dogs with the defective gene may not show the disorder. Roughly half their offspring, however, may be affected. If a genetic

test is available, this is not a problem. Otherwise, relative-risk assessment can identify which dogs are at risk of carrying incompletely penetrant dominant genes.

**Sex-Linked Disorders**

For sex-linked (also known as x-linked) recessive defective genes for which carrier tests exist, breeders should follow the same "breed and replace" recommendations as are outlined above in the discussion of autosomal recessive disorders. If there is no test, the defective gene can be traced through the pedigree. If a male is affected, he would have received the defective gene from his carrier mother. All of his daughters will be carriers, but none of his sons. By using relative-risk assessment to breed him to a female that is at low risk of being a carrier, you can prevent affected offspring, and select a quality son for replacement.

There are rare instances in which a female is affected with a sex-linked disorder. In such cases, she would have received the defective gene from both parents; specifically, an affected father and a mother who is either a carrier or is affected herself. If an affected female is bred, all the sons will be affected, and all the daughters would be carriers, so affected females clearly should not be bred. A normal male that is a littermate to an affected female, however, would be able to carry on the line without propagating the defective gene.

Sex-linked dominant disorders are managed the same way as autosomal dominant disorders are. The difference is that affected males will *always* produce all affected daughters.

**Polygenic disorders**

Polygenic disorders are those caused by more than one pair of genes. Most polygenic disorders have no tests for carriers, but they do have phenotypic tests that can identify affected dogs.

With polygenic disorders, a number of genes must combine to cross a threshold and produce an affected dog. These are known as *liability genes*. In identifying a dog's liability for carrying defective genes for a polygenic disorder, the breadth of the pedigree (that is, consideration of all siblings of individuals in the pedigree) is more important than the depth of the pedigree (consideration only of parent-offspring relationships.) A clinically normal dog from a litter that had one or no individuals affected with hip dysplasia (which is a polygenic disorder) is expected to carry a lower amount of liability genes than a dog with a greater number of affected littermates. This is why it is important to screen both pet and breeding dogs from your litters for polygenic disorders. Information on the siblings of the parents of potential breeding dogs provides additional data on which to base your breeding decisions.

Genetic disorders without a known mode of inheritance should be managed in the same way as polygenic disorders. If there are multiple generations of normalcy in the breadth of the pedigree, then you can have some confidence that there are less liability genes being carried. If a dog is diagnosed with a genetic disorder, it can be replaced with a normal sibling or parent and bred to a mate whose risk of having liability genes is low. Replace the higher-risk parent with a lower-risk offspring that equals or exceeds it in other aspects, and repeat the process.

Genetic tests are extremely useful tools to help manage genetic disorders. Even when there is no test, or a known mode of inheritance, much can still be done to reduce the incidence of affected and carrier animals. The use of these guidelines can assist breeders in making objective breeding decisions for genetic-disease management, while continuing their breeding lines.