Genetics Primer

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Dogs are the most genetically engineered species on the planet, said Dr. Anita Oberbauer. This reflects breeders' efforts to maximize or minimize specific heritable traits. As far back as ancient Egypt, dog owners would "try and breed the best to the best," but the outcomes were based on likelihood and probability. Genetic tests have introduced more certainty into the selection process.

Dr. Oberbauer gave participants an overview of the terminology and dimensions of canine genetics:

- An animal's appearance is its *phenotype*. Its genetic characteristics are its *genotype*.
- The animal's basic genetic characteristics are carried in its DNA located in the nucleus of the cell. Each strand of DNA is made up of *nucleotide bases*—labeled A, C, G, and T—that combine into the template for a gene.
- *Genes* are regions on a DNA strand governing a particular aspect of the genotype, such as hair length. A gene is the blueprint for a protein.
- The DNA in the nucleus is made into *RNA*, which is then translated into protein.
- Canines have just over two billion nucleotide bases, translating into about 20,000 unique genes. The genes are packaged into 38 DNA regions, called *chromosomes*. Every dog has 38 pairs of chromosomes, called *autosomes*, as well as the XX or XY chromosomes that govern gender.
- Chromosomes come in pairs, and the two *copies* of each gene are called *alleles*. The underlying DNA governs differences between the alleles. Each pair of alleles is called a *diploid*, and each one governs a specific genetic trait, like growth, fat, or hair color.

The location of each diploid on a chromosome is the identifying address for that gene, known as the *locus*, and the locus is always the same; for example, the gene for von Willebrand's disease (vWD) is always in the same location on chromosome 10 in dogs. Humans have a comparable genetic structure, but the addresses often differ. vWD, for example, shows up on chromosome 12 in humans.

Changes or mutations in a breed's DNA may or may not be favored by breeders and may be positive, negative, or neutral for the health of the animal. Although an individual dog can only have two alleles in each chromosomal pair, there may be many different alleles across a breed population.

Alleles can either be identical (*homozygous*) or different (*heterozygous*), and may be dominant or recessive compared to other alleles in the breed population. In Labrador Retrievers, for example, black hair is dominant and brown hair is recessive, so a chocolate Labrador only results from the combination of two recessive genes. In a combination of dominant and recessive alleles, the black trait would mask the brown, although the dog would still carry the recessive gene.

The Merle gene in the Shetland Sheepdog is an example of incomplete dominance of one allele over another. While the classic Merle coloring results from a heterozygous pair, the combination of two dominant Merle alleles results in white patching and a number of serious health issues for the dog.

The essence of a breeding program is that the offspring take half their genetic material from each parent. Through the process of *meiosis*, one allele from each pair is selected and recombined with one corresponding allele from the other parent. The separation process is governed by Mendel's Law of Segregation, which holds that offspring only receive one copy of each paired chromosome from each parent, and Mendel's Law of Independent Assortment, which reflects the random way in which genes are selected.

Dr. Oberbauer said the structure of genes allows for a great deal of crossover, i.e. recombination, during meiosis. Others are packed more closely together on a chromosome, so that the alleles of two linked genes are more likely to travel together. These linked alleles are called *haplotypes.*

Some diseases are genetic but not inherited, she said. A chemically induced leukemia or a developmental anomaly might change an animal's DNA, but "it's not in the sperm, it's not in the egg, and it will not be passed on to the next generation." If a trait is passed on, it is important to estimate the degree of its heritability and determine whether it is regulated by one, two, or several genes. These factors "determine how well you can make genetic progress in engineering your animal."

Some traits are also influenced by sex. With one X and one Y chromosome, the male determines the sex of the offspring, but might also pass on sex-linked traits like hemophilia in humans or calico markings in cats. Some traits are also *polygenic*, or complex, meaning that both parents contribute alleles that influence their expression.

Dr. Oberbauer identified inbreeding, linebreeding, phenotypic breeding, outcross breeding, and compensatory breeding as the main strategies for encouraging or discouraging specific genetic traits. Inbreeding and linebreeding promote uniformity—"that's how breeds are created," she said. By narrowing the gene pool and increasing the prevalence of recessive traits, the practices can also make deleterious alleles more visible in a breed population. If fewer alleles are present and one of them happens to be defective, "you basically have that allele in your population." This is particularly true when a "popular sire" is overbred.

Phenotypic breeding focuses more on a dog's appearance and less on its pedigree, but Dr. Oberbauer said the larger range of possible allele combinations makes it less likely that specific traits will be passed on to offspring. Outcrossing is a method of improving a breed, by introducing heterozygocity and compensating for a deleterious recessive allele. Compensatory breeding is used over a period of generations to correct an obvious phenotypic fault.

The ultimate goal is to combine genetic knowledge with breeding strategies that address the risk of disease or the likelihood of repeating a desirable trait. Dr. Oberbauer emphasized the need to prioritize traits, suggesting that a dog testing positive to develop cataracts late in life might still have enough positive characteristics to be bred. Over the longer term, new genetic technologies will challenge breeders to "make more distinct and difficult choices," while still setting out to breed the best of the best.

Noting that he sees genetic disease in a large proportion of his patients, Dr. Jerold Bell emphasized the need to breed responsibly and identify diseases that can be reduced through careful selection. He said the preponderance of genetic disease traces back in part to changes in breeding practices over the past century.

"Old-time breeders spent a lot of time working on breed histories, and understanding selection parameters for their particular breeds and the breed characteristics that should be selected for," he said. For working breeds, selection was as simple as not breeding a dog that could not perform its function. "Their genetic testing was seeing a hunting dog that couldn't hunt, or didn't have the right temperament." Today, many more people are breeding dogs, and much less time is spent scrutinizing each breeding decision.

The latest development is the introduction of so-called "designer breeds." "The majority of new puppies coming into my practice for the past two years are designer-bred dogs, not purebred dogs," Dr. Bell said. "The fraud being perpetrated on the American public is that somehow these dogs are going to be healthier than purebred dogs," when "the only way we can ensure the increased health of the offspring is through genetic testing and the selection of healthy parents."

Dr. Bell said he sees as much genetic disease in mixed-breed dogs as in purebreds and designer breeds, if not more. The difference with purebreds is that breeders undertake genetic testing and "scream out loud" if something is wrong. One study of canine hypothyroidism found an average rate of 7.5% across all AKC breeds and 10.7% in mixed breeds, based on a pool of more than 55,000 samples. The results may have been skewed, since mixed breeds were only tested based on clinical signs. "But it tells us that this disease is present across all dog types," showing that the cause is probably an ancient gene inherited by multiple breeds.

For the 10 top diseases identified in CHF's 2002 and 2004 breed health surveys, Dr. Bell said rates are often far lower in purebreds based on genetic selection than in the general canine population.

The availability of genetic testing means taking a second look at the definition of a reputable breeder. "The times have now changed," Dr. Bell said. "It's not a crap shoot anymore. It's still a roll of the dice, but the dice are now loaded." As custodians of their breeds, reputable breeders must take advantage of genetic testing to deliver a healthier product to the American public.

Gene frequency is not altered by breeding practices, he said, but by selection. With a finite number of quality dams, overbreeding of popular sires prevents other males from contributing to the gene pool, and genetic diversity suffers.

Managing genetic disease means relying on genetic test results and registries to confirm genotype, since phenotypic linkage tests can yield false positive and negatives. When a test is available for carriers, a breeder has the option of breeding a quality carrier to a genetically normal mate, then replacing the quality parent with a quality, genetically normal offspring. This practice reduces the frequency of the defective gene with each generation, and eventually eliminates it.

By the same token, Dr. Bell warned that genetic testing could be the Trojan horse that devastates a breed. The worst decision a breeder can make is to refrain from breeding a favored dog because of one genetic test result, he said. "You've already decided it was a quality animal, and a single testable gene result should not alter the decision about an entire animal" that has 20,000 to 30,000 genes.

Without a test for carriers, the only option is to breed higher- and lower-risk individuals and continue replacing the quality parents with lower-risk offspring, a practice that depends on open health databases, registries, and open communication among breeders. Dr. Bell identified the Canine Eye Registry Foundation (CERF), the Orthopedic Foundation for Animals (OFA), and the Canine Health Information Center (CHIC) as powerful resources for both veterinarians and breeders.

The databases can also be used to educate new owners about the characteristics of their breeds. "I don't know how else to do it except one owner at a time, to educate the public that they need to do as much research when they buy a puppy as when they buy a refrigerator."

At a time when no dog is likely to be perfect, the databases become a tool for promoting health consciousness, not health normalcy. "As long as we keep the problems secret, we will not be able to deal with them," Dr. Bell said. "We here represent every AKC breed, and we need to go forth and pass the word that this is a new age. It's different now, and this is the way we go forth."