Doggenetics.com *News*

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New Newsletter

Welcome to the first edition of **Doggenetics.com** ***News*****. We hope to give you a quarterly overview of interesting new research into genetic diseases, the genetics of behavior, and other interesting canine traits. We'll also talk about population and quantitative genetics and how you can put their principles into action in your breeding program.**

We'd love to hear your suggestions about future topics, so please send suggestions to newsletter@doggenetics.com.

Allergies like Mama's?

Allergies seem to be on the increase in many dog breeds, and there is a lot of speculation about whether allergies are caused by genetic or environmental effects. As with many traits we're interested in, the answer is that it's probably a combination of both. The genetic background gives the dog the building blocks for the immune system, including a variety of proteins important in the recognition of allergens, but the environment has a definite role in "selecting" which of these are more important as the animal develops.

Recently a small study (Barrett *et al.*, 2003) found that Beagle parents that had allergies to ragweed tended to have puppies with the same allergies. Pups were regularly exposed to either ragweed or filtered air starting at one week of age. The pups of allergic parents were more likely to develop respiratory signs of allergy and increased blood levels of IgG and IgG4. These are substances produced in the immune system that are known to be associated with ragweed.

We are just scratching the surface of understanding canine allergy. This test was with one specific type of airborne allergy, and we still have to learn about allergies to food and skin allergies. As we learn more, we'll have more ideas for treatments, and about how to breed dogs that are free of allergies.

Barrett, E. G., Rudolph, K., Bowen, L. E., and Bice, D. E. Parental allergic status influences the risk of developing allergic sensitization and an asthmatic-like phenotype in canine offspring. *Immunology* 110(4), 493-500. 2003.

Using the Dog Genome to Build the Canine Family Tree and Identify Breeds with DNA

A very large and important study involving several leaders in the field of canine molecular genetics was published in the May 21 issue of *Science Magazine*. The collaborators used genetic markers to compare the genetic variation in 414 dogs from 103 breeds and eight wolves to analyze the genetic history and evolution of canids. By statistically analyzing this data, they were able to construct a family tree showing the genetic relationships among dog breeds, tracing all the way back to the wolf. The study also showed that almost all the time, a dog's breed can be identified by using these genetic markers. For a long time, we thought this would be impossible. Now, we know more about the histories of breeds and how they are related to each other, with some surprising results. The promise of extending this research is exciting because there is a lot more to learn about breeds and how they were created, diseases that cluster in related breeds, and how evolution with selection works.

Two classes of genetic markers were used: microsatellites and single nucleotide polymorphisms (SNPs). DNA consists of a long strand of molecules called nucleotides, which are the basic units of the genetic language. A gene consists of a linear sequence of nucleotides (although sometimes there are intervening sequences that are not part of the ultimate protein product). Microsatellites are short regions of DNA where a sequence of nucleotides, like 2 or 4, are repeated. In this area, changes in DNA sequence are common; the DNA replication mechanism often mistakenly adds or skips repeats. These sections of DNA have so much variation that we can track evolution by looking at what repeat number different animals have. When you look at lots of microsatellite locations at lots of loci (96 were used in this study) in lots of animals, you get a lot of statistical power for comparison. Eighty-five SNPs, variations in only one nucleotide, were used in a similar manner.

Complex statistical models that take all of these markers into account were used to determine which animals or breeds were genotypically, and therefore

evolutionarily, close together. In general breeds that are more closely related have more microsatellite repeats or SNPs in common than breeds that are farther apart in an evolutionary sense. This approach detected four clusters of dog breeds: Asian Spitz types (Shar Pei, Shiba Inu, Akita, and Chow Chow), Arctic spitz types (Alaskan Malamute, Siberian Husky, Middle Eastern sighthounds (Afghan Hound, Saluki) and a large cluster of "modern European breeds." The latter are more difficult to distinguish because of their relatively recent origins (Golden Retrievers and German Shepherds have only been around for about 100 years, for example). This is attributed to the advent of dog breed clubs, dog shows, and the interest in keeping pedigree information, leading to a stricter separation of dog populations. Also, in some cases breeds have been crossed to form new breeds. After further analysis, a new cluster emerged containing the Mastiff, Bulldog, and Boxer, and related breeds. Surprisingly, the German Shepherd dog is included among these Mastiff types. Also surprising to me is that retrievers do not fall in the same cluster as a group– some are in this Mastiff group, and others have different origins. Yet another surprising finding is that some breeds we thought were distinct breeds for thousands of years, like the Pharaoh Hound, Ibizan Hound, and Norwegian Elkhound, actually appear with modern breeds, suggesting that they have been crossed with other breeds over the years. With further study with more individuals, it may be possible to resolve the history of modern breeds in more detail.

It is interesting that in this study, it was possible to identify a dog's breed from its marker data 99 percent of the time. The mistakes were

- a Beagle classified as a Perro de Presa Canario
- a Chihuahua classified as a Cairn Terrier
- a German Shorthaired Pointer classified as a Kuvasz
- a German Shorthaired Pointer classified as a Standard Poodle

These four dogs came from breeds that had less distinct clusters than most other breeds. When I saw Standard Poodle there as a breed, I was curious about the distinction between the sizes of Poodles, but the Standard was the only size included in this study. That is as it should be, since there is gene flow between the different sizes of Poodles and they are not distinct breeds. For similar reasons, the Belgian Tervuren and Belgian Sheepdog were considered as one breed for this study because they are color variations, and some countries' dog organizations consider them to be one breed, while others consider them as two separate breeds.

There will probably be a lot of uses for this ability to assign a dog to its breed based on microsatellites and SNPs. In areas where certain breeds are banned, or forbidden by insurance companies, it could be used to identify the ancestry of a purebred or even a mixed-breed dog (Analysis methods allow a model where an individual or breed is a mixture of multiple breeds.) It might be used by canine registries to confirm a dog's breed, or in cases where there are multiple sires of a litter (some of the groundwork for these new findings is related to the work done on parental identification in dogs). It may help me learn what kind of dog sired Sailor Blue, my sister's awesome and intriguing-looking half Labrador-half Mystery Dog.

Parker, H.G., Kim, L.V., Sutter, N.B., Carlson, S.; Lorentzen, T.D., Malek, T.R., Johnson, G.S., DeFrance, H.B., Ostrander, E.A., Kruglyak, L., Genetic structure of the purebred domestic dog. *Science* 2004 304:5674 1160-1164. http://www.akcchf.org/news/press/releases/2004/dogbreeds.pdf

Genetic Testing: Direct or Indirect?

As the canine genome is mapped, we learn more about genetic causes of disease (and other traits, like coat color). We also learn where they are located on the dog's chromosomes. In the early stages of creating a map, we try to see if there is a statistical association between a trait and a known genetic marker. For some traits, we start out knowing a general area, like which exit to take off the interstate highway. As more and more specific detail about the map is obtained, we learn which road to take next, which block our destination is on, and finally, which building we are interested in and what's going on there.

Genetic tests take advantage of this association at different levels. Sometimes we can test for the exact location (the actual relevant gene sequence) to determine if there are differences in nucleotide sequences. This is a direct test, At other times we are testing to see if we are in the right block or zip code, and this is indirect testing. We are testing for a marker that tends to be associated with the gene, and at first are often unsure of whether the marker is in the building we're looking at or just in the neighborhood.

One of the interesting phenomena about genes is called linkage. Genes are arranged sequentially along the chromosomes, with one copy on each strand. When DNA replicates to form a new cell, the strands break off in some places and reattach, but not always in the same configuration– the two new strands each

contain some of each individual strand. This is called crossing over. Genes that are far away on the chromosome are often not associated with each other, because there are so many crossing over events between them. But the closer they are located, the more likely they are to stay together and be inherited together. This is how we get our indirect genetic tests.

The *MURR1* gene causing copper toxicosis in Bedlington Terriers has been associated with a marker that was ussed in the detection of the disease for several years. It wasn't a perfect genetic test, though. The marker associated with this disease wasn't in fact always associated with it because at times a crossover point occurred between them. But now that the *MURR1* gene has been mapped and sequenced it will be possible to use a direct genetic test (van de Sluis *et al.*, 2003.

Copper toxicosis involves an inability to remove copper from the liver. Because it cannot be properly removed, it accumulates and becomes toxic to the dog. The disease is progressive and symptoms usually appear when the dog is at least four years of age. The condition is quite common in Bedlingtons, and is found with less frequency in 52 other breeds.

van de Sluis B, Peter AT, Wijmenga C. Indirect molecular diagnosis of copper toxicosis in bedlington terriers is complicated by haplotype diversity. *Journal of Heredity* 2003; 94: 256-259.

What do *you* want to read about here?

Please send suggestions to
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Yes, We Have *Two* Hips

Dog genetics enthusiasts have been studying hip dysplasia and hip joint laxity for at least four decades, but we've always thought about it as one trait. The human form of this disease, however, often appears on one side only, and much more often on the left than the right side. What about dogs? Norberg angle (a method of hip joint evaluation widely used in Europe) was measured in Portuguese Water Dogs, and the scores were studied for association with Quantitative Trait Loci (QTL). QTLs are areas on the chromosomes that are statistically associated with the presence of a trait of interest. In this case, there were two detected QTLs related to hip joint conformation. Surprisingly, one had more effect on the left side, and the other had more effect on the right. Heterozygotes at these loci appeared to have Norberg angles more strongly indicative of laxity. It isn't clear yet how this works, but it gives us some interesting stuff to think about!

Chase, K., Lawler, D. F., Adler, F. R., Ostrander, E. A., and Lark, K. G. Bilaterally asymmetric effects of quantitative trait loci (QTLs): QTLs that affect laxity in the right versus left coxofemoral (hip) joints of the dog (*Canis familiaris*). *American Journal of Medical Genetics Part A* 124A(3), 239-247. 2004.

Epilepsy in Belgian Tervurens and Belgian Shepherds

Genetic markers of various types act like road signs on the dog's genetic map. They are scattered throughout the genome and can be composed of many different kinds of recognizable DNA sequences. These are often small pieces of highly repetitive DNA, and important variations cane be changes in the DNA sequence or changes in the number of repeats of a short sequence(microsatellites). To find the gene for a particular trait on the map, we use statistics to determine whether the road sign is associated with the trait we're interested in. Previous research has suggested that there is a single gene for epilepsy in Keeshounds and Vizlas, but most researchers expect epilepsy in many breeds to be due to several genetic and environmental factors, possibly with one gene of major importance.

In the case of Belgian Tervurens and Belgian Shepherds, Oberbauer *et al.* (2003) have found three areas of the genome (road maps) that seem like they might be associated with epilepsy. These authors believe that although there are multiple genetic and environmental factors in the development of epilepsy, there is probably a major gene that contributes to the disease phenotype. As the dog genome continues to be mapped and more detailed signs posted, this work will lead to a more precise definition of one of the important genetic factors in this disease. Hopefully, knowing the protein and mutation associated with epilepsy will improve out understanding of how this disease works in other breeds as well.

Oberbauer AM, Grossman DI, Irion DN, Schaffer AL, Eggleston ML, Famula TR. The genetics of epilepsy in the Belgian tervuren and sheepdog. *Journal of Heredity* 2003; 94: 57-63.

A Shameless Plug

Want to learn more about dog genetics? Cornell University offers an on-line, distance-education class in canine genetics. Some of the topics include

- The evolution of the canine species
- Understanding basic inheritance patterns for 1, 2, and 3 loci
- Using probabilities to predict genotypes and phenotypes
- Coat color genetics
- Detection of carriers
- Genetic tests and their interpretation
- The concepts and relevance of genome mapping.

This class includes 8 voiced-over PowerPoint lecture presentations, 4 problem sets, 4 veterinary lectures about important disease research. There is a web-based bulletin board where students are encouraged to post their thoughts and questions about anything related to dog genetics. We have offered this course for about 4 years and it's a lot of fun. For more information, please check http://www.ansci.cornell.edu/cat/cg01 /dog-courses.html

Behavior and Genetics

A dog's behavior is another one of those complex traits that has both genetic and environmental factors associated with its development. It is particularly challenging (but very interesting!) to study, because it's hard to define very specific traits and measure them in real dogs. What *is* intelligence? Aggression? Trainability? How can we measure these things reliably?

Over the last 15 to 20 years, there has been a form of uncharacteristic aggression in Golden Retrievers. Anecdotal evidence suggested that it ran in families. It was quite distressing to the many people who love the normal easygoing temperament of this breed.

In one study, goldens were exposed to very specific situations and interactions that could elicit aggressive behavior (van den Berg, Schilder, and Knol, 2003). The number of times the dog snapped or attacked a tester or its owner was carefully counted. The tests made many distinctions like aggression towards dogs or humans, toward strangers or their families, and aggression with and without fear, This work, which included some related goldens, has provided great data that can be used to find associations with genetic factors. This can lead to breeders' ability to avoid breeding dogs who have the potential to be aggressive, and may help us develop treatments for problem aggressive behavior.

van den Berg L, Schilder MBH, Knol BW. Behavior genetics of canine aggression: Behavioral phenotyping of golden retrievers by means of an aggression test. *Behavior Genetics* 2003; 33: 469-483.

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