

EPILEPSY STUDY

From a researcher at U of Minn - I think perhaps there was a little misunderstanding that needs to be cleared up in regards to the DNA sample sharing and use between the University of Missouri and the University of Minnesota. To my knowledge, the University of Missouri is not actively "using" any of the Vizsla DNA samples at this time. Any DNA sent there gets isolated (ie, put into a form for long-term storage) and then stored in -80 degree C freezers. DNA can last just about forever in these conditions. DNA sent to us in Minnesota is treated the same. At both Missouri and here, an electronic database (as well as the paperwork database) are maintained - so, for example, when a litter of puppy tail tips comes in, they are entered in the electronic database, the paperwork is stored and the DNA is treated as described above.

We have an ongoing collaboration with Missouri, such that, when we're preparing to use more/new DNA samples (from Vizslas, and other breeds as well) we can access THEIR electronic database, compare it with ours, and see which samples they may have that we don't, and those that we are interested in, we are allowed access to. The partnership works in reverse as well.

Therefore, even if the DNA is in Missouri, we can still access it if/when we need to. However, if you are more comfortable, you can certainly send all your new samples to Minnesota in the future, as the Vizslas are a breed we specifically work on in Minnesota. As recently as last month, we at Minnesota scoured the Missouri database to acquire any Vizsla samples that might prove useful in our upcoming new study (more on that in a bit), and only four were found (and these later proved not usable for various reasons).

A couple things that you (and all owners submitting dog DNA samples to the epilepsy study!) need to do to help US be most successful at this research, is to give us follow-up information. Everything from new contact information (an owner moves and we can't get ahold of them), to the eventual registered name and owners for the puppy tail clips are all needed. You can imagine that, while we have the DNA saved and identified with a litter ID and a "color" from a puppy tail clip, that without that pup's eventual name and owners, we know nothing and that sample is essentially useless without further information.

This brings me to phenotype information (whether the dog is affected or not affected). Again, puppy tails are wonderful sources of DNA, but we NEED the adult information, because, of course, the puppies do not have seizures. But if they grow up and have seizures and we don't KNOW that, then how can we use the samples? Or worse, if we used them blindly, and had incorrect phenotypes, then this would cause us to lose statistical power and decreases the likelihood of us ever finding the mutation. Even for blood samples submitted from adult dogs, we need follow up information. Did the dog start seizing two months after submission of the sample? Two years after? Then, even if we DO want to use a sample, and without updated owner contact information, we don't know the dog's phenotypic status and we can't use it. So, you can see how vital keeping current is! This is why we are trying to update some of our phenotypic data - some of the dogs in our study have died and having that "lifetime" data is also so useful. However, it is impossible for us to contact every dog owner from every sample (we have almost 700 Vizslas in our freezer!) and one of our graduate students has spent the last two months trying to get caught up on just 96 of them.

This brings me to sample usage. It is very true that some samples that are submitted are not used in these studies, at this point. This is due to several things:

1. **The design of the studies.** For example, in this new upcoming study we're getting ready to run, we're looking for discordant sibling pairs. In other words, one affected sibling, one unaffected sibling. Full siblings are preferred, but even then we can't get enough pairs, so we're using half siblings. If an affected dog has six unaffected half-siblings in our freezer, we have to pick one. And we want our unaffected dogs to be over five years of age and free of seizures (as a safety measure - we don't use dogs that are under that age that are seizure free, because they may still develop seizures as they get older). In the past, we've performed linkage studies, where whole families were utilized. With this new technology, (called an

association analysis) the sibling pairs are preferred. This doesn't mean the other samples won't be used! If we can finally find the mutation that is causing this disease, you can bet we'll be testing every Vizsla in the freezer!

2. Money. Research money is not endless, and these new SNP arrays (for the association analysis) are expensive. They also come in multiples of 12. So, to start with, we are trying to assemble 96 dogs (48 pairs of discordant siblings), which is why we're trying to follow-up with those dogs right now. Again, this doesn't mean that we won't use more dogs in the future (but we're also hopeful that these 96, selected in sibling pairs, with good cases (no ambiguity as to the diagnosis of epilepsy) and old dog controls, will help us locate the mutation! So, in short, we will never turn down a sample, because they always prove useful eventually, it's just that we cannot use every sample every time. That's always true in science.

Hopefully I've also stressed how important it is for use to have updated information for these dogs too, particularly when it comes to possible seizures, and ESPECIALLY if they've been submitted as "seizure free" and subsequently develop seizures! We know that you and all the owners who take the time to get their dogs' blood drawn, forms filled out, shipped, etc., have gone to great lengths to help us in this study, and hopefully you see how great a lengths we go to ourselves to use the samples that are MOST likely to help us succeed. We appreciate your effort and time so much, and every time we speak with an owner for follow-up information, we express that gratitude as well. We couldn't do this research without you. Rest assured that your Vizslas' DNA samples have been entered in the "Vizsla Epilepsy Study" even if they're in MO and not MN. It's just that they can't all be used simultaneously.

Finally, there are breeders, and believe me, they exist in every breed, who are NOT helping advance the health of the Vizsla breed due to their denial, intimidation, etc., when epileptic pups show up. It's interesting to look the bloodlines (for us) for sure, but obviously, without samples, there's little we can do. We'll keep this information completely confidential (as we do with all submissions - we only speak with dog owners about their own dogs). I will tell you that we know of at least one prominent sire (in another breed) DNA sample that was sent to us which we are CONVINCED was from another dog, may not have even been from the samebreed, but labeled with his name...unscrupulous people abound. That's why folks like you who are honest and really want to help the Vizsla breed be improved are so vital. I'll confess, it takes help from concerned people (such as yourself) to motivate people to send samples in and to remind them to update us...it's too much for the 2-3 humans working on this project in this laboratory to keep up with! I can't comment specifically on whether an individual has been contacted for updates, but as I mentioned above, we're starting with a subset of owners to contact. Also, we're TRYING to start tracking down the dogs that these puppy tails grew up to be so we can find out what their registered names ultimately were, whether they've had seizures, etc. If any contributor has that information (at least registered names and the dog's owner's contact information) she should send it to us and we'll start tracking them down. Better yet (it would save us time here) if she can, she can have those dog's owner's contact us! (If the puppy tails came in to us as a litter ID and a color, it's also helpful if the owners know what color string was tied around their pup's neck all those years ago!).

To address your final questions: We do not typically call an owner just to tell them that we'll be using their dog's DNA sample in the study. All Vizsla DNA samples are "in" the epilepsy study, it's just that we can't use them all at once (as above). We do typically try to let the owner (or whoever shipped the package) that we received the blood samples. At that point, they can consider the dog "in" the study. The dog's identifying data is entered in our database, it's assigned a unique identifying number and stored. Which samples we use depends on the exact experiments we're conducting on any given day. I also know that the graduate student who's spent the last two months on the phone and emailing Vizsla owners in an attempt to get all the updated phenotypic information, ALWAYS acknowledges when she's gotten all the info she needs (for example, the seizure survey filled out, or whatever) and profusely thanks the owners for their time. Truly, without them, we couldn't be doing this research. And yes, you can just tell everyone to send the samples to our laboratory. Because, certainly, we have access to them when they are in MO, but it's easier when they're already in MN!

In March of 1999, the AKC Canine Health Foundation awarded a grant of \$57,500.00 to researchers at the University of Minnesota College of Veterinary Medicine to study the molecular genetics of canine epilepsy in Vizslas, English Springer's and Beagles. The goal of the study is to identify a marker or gene for epilepsy and to develop a screening test to determine normal, carrier and affected status, thus allowing breeders the potential to eliminate epilepsy.

CVVC is proud to support this research by holding clinics for the collection and submission of blood from as many vizslas as possible. Go to <http://clubs.akc.org/vizsla/health.htm> and follow the links for the Epilepsy Study.

Update from Kari Ekenstedt at University of Minnesota, July, 2008:

We've run approximately 450 microsatellites spanning the entire canine genome on our linkage plate over the past years. These are each a unique location in the genome and then we look to see if that location and the disease are segregating together. While there have been a couple locations that may be interesting, nothing has jumped out at us yet. In addition, we've run about fifty more specific microsatellites near candidate genes that seemed likely to be involved based on what we know about human idiopathic epilepsy. Again, there may be a couple that are interesting, but nothing specific.

The exciting news is that we now have a new genetic tool available for canine research, called a genome-wide SNP array. These have been in use for years in humans and are now available for dog studies. The SNP markers are also unique locations in the canine genome, but the great part is that we can simultaneously query almost 23,000 locations across the genome and get the results within months. Obviously this is a huge advance in technology and we're gearing up to run about 100 of these arrays on the Vizslas. As always, highly accurate phenotypes (seizing or seizure-free) are critically important, so getting updates from owners are vital. Even getting updated owner contact information is necessary, because there are some dogs that were entered in this study originally that have been lost to follow-up due to the owners moving and we cannot track them down. It is even useful for us to get updates on dogs that have died, as having the lifetime data is wonderful (ie, the dog was seizure-free until it died at the age of 13 from hemangiosarcoma, for example).

A nice update article is going to be published in the October issue of the AKC Gazette, so folks can keep their eyes peeled for that!