NHGRI Webinar

The Long and Short of It: Finding Genes for Complex Traits In the Domestic Dog

Moderator: Sarah Harding
January 8, 2008
12:00 p.m. CT

Coordinator: Welcome ladies and gentlemen and thank you for joining today's teleconference.

At this time all party lines will be in a listen only mode throughout today's call. A question and answer session will be held, at which point you may press star 1 on your touchtone phone if you'd like to ask a question.

As a final reminder, your call is being recorded. If you have any objections you may disconnect your line at this time.

And I will now turn the call over to your host, Mr. Vence Bonham. Thank you. You may now begin.

Vence Bonham: Thank you and good afternoon to everyone on the phone. Welcome to the fourth Webinar in the National Human Genome Research Institute's Webinar series.

We will be talking today about the latest research on the dog genome. And why this information is important for the broader field of genomic research.

A few technical notes for the call first. If you have any technical problems during the call, for instance if you're having trouble accessing the Web portion of the call, dial star 0 to talk to the operator. And hopefully the operator can assist you.

We will hear from Elaine Ostrander, Chief of the Cancer Genetics Branch. And then we'll take questions from you. So please be thinking about your questions as we move forward.

We will be taking the questions over the phone. Dial star 1 to speak to the operator and you will be put into the queue to ask your question.

Please move any BlackBerrys or cell phones away from your phone because it can cause interference.

We will be recording these presentations and the question and answer session that follows. Our hope is to post this on line for the benefit of others with regards to the Webinar today.

So please now let's welcome Dr. Elaine Ostrander, Chief and Senior Investigator in the Cancer Genetics Branch here at the National Human Genome Research Institute.

Dr. Ostrander's laboratory maps genes responsible for cancer susceptibility in canines and in humans.

The clinical presentation, the histology and biology of many canine cancers very closely parallel those of human malignancies. So compare to studies of canine and human cancer genetics should be a significant clinical benefit to both.

Dr. Ostrander's laboratory is interested in prostate and breast cancer susceptibility genes in high-risk families, as well as the frequency and distribution mutation in known cancer susceptibility genes in the general population.

The talk today however will focus on her work with the dog genome, Dr. Ostrander.

Elaine Ostrander: Thank you very much Vence and welcome to all of you. I'm actually not going to be talking about cancer. Today I'm going to be talking about a project that our lab began in recent years, which focuses on understanding the genetics of morphology in the domestic dog.

And you'll see why in the first few slides that's really such a very, very interesting topic.

So if we think about dogs as a species, it's important to remember that all breeds of dogs are all members of the species canine (atrimiliarse).

And there are over 400 breeds of dog recognized worldwide, and about 150 of those are sanctioned by the American Kennel Club or the AKC.

Now as you can see on the picture, every breed is defined by a unique constellation of both morphologic and behavioral traits.

And we see a huge range in variation as we look across these dog breeds in terms of their body size, their head shape, their back shape, their coat color, their coat length.

Really anything that we can think of to study, there's an opportunity to study it by thinking about (term) combinations of dog breeds.

What you may not know is that most dog breeds were created quite recently, within the last 2 or 300 years through a combination of both hybridization and selection.

And breeds are maintained through very stringently controlled breeding programs. So in other words to be an AKC registered standard poodle, both of your parents have to have been AKC registered standard poodles and the grandparents in turn.

So every dog breed effectively represents a closed breeding population, with many of the same advantages that we have when we think about human restricted population such as those from Finland or Bedouin pedigrees or those from Iceland.

We have a limited amount of genetic diversity. And that really simplifies a lot of the problems we face in trying to understand the genetics of fairly complex traits, which is really what this talk is going to focus on today.

So in the last couple of years our lab has had tremendous success in navigating the canine genome and beginning to identify genes responsible for some of the complex traits in dogs.

What I want to do in the next half hour or so is tell you a couple, just a couple of the stories that we've done. And maybe give you a little bit of insight as to where we're headed now, where our thinking is going over the next couple of years.

So overall the canine portion of the lab and as Vence told you, half my lab works in human genetics and half works is in canine genetics.

The group that works in canine genetics is interested in lots of different things. They're interested in mapping genes for morphology. We're interested in the genetics of population structure.

We want to find the genes for cancer susceptibility, which is what Vence highlighted during his introduction.

And we're also interested in identifying genes that are important in performance.

In the interest of time today, and we have just a half hour for the talk portion of this, I'm going to talk a little bit about finding genes for morphology. So the physical differences that define the different breeds of dog.

And I'm going to be talking about approaches we use to finding genes for behavior or performance.

So let's start with morphology - dive right in. I really love this particular picture which features this Harlequin Great Dane, among the largest of the dog breeds.

And this little mix down here, which is a combination of a couple of the smallest of dog breeds.

And this picture was featured on the cover of Science in April of 2007. Because within that issue was a paper by a group of collaborative investigators, including people from Bob Wayne's lab at UCLA, Carlos Bustamante's group at Cornell, Gordon Lark at the University of Utah as well as others and lead by Nate Sutter, (then a post-op fellow in my lab).

That described an approach for finding genes that control the genetics of body size. And that's really what I want to take you through in the first story today, body size genetics.

So when we began this project, we sat down and we talked about an approach, or a mechanism, how we would go about finding genes that control the enormous differences that we see in body size in different breeds of dog.

And keep in mind the very largest to the very smallest dog breed as shown on the previous slide, different size by about 40 fold. So some really amazing genetics to try and access there.

So we decided our approach would be the following. We would start out by doing a genome wide scan in a single breed. And we picked the Portuguese Water Dog for a number of reasons which I'll highlight in a moment.

To try and identify quantitative trait low sight or regions of the genome where we thought there would be genes that were important in controlling body size across breeds.

We would then analyze very large and very small Portuguese Water Dogs to try and narrow the associated interval.

And finally we would move away from just thinking about Portuguese Water Dogs and see if our findings translated across dog breeds. So we would analyze dogs from very large and very small breeds to identify shared haplotypes, or shared patterns of alleles among size selected groups, very small and very large. Hopefully reducing the region down to a single gene.

And as you'll seen in the next few slides, this turned out to be a really, really successful strategy.

Okay, why do we start with the Portuguese Water Dog? Well this is a breed that the American Kennel Club allows enormous variation in terms of body size and shape.

Now that's not true for all dog breeds, but it's certainly true for the AKC where AKC registered Portuguese Water Dogs can differ in size certainly by twofold and perhaps even more than that.

In the United States today there are about 10,000 Portuguese Water Dogs, and they're all dissented from a group of about 30 dogs that came to the US maybe 50 years ago that originally were dogs that were found on Portuguese sailing ships.

We hypothesize that there are probably very few genes therefore that are segregating the major alleles that are important in defining these difference in body size that you see in the Portuguese Water Dog.

So this was a good place to start. Practically it was also a very good place to start because we had a terrific collaboration with Gordon Lark and Kevin Chase as the University of Utah who had for some years been studying the genetics of the Portuguese Water Dog.

They had a project which is still ongoing called the Georgie Project. And at that point there were about 1000 dogs that were enrolled in the Georgie Project. And the Web site for it's up there in case you want to go and check it out.

And the idea behind the Georgie Project was to collect as much genotype data as well as physical or phenotype data as we possibly could on as many living AKC registered Portuguese Water Dogs.

We were able to collect genotype data on about 500 Portuguese Water Dogs at the time this analysis was done using a set of about 500 markers.

And markers of course are places where there's variation in the DNA sequence that segregates through multiple generations in a family, and the flavor markers that we use for microsatellite markers in this case.

Now importantly Gordon, Kevin and their collaborators had also collected 91 skeletal measurements from a series of five x-rays that they took on each one of the dogs.

And you can see the five x-rays and the 91 metrics indicated by the black line on the right of the slide.

They then did and published in 2002 a principal components analysis. And what a PC analysis does is it classified phenotypic variation into independent systems of correlated traits.

So very practically, to give you an example, if we were to cross that Great Dane you saw in the previous slide with a Chihuahua or a Pekingese mix. You would not end up with a dog that had a giant body like a Great Dane and a tiny little Pekinese head on the - sitting on top of it.

You would end up with an animal that was proportioned. And the genes to control that proportional variation are really what we want to try and find.

The important thing to remember is that principal components are phenotypes. And as such, they're amenable to genetic analysis. That is we can try and find the genes that are responsible for that variation.

Now on this slide you're looking at the results from a single, critical marker in the initial genome wide scan, marker FH2017. You're looking at the rank order of 500 or so Portuguese Water Dogs as a function of trait value.

So small dogs are graphed to the left and to the - dogs, excuse me, on the left are indicated small trait value, or small skeletal size and on the right large dogs, or large trait value.

And the dogs were graphed according to their genotype. So the AA diamonds and the homozygote BB triangles, and then dogs who are heterozygotes are the open squares AB.

And what you see when you graph these according to their genotype is that they form three really nice lines. Dogs who had the AA homozygotes are in general the largest of the dogs.

You can see that that line is the furthest to the right. The BB homozygotes were the smaller of the dogs. And you can see that line. It's the furthest to the left.

And as expected the AB heterozygotes were intermediate in size. So this gave us an indication of a region of the genome where there was likely to be a locus that was important in controlling overall body size.

So the next task was to try and narrow down that region because the original region that was described by the genomes scan was pretty big. It was about 15 million base pairs.

That was an interesting region. It included some provocative candidate genes. But our task was before we got excited about any of those, let's try and narrow down the region.

And we did that using a series of single nucleotide polymorphisms, or snip base markers. These are biallelic markers. So at a given position there's either one or another base pair.

We initially genotyped a set of very large and very small Portuguese Water Dogs to find the most useful snips. And then we genotyped about 500 Portuguese Water Dogs using 122 of the snips that we had deemed to be particularly useful or informative.

And to do that for those of you that are curious, we use the ABI snip plex system.

And this is what we saw. You're looking now at a graph of the relevant chromosome. And you're looking at a span of about 15 million base pairs from 35 megabases up to 50 megabases.

And you could see this huge density of spots covered under the red rectangle indicating that that's the really hot region where we think the relevant gene is likely to be located.

Now this particular region spans about 4 million base pairs. So we've cut it down from 15 million to 4 million. But there's still quite a bit under that 4 million to think about.

But we were pretty excited because there was a wonderful candidate gene in that 4 million base pairs. And that was the insulin-like growth factor 1 gene.

And why is this such a great gene? Well we know from studies in mice that it's a gene that's really important in controlling growth, both prenatally as shown on the left where you're looking at both a wild type and a knock out mouse.

And then on the right where you're again looking at a wild type and a knock out mouse, that is both copies of the gene have been destroyed in the knock out mouse.

And in each case the wild type animal significantly larger then the individual which the gene has been knocked out.

Now there were other candidates in the region. But this is the one that got us really excited.

So remember we don't want to find a gene that’s important for making small Portuguese Water Dogs small and large Portuguese Water Dogs large. We really want to find something that's important across all dog breeds.

So we selected a set of several breeds in which to focus the next stage of the study.

On this particular graph you're looking at the height of the male, the shoulder, or the withers on the Y-axis. And that's graphed as a function of the weight of the male in pounds for each of about 20 breeds.

Now the shape of each one of these triangles gives you a sense of the proportionality of body weight to skeletal size.

The Portuguese Water Dog is indicated by the red circle is pretty much right smack in the middle. So that was actually a really good fortuitous choice in which to begin our studies.

To continue our studies though we picked lots of small dogs, several from the left portion of the line. And then some large dogs like the Irish Wolfhound and the Mastiff from the upper right portion of the slide.

And one of the first things that we did was to look at heterozygosity. And in this particular slide we're focusing on 14 of the small dog breeds. So this includes things that, you know, maybe weight just one or two or three pounds.

So think about Toy Poodles and think about Pekingese and think about Chihuahuas and any of those really miniature breeds.

This is also the result that got us really, really excited and told us that we were really there. We were really probably looking at the right gene.

It's a heterozygosity plot. And what it does is it measures the amount of variation as you're moving across a chromosome. Now we're showing you the data from Position 43.5 megabases to 45 megabases.

And you can see the heterozygosity level starts out as you expect, around one. And as you move along the chromosome it stays around one until you reach a position where there's been selection.

Where breeders have deliberately been selecting a particular allele or group of alleles because they're after a particular phenotype that encoded within that gene.

And then the heterozygosity plummets down to zero. And once you pass through that gene it shoots back up to one.

And you can see that the position of that selective suite coincided absolutely perfectly with the idea of one gene.

So this is really the result that told us that we were there and we really had something to be excited about.

Now this next slide is actually a pretty busy slide. It's the last really busy data slide I'll show you. But I think it's an important one so you sort of gain a sense of how much work really went into this.

Let's start by looking at the upper right. Now we're just focused on the IGF 1 gene itself on chromosome 15. And everywhere that there was a snip that we interrogated is a horizontal line.

And then you see this pattern of blue and yellow boxes with As and Ts and Cs and Gs with the letters A through L at the top.

Those are the possible haplotypes or allele combinations that we observed in all of the dogs that we looked at. And we looked at dozens of small breeds and lots and lots of large breeds.

The breeds specifically that we looked at are listed in the middle of this slide. Those in the top portion from Chihuahua down to the Boston Terrier we considered small.

And their size in kilograms is indicated to the left of the name of the dog. And then the giant breeds like the Bullmastiff and the Saint Bernard and the Great Dane and the Mastiff are listed below those.

And what was very, very striking about this as indicated by the first red rectangle is that the small dogs almost exclusively carry the B haplotype.

Suggesting that there had been a single ancient mutation that breeders have been selecting on for decades and decades and decades and decades in order to make small dogs small.

It doesn't mean there weren't other genes. And in fact we know there are other genes that contribute to body size in the domestic dog. But this was clearly one of, if not the most important one.

The story with large breeds is a little bit more complex. We can see that there are two haplotypes that predominate. The I haplotype, which is actually the one that we saw in the Portuguese Water Dog, as well as an F haplotype.

And the vast majority of dogs that fit into that large category had either that F or that I haplotype.

So there were a couple of different things for breeders to select upon in order to increase the overall size of the dogs.

Now we followed this up a little bit to see if we could break down and figure out exactly where within the IGF 1 gene the relevant mutations are.

And we now know it's contained around axon 3. Now linkage disequilibrium extends for quite a long range in dog breeds.

And by linkage disequilibrium I mean chunks of a chromosome that are inherited as a unit through multiple generations in a pedigree.

So there are several incidences of variation around axon 3. Any one of which or all of which could be important for contributing to the body size differential.

We don't have a way to really break that up. But we've been able to go from a whole genome down to chromosome 15, down to a small region of chromosome 15, down to a single gene, IGF 1.

And then down to the region around a single axon, axon 3. And demonstrate that that's really, really critical for controlling about 28% of the phenotype of,

or the variation associated with the phenotype of body size in the domestic dog.

And those of you familiar with 2/TL analysis will know that that's a huge, huge amount to be attributed to any one single QTL.

And other people in the lab, since Nate Sutter has moved on to Cornell where he's now an independent faculty member, has continued to follow up on this work.

So we've looked at many more breeds of dogs. We've generated a much, much, much larger data set. And then identified three or four additional loci which are clearly important in controlling body size.

And (Jeff Shonanbeck) in the lab is in the process of following those up. In addition to body size, people in the lab are pretty much interested in anything that you can think about.

So on this next slide I've just shown you a range of the variation that the lab is preoccupied with these days.

We're interested in genes to control leg length. We're interested in genes to control body size. We're interested in genes to control tail position. And we're interested in genes to control skull shape.

We're interested in genes to control the line of the back, from the slope all the way to the arch. And we're interested in genes controlling fur. That is the length of the fur and the curl of the fur and just the pattern in which the fur grows.

So again dog breeds, the take home message here being that dog breeds offer just an amazing array of variation that we can study with the appropriate tools to try and gain an understanding of the underlying genetics of mammalian variation as a whole.

Now the next slide, and on my computer some big pop up box is sitting in the middle of the slide. So I don't know if everyone else can see.

But the next slide shows you a dog's skeleton with 27 standard measurements. And every DNA sample that we collect, we also collect the set of 27 standard measurements.

And if you want to look up a recent paper that Nate Sutter again took the lead on and published in Mammalian Genome, you can see some work we've done in characterizing dog breeds and how well they fit the breed standard using the standard set of 27 measurements.

And which ones are really critical? Which are the things that the breeders are really selecting on in order to meet the breed standard? But that's a growing and very large data set that the lab has been focused on.

Now in order for these experiments to be successful, we're using the approach of a whole genome scan. So we start with an evenly spaced set of markers that cover all the chromosomes.

And we generally have a set of dogs that we consider cases and controls. We can either try and collect families and look for segregation of alleles associated with, in this particular slide, a disease.

Or we can look for differences in alleles in the population of cases versus the population of controls.

And in either case what we're doing is we're starting at the top of chromosome 1 and then we're combing through the genome looking for places where we see statistically different results between individuals who have a phenotype versus those who don't, or who have a different phenotype.

Key to our success has been the availability of the canine snip chip. This is developed by Affymetrix and it's been widely available now for a couple of years.

It has 127,000 single nucleotide polymorphisms on it. Of which that data set distills down to about 50,000 usable snips once we've put through a set of quality control measures.

And the hard work in developing the snip chip was done by (Shoston Blato) and her colleagues at the (Broad). So a very useful resource for all of us in the field.

And this just gives you a visual to think about, a set of cases, a set of controls, looking for statistically significant differences between those.

And then those are the places that we hone in on and start thinking about candidate genes and start thinking about particular patterns of alleles that we see in cases versus we see in controls.

Now having given you all that information, I'm going to change gears a little bit in the next few minutes here.

And I want to talk about a completely different kind of phenotype. We've been thinking about the phenotype of size. And we've been thinking about morphology.

But one of the things people always ask me about when I tell them I'm interested in dogs is well, you know, what about behavior? Can you map the genes for hurting? Can you map the genes for hunting? Can you map the genes for pointing?

And what about just the things that some breeds are good at and other breeds are not? Are there ways to access the underlying genetics of those?

And this is actually a very simple story lead by (Dana Mosure), who was then (SAMPA)'s manager in the lab. And she's now a vet student at Penn.

And she came to me a couple of years ago and she was very interested in a phenotype and Whippets. Now shown on the upper right is a normal Whippet.

And this is a dog that appears very similar to Greyhounds. But she began receiving a set of calls reporting a phenotype of extreme neck and chest musculature.

And these were dogs that the breeders and owners were referring to as the Bully Whippet. And a typical Bully Whippet is shown for you on the lower right.

You can see that that looks quite a bit different then the typical Whippet shown standing on the grass up above.

So (Dana) asked me if she could work on trying to identify the gene that was important in this. And I have to admit, originally I wasn't really enthusiastic because I was pretty focused on skeletal issues.

But she convinced me that this was really an interesting problem. And she really took this on fairly single-handedly.

So she realized very quickly that Bully Whippets look quantitatively similar to other species that show a phenotype of so-called double muscling.

And a good example is the Belgian Blue cattle, which is shown in the right of this slide, described by (Michelle Georgis) and his colleagues.

And they have the same phenotype of over or double muscling. And it's caused by mutations on the myostatin gene.

So she sequenced the myostatin gene in a number of cases and a number of controls, as well as dogs that had to be carriers.

And she then quickly identified the mutation. It was a two-based pair deletion that removed about 20% of the protein, as well as destroying a very critical (unintelligible).

Now she was interested in finding out how often this mutation occurred in the -with the population. So she sampled another 146 dogs from both confirmation or dog hill events, as well as dogs who had racing history.

And when she genotyped them she found a couple more Bully Whippets as indicated by the MH MH. And she also found a large number of wild type dogs, as indicated by the plus plus.

But to our surprise she found that about 20 dogs were heterozygotes. So about 9% of the samples that she looked at. And what was interesting wasn't so much that number, it was the fact that the majority of the dogs that were heterozygotes seemed to be coming from the racing population, rather then the conformation group.

So we asked ourselves how these dogs really differed. And you're looking now at a slide where we looked at three different phenotypes. We looked at mass to height at the withers.

We looked at neck girth, and we looked at C, chest girth. And we looked at females and we looked at males. And we looked at for female dogs who had all three genotypes.

For males we looked at the wild types and the heterozygotes. And we wanted to see if the morphologic features really differed between the dogs who had the different genotypes.

And we used a fairly rigorous statistical test and we showed that indeed, they did. The heterozygote dogs really were different then both the wild type dogs as well as the bully dogs.

They were closer with regard to all three phenotypes or all three measurements to the wild type dogs. But they did differ significantly.

And so that really begged the question for us, could that increase in musculature actually be contributing to the racing phenotype for which these dogs are so well known?

So Whippets race both the straight and oval track. And it's an all out sprint. The distance is pretty short, 200 to 400 yards. Whippets are grouped into heats based on how they've done in their last several performances.

So A racers are the fastest, then B, then C, and then D are the slowest. And (Dana) was able to obtain racing grade for about 85 of the Whippets in our data set.

So we asked ourselves of those dogs for which we could obtain racing grade information, where was the mutation? And the answer came through loud and clear.

It was in the A racers. And that was true if we looked at A racers compared to B, C, D using (Fisher)'s exact test, or if we grouped them A, B versus C, D.

And if you look at the data, the mutation really seems to be in the A racers, a little bit in the B. And we're seeing almost nothing in the C and the D.

And when we did a Kendall's non-parametric test. Again we saw very statistically significant results.

So we got pretty excited and working with Carlos Bustamante on the statistical analysis we wrote the whole paper up. And we're just about ready to submit it when we all simultaneously had the same thought.

And that is what if this mutation actually wasn't responsible for improved racing performance? What if it was just something that was being carried along in the A racers because of population substructure effects?

So this is a really, really important point. If you're a dog breeder and you're breeding, and you're interested in racing speed. And you have A racers. And you want to produce more fast dogs. Well then you're going to breed dog who are A racers to A racers in the hope that you get more A racers.

And so it could be that the mutation was just being carried along because we had now a very close-knit sub-subpopulation within the breed. But it didn't actually have anything to do with racing speed.

So to address that Carlos did a principal components analysis. We generated microsatellite barker data for all the dogs in our data set. And this was data that spanned the entire genome.

So we don't want to just look at the region around the critical mutations. We want to look all the way across the genome.

And then we did a PCA analysis. And in the slide you're looking at the A racers are red. The B racers are green. The C are the blue. And then D are the slowest, those are the yellow.

So right away you can see that the A racers separate pretty nicely from the rest. But the question is where's the mutation? And that's indicated on this slide by the individuals who have the circle.

And certainly those are largely A racers. But what's really, really interesting is if you focus not just on those A red racers to the left, but if you look let's say at 12 o'clock on the slide.

You see a genetic space that's occupied largely by B or green racing dogs. So B race class dogs. But you see in that same genetic space one dog who is carrying the mutation and who's an A racer.

So it's as though this dog is in a genetic space that's occupied largely by B racers. But in the presence of the mutation becomes elevated to an A racer.

And that's even more evident in the middle and lower portion of the slide, which is occupied largely by dogs who are B or C class racers. But everywhere you see an individual who has the mutation, they've been elevated then to A class racing.

Again, as though the mutation takes dogs who were mediocre racers and it gives them a bit of an edge, making them a little bit faster, a little bit more muscle and then they perform that much better.

Now I don't want to be misleading and say that this single mutation takes individuals or dogs who have been sitting on the couch with you watching TV for the last three years eating nachos, and turns them into lean, mean racing machines.

It doesn't do that at all. But it's probably one of a class of what we now know are at least 100 different genes that do contribute to performance.

So when we published this paper, which was featured in (Plus Genetics), it got a huge, huge amount of publicity. It was featured in lots and lots of news media articles.

It actually got a full page in the National Inquirer. And people were interested inherently in this issue of performance. And the questions come up are similar mutations found in other competitive, high performing groups?

How important are they in humans? How important are they in horses? And while we know they exit in humans, we think it's quite rare to find a homozygote.

We only know one medical report of an individual who's a homozygote. But how important is the heterozygote state? We really don't know.

What this did is it opened up a dialogue, actually a really comfortable dialogue that we could have about sort of our genetic mandate.

So what sorts of genes or mutations or genetic variation are all of us born with? And how does that affect our capacity to do anything? To perform in athletics, to perform a particular trade, to perform intellectually, really to do any of the things that we go about doing in our daily life?

And what will we do with that information if and when we ultimately have access to it? So a lot of dialogues came from that. But because we had the dialogue and the context of dog genetics, it took something that's kind of uncomfortable for us to talk about and think about ourselves as humans.

And it gave us a really comfortable forum to think about it. And to this day that dialogue really continues.

So I'm going to go ahead and stop now. What I've tried to do is just give you lots of things to think about in terms of canine genetics.

I know we always think about finding genes that are important in human disease by studying canine disease. But I kind of wanted to stretch you and help you think about some of the other things.

In terms of specifics, we now know that there's a specific haplotype, it's a very small region that underwent a very strong selective sweep.

And now we know much more then just 14 small breeds. And that it's a very small region of the IGF 1 protein that's contributing to body size across dog breeds.

Variation in the myostatin gene is clearly important in racing performance. What else that increased musculature is important in? And how important it is in species outside of dogs?

We really have a lot to learn. One of the things to take away from this is that mapping genes that contribute to complex morphologic traits is absolutely feasible in dogs.

And I gave you a whole range of things to think about. Everything from body size to tail position to coat color to coat texture to leg length.

Particularly if those are traits which are fixed within the breed, if they're part of the breed standard or the things that dogs who do well or define the breed are really expected to have.

And so we and other labs are now in the process of really plucking off those genes as quickly as we can. And we're building really a vocabulary that's helping us understand mammalian genetics and mammalian development as a whole.

So I'll go ahead and stop there and the powers that be on the Web can go ahead and open this up for questions.

Vance Bonham: So thank you Dr. Ostrander. It was an excellent talk. We will now open the lines for questions from all of you. Please dial star 1 to reach the operator and enter the queue for questions.

Coordinator: It will just be one moment for any questions to queue in. And again ladies and gentlemen that's star 1 on your touchtone phone if you'd like to ask a question.

Vence Bonham: While people are thinking about questions, Elaine I would like to ask you a question.

Elaine Ostrander: Sure.

Vence Bonham: So what do you see as some of the major advances in canine genetics that we can expect in the coming years as we look forward?

Elaine Ostrander: Well we didn't talk about disease today, but certainly that's an enormous area of interest. So dogs get essentially all the diseases that humans do.

And the clinical presentation of those diseases is much more similar between dogs and humans then for instance between mice or rats and humans.

And particularly in terms of genetic disease, whether it be retinas stigmatosa or forms of epilepsy or forms of motor neuron disease, heart disease, arthro - arthritis or, you know, really all the thing that we think about.

And cancer is certainly a huge one obviously. All the things we think about as being important in human health are important in canine health as well.

And veterinarians and dog breed clubs have been really awesome about collecting data and DNA samples that they've now made available to researchers. To try and find the genes that are responsible for cancer, for epilepsy, for deafness, for blindness, for all the things that we care about in our own health and biology.

And I think we're going to see just an absolute explosion of that health information coming out. As a matter of fact I know it's coming over the horizon quickly.

I think the other thing we're going to see is a growing understanding of genetic variation as a whole.

You know, we just don't have an enormous range of variation in other model organism species, like the mouse or the fly or the worm.

And so we really don't have access to a very deep vocabulary of genetic variation if we restrict ourselves to limited model organisms because different breeds of dogs display so much variation.

And because that variation breeds through - breeds true through multiple generations in the pedigrees for, you know, decades and decades and decades.

We have just an amazing opportunity to understand the genetics of head shape, genetics of body sizes, genetics of leg length.

And all those genes play some role in growth regulation. And in doing so they really become part of the vocabulary that we think about for any disease associated with growth gone awry.

And whether that's cancer or whether that's any of the number of other diseases, I think we're going to gain this enormous vocabulary that we haven't had access to before because we've been able to unlock so much the mystery of growth regulation by looking at cross dog breeds.

Vence Bonham: Thank you.

Elaine Ostrander: Any other questions?

Coordinator: And at this time I'm showing no questions that have queued in.

Elaine Ostrander: Okay, thank you very much.

Vence Bonham: Okay.

Elaine Ostrander: All right.

Vence Bonham: All right. So at this time we want to thank everyone who's participated in this Webinar. And we've - and are looking forward to the next Webinar which will be in two months on March 12 at 1 pm.

The Webinar will feature Dr. Eric Green, who is the Scientific Director for the National Human Genome Research Institute.

You will receive more information from Sarah Harding as the time draws closer. Again, thank you for your participation today.

END