Functional Genomics
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Lecture No 15
Comparative Genomics: Genomic Insight into Evolution

Thank you for being with me again in the fourth week of this NPTEL course functional genomics. In the last three weeks we have been looking at how technologies have changed, how we have understood the genome, how we have understood the transcriptome, the expression profile and how we can engineer the genome and so on. So in the last this lecture and few more lecture that we are going to look at is to you know sort of go back and look at how evolution has to how the genome has changed over millions of years as we evolved from simpler microbes to multicellular organisms that are invertebrates and two vertebrates like through fish, frogs and mammals.

How our genome has evolved and how the complexity has come in and how you the information that we can go back and look at the genome of diverse organisms can help us to understand the neatness of certain species including humans and that would contribute in our understanding of disease or to making better animals that are domesticated to identify even the evolutionary time points at which genome has changed so we are going to look into some of these issues that field is called as comparative genomics wherein we are going to compare the genome of various species and then try to infer as to what possibly could have changed and how that change has really result in the species which is very successful in its own and environment.

So these are the issues that we are going to look at it. So let us first look into the difference between the genomics that we have looked at as compared to what you call now as a comparative genomics.

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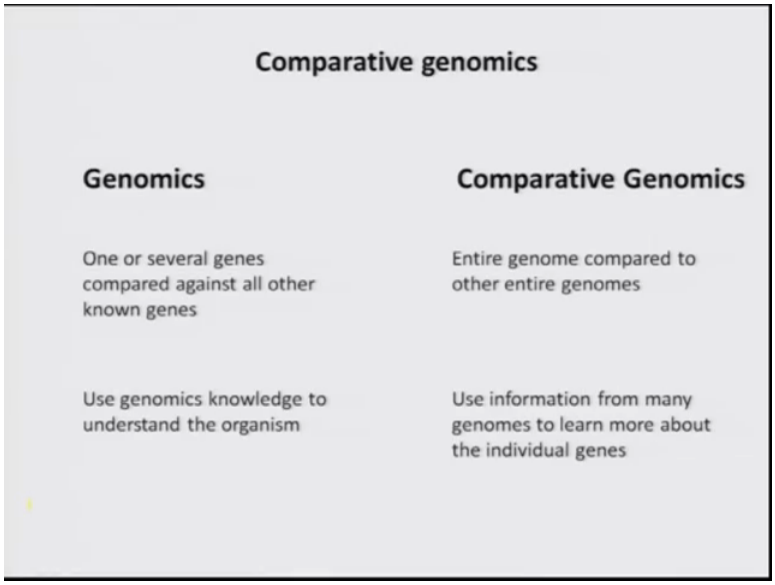

In genomics normally what you look at is that you are looking at one gene its function at the various stage or several genes of a given species and compared against all other known genes you know try to understand how the gene has evolved and so on. And comparative genomics what normally is done is that the entire genome of a given species is compared with the entire of the large number of species wherever you have the genome sequence that would give you an idea as to how the genome per say has evolved. In genomics you use genomic knowledge to understand the organism so how successful the organism is and how that gene contribute to that fitness so here in comparative genomics normally you try to use the information from many genome to learn more about the individual genes.

How a given gene has changed over time therefore the function of the gene is altered in different species and give example is some of the venom you know the toxin that is produced by many of the reptiles and other species are nothing but very similar kind of protein that your you know your skin makes, your intestine makes but here this particular protein is there to kill the microbe that enters your digest system or that you know try to grow in your skin but you know this is specialized in certain species there is become a venom which is able to kill even much larger organisms including human.

If you look into for example snakes that they have venom that could be neurotoxic and so on. So it is a same set of gene depending on the species there were some alteration that led to a

specialised function so that is that these are the information that you are able to get by looking into the comparative genome aspects.

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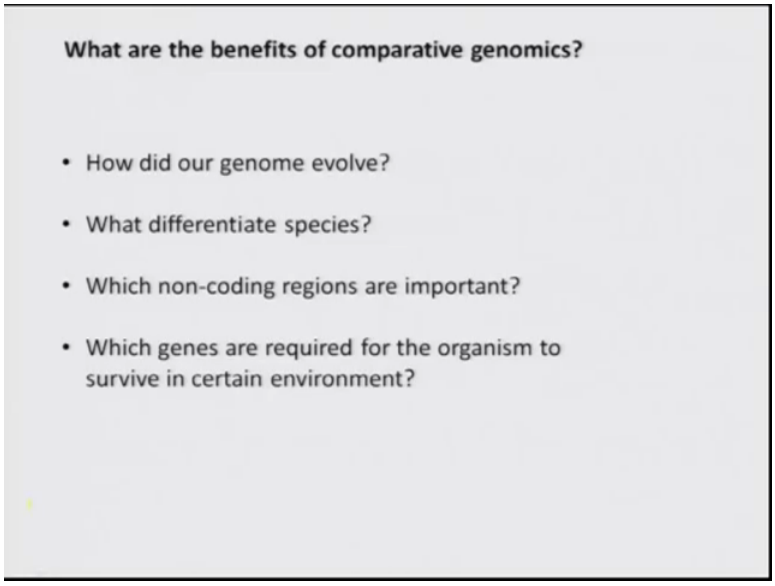

So what are the benefits lets first look into some of the well-known established benefits of these fields or emerging fields called comparative genomics that would give you an idea as to how powerful the tool is in sort of comparing the genome. What kind of information otherwise you would not have gotten by looking at simply a genome of a given individual or given species so this would help us to tell as how did our genome evolved. So we talk about human homosapiens they are very different from for example primates, the apes.

We believe that we evolved from a common ancestor for us and the apes but why we become so successful as a species that we are able to rule this planet whereas the primates still remains primates right and we will give one example as to how a change in the genome a particular sequence probably altered the way this you know your skull can hold much larger brain that probably helped in evolution of the human or homosapiens.

And like ways the language for example you are able to speak right, the ability to speak is because of the way you are wise box is organised the way the muscle is there so you can imitate a crow you can imitate for example many of the birds and animals we can produce sound we can use language to communicate. This again is because of some changes that happen in the genome

which led to the formation of certain different kinds of proteins which helped to make these sounds and then off course the ability to you know develop a language process it analyse and you know and develop.

So that it you know you know it two way process one you have a better cognitive abilities two you are able to produce sounds. These are the two things. What differentiates species we here talk about species the species is you know we always say that species X and species Y you know common ancestor so that means they both of them evolved from a common ancestor with time they become two different species.

So what how really that change has happen that really help us to understand and which non coding region is important say more often when you have discussed in the previous lectures. We are talking about you know the great majority of our genome are transcribed but not coding any protein but the transcript what you call as noncoding transcript have very very critical functions.

There is one and still we do not know what other functions and two, and two there are regions within the genome which represents control (())(06:31) for example there are some proteins come and bind to either to activate a given gene or inactivate a gene or to modify the chromate in the way it should function. So these are the elements that are hidden it would be very difficult to you to understand where is element and what is a function. One way to look at is to come compare the genome and if there are regions that are very critical for function they will not change much therefore looking at region that are not so diverse that are conserved across species will help you to understand regulatory elements we will give we will have some examples for that.

And which genes are required for the organism to survive in certain environment. You know this is another important aspects for example we we have you now of course the human population spread across the different continents some of them are living in very high altitudes and some of them living close to the sea shore some are in tropical region, some are in desert but still it is not as harsh because we are able to change our environment right so when it is cold you are able to you know put on some pull over and keep you warm or make little huts and protect you from the environment and so on but the animals are not like that they live in the wild and still some of them are extremely successful.

For example there fish that live in the deep ocean where there is no light but there is tremendous pressure from the top so the bodies are adjusted such a way and they are able to produce lives like ways there are species that live in desert and in condition that are hypoxia things like that we will discuss some of those issues as to un-models animal which really can help us. There are animals that that do not get cancer no matter what kind of mutation try to produce they never get cancer.

So the genome has the ability to withstand any such damage and and produce you know get rid of the cells that can produce cancer and they do not age. I will give an example of one such animal you know there is absolutely no ageing process they live beautifully as young and they have all the resistance that you talk about. They can live in extreme conditions. If we can understand what are the genes that really helped them to survive possibly it can we can learn from them so these are some of the examples. We will go more detail as to some other aspects that is some outcomes of comparative genomics.

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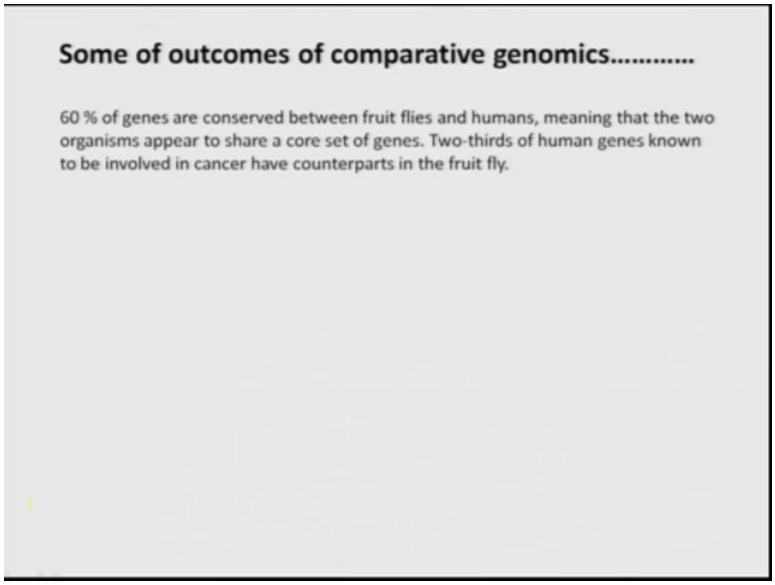

I am going to give some 5-6 examples before we get into the way we study comparative genomics so what we say is 60 percent of the genes are conserved between Drosophila and humans. This essentially means that the two organisms appear to share a core set of genes, now if that is the case we can say that two thirds of the human genes known to be involved in cancer have counter parts in the food flag. What does it mean?

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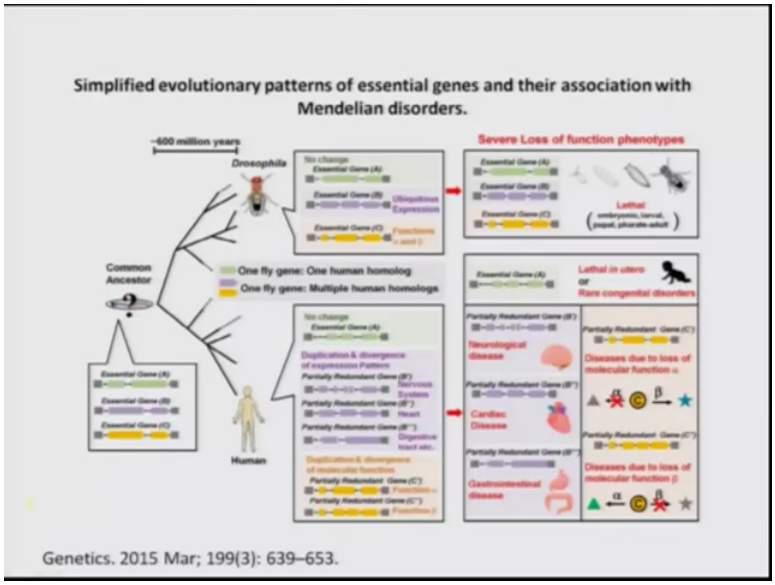

So you can use the you know Drosophila as a model to understand how genes that are conserved between human and fly or involved in the process of you know the tumorigenesis right. There are some you know I am giving you some example how people have used it. Its separated by 600 million years that is the evolution we are talking about fly and the human but still there are large number of genes where you know you could really look at several phenotype. If you lose a particular gene what is the kind of phenotype that you see in fly, what is the you know phenotype that you see in the human there are many that show extremely high conservation that is what shown here.

Now we can we can see here for example wherever you have this green colour arrow bars that represent you know one gene in fly and one human homologue and then what happens to such conditions. So there are genes that what you call as essential genes if you delete the gene then the fly do not develop and same thing happens in case of humans. The still birth or the embryo do not survive and there are problems what is called as a rare congenital problem there are developmental anomalies. There are number of examples and there are examples wherein you have one gene in in Drosophila but there are more than one gene very similar genes in the humans.

Probably it evolved what is called as a duplication process this because you know they the genome has undergone lot of changes we will discuss some of those issues, in this process the

gene number would have increased made multiple copies and each one you know slightly differentiated from the other but they have over lapping functions but if you have three such copies of all three are imitated you may have a cancer. So that is one of the common example and and so on.

So there are number of genes that shows that kind of a similarity which really helps us to understand how the genome functions in the larger context and you can see it even in the case of not necessary only in development but you can see for example there are neurological disorders, there are cardiac disease there are gastointeritis disease and then you can see that all these happening even in case of fly. You can compare the genome functions very similarly.

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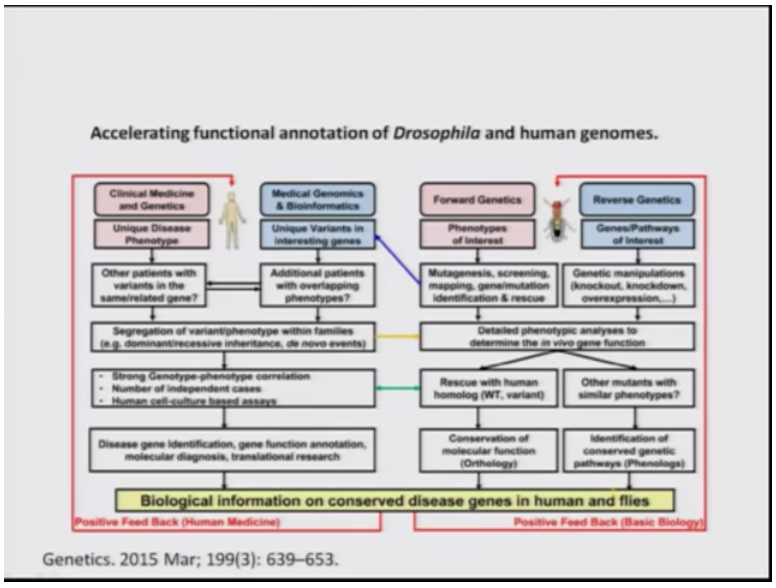

So this is one of the ways by which people are trying to use the information that we have obtained from the fly to understand the human genome and its functions in normal development and in pathologies, so what you this something that already informed you that you have the process of what is called as reverse genetics and forward genetics. Reverse genetics is that you take a gene delete it or mutate it and see what happens from the phenotypes. And then you have a large number of you know papers and observations with regard to how deleting a gene in fly results in a phenotype or changes in the cellular mechanisms.

Now whatever you have gained from this kind of study you can apply this knowledge to the human because you cannot do that kind of studies you see in the human population. So you have to infer from what would happen by one way or the other in mutations in a families but this information that you gained from fly can be applied to the human and you pretty much sort of figure it out what could possibly the functions of this gene in humans.

And if for example in a fly if you delete a given gene or over express a given gene in a tissue if it develops tumor, now you can ask a question if similar tumors in the human you know does it have role for the homologuous gene in the human so you can go and straight away look into whether that particular gene number is gone up, copy number is increased or is mutated and so on, that is one important contribution.

The other one that I something I have discussed in one of the previous class is to model the fly depending on the genetic changes that happened in a tumorous condition, or a cancerous condition of the patient. So you have a patient as we explain that every cancer patient is unique in terms of whatever genes that are modified resulting in the cancer, so you need to have a drug which is could be more appropriate for that individual.

So we can model that in the fly, you can create all these similar changes in the fly and then it will develop the tumor and then you can quickly screen for the drug in a matter of 40 days 50 days. They should be able to see whether which drug works. You know very good and then go on use the same drug because that gives you the speed which you can create such models, test the drug and come back and try patients because you do not want to really waste time in patient by giving one drug and other because it is going to be a normally the chemotherapy and it takes long time and before you understand that this particular combination of drug works or does not work and you lose time because the patient the tumor grows and the chemotherapy itself is very very toxic to the patients and so on. So fly really helps so that is where the power of you know the the in such kind of comparative genomics helps us.

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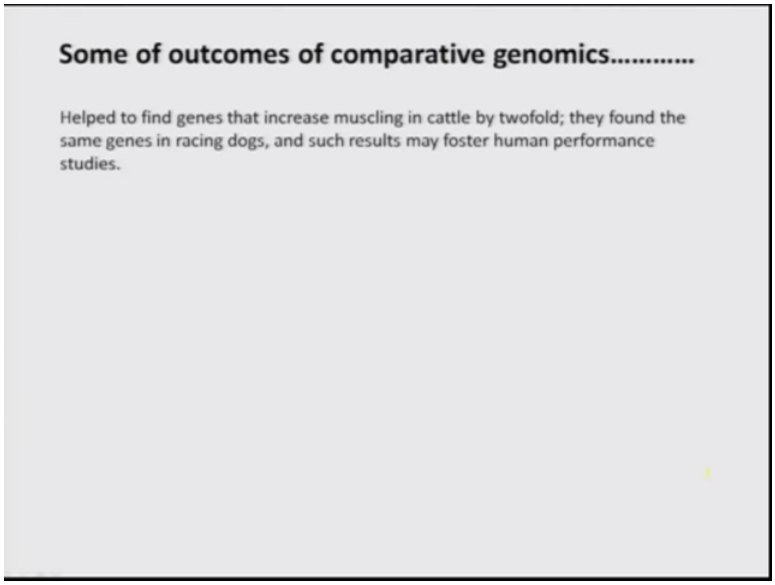

Other example is that you know this approach is helped to find genes that increase muscling in cattle by two fold its very interesting phenomenon then because there are variants in the genome which increases the muscle mass ok and what is interesting is this is not such kind of a variation resulting in the increased muscle mass is not you know restricted to the cattle that is what first they were identified. But you can see it in human you can see it in dog and many other animals that could have you know help in understanding the pathophysiology also to make our domesticated animals much more efficient right.

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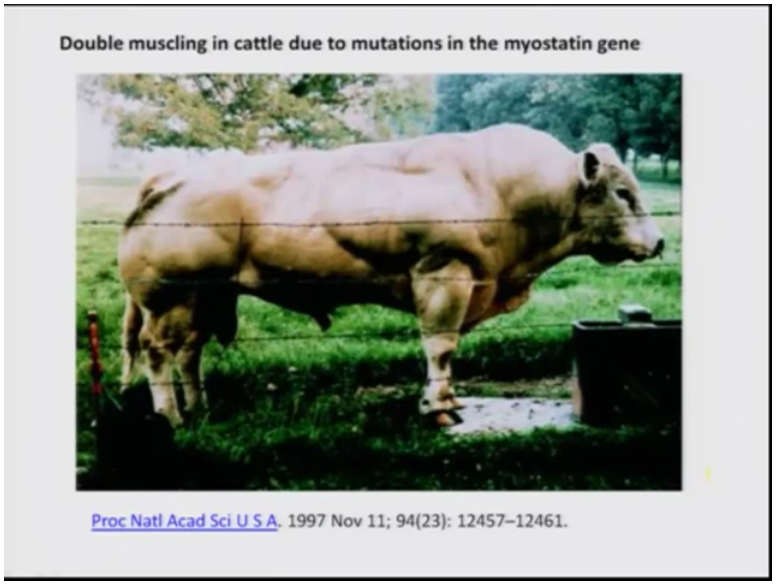

There is one example I am going to talk about is that you can see this you know this cattle is really muscular and it is because of a gene myostatin gene is mutated. What happens is this gene or its protein is sort of regulates the negatively regulates the muscle growth and if the gene is mutated then what happens it does not restrict the muscle growth as a result the animal becomes extremely muscular. So they have of course because of the muscle they have more power which could possibly help us but that is how you know it was identified to begin with.

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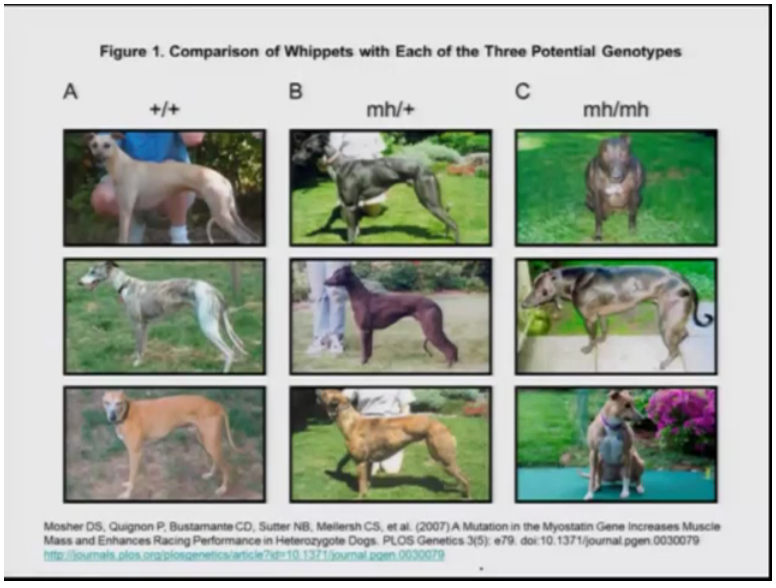

But it is not restricted to the cattle now we have a large number of breeds of dogs also have similar gene mutation what is shown on the left side is three different strains of dog and these are all wild type as show here. So you have the same what you call as myostatin gene one of the allele is mutated what is called as heterozygous or both alleles are mutated homozygous and you can see that.

The same animal if both copies are deleted and you will find that dog which is extremely muscular right and it is true for this species this is true for this species you so there are dogs are used in different capacity either you know for example in western world they used it for in the farm land to you know take care of the territory to help in gathering the grazing animals and there are many applications.

In snow field they use it for pulling the sledge and things like that, if there are dogs that are extremely powerful it is going to help so there are dogs that can run faster because of the muscle mass. So that you know you can you can develop breeds and you know this is not unusual because whatever you see the different breeds of dogs, dogs that have long fur, dogs that have long ears, dogs that are lengthy but not tall all these are nothing but changes in the genome that results to the phenotype.

So it is very common in dog breeding to identify a phenotype that is very different from the wild type to selectively breed them and therefore it gives you phenotype which can be used that animal can be used as a pet or in you know different context be it in the farm land or for the pulleys and so on, so that really helps right.

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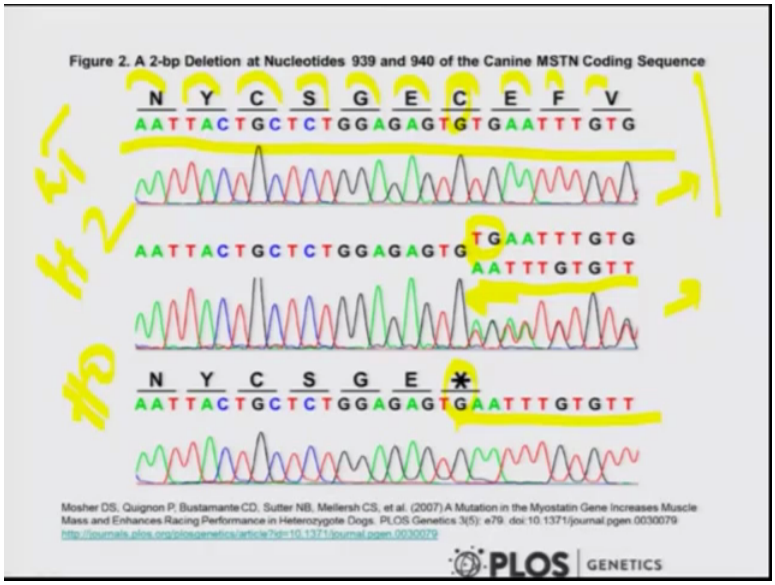

And what really happens to the gene this is what it is this particular dog sequence that you can see here this is just to give you a glimpse of how the automated DNA sequence electropherogram looks like this is what you see here is a the readouts of a automated DNA sequence and these are the bases that are called and these are the triplets codon in a coding further amino acid right, these are wild wild type what you are seeing is a wild type.

You can see this is a wild type. This is heterozygous this is homozygous right and you can see that in heterozygous condition from here you find there are you know two alleles coming up so one that is having identical to what you see it the wild type that is TGAATT and so on. But whereas here you know the lower one represents a deletion actually this T and G base is deleted as a result you know there is a frame shift and you have AATT that should have started here as coming, so here is heterozygous and obviously there is homozygous both alleles carry this mutation.

As a result there is a shift in the reading frame and you have a stop codon instead of you know the amino acid system right, which clearly tells you how you know by looking at several species and and comparing the genome we can identify a gene that gives you the phenotype right.

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So this again is not restricted to the dog or cattle this also the same mutation. The first seminal paper I am showing after that there are many other papers there are rare conditions even in the human wherein you know you have such condition. Same myostatin mutation loss of function mutation results in gross muscle hypertrophy, this is excessive growth of the muscle in a child you can see that there is a neonate meaning new born baby and this is seven month old you now baby but you know you can look at the muscle mass they are extremely you know grown up kind you know look that is what it is and it runs in the family you can see that it is an dominant disorder that from father it goes on and so on.

And and of course these are you know conditions which really make an individual powerful so that is what there is a even editorial commentary in the journal which talks about what is called about as a powerful genes right. So here it is completely loss of function but it possible that in some of us there could be variation that altered to some extent the protein functions it is not as sufficient as it is there in other person therefore you could have really you know gained lot more muscle mass than you know normal person that could be an advantage for me. Depending on what kind of you know profession I have it could help and if it is selected if there is no other heal affect then probably it would help so this is you know example of that.

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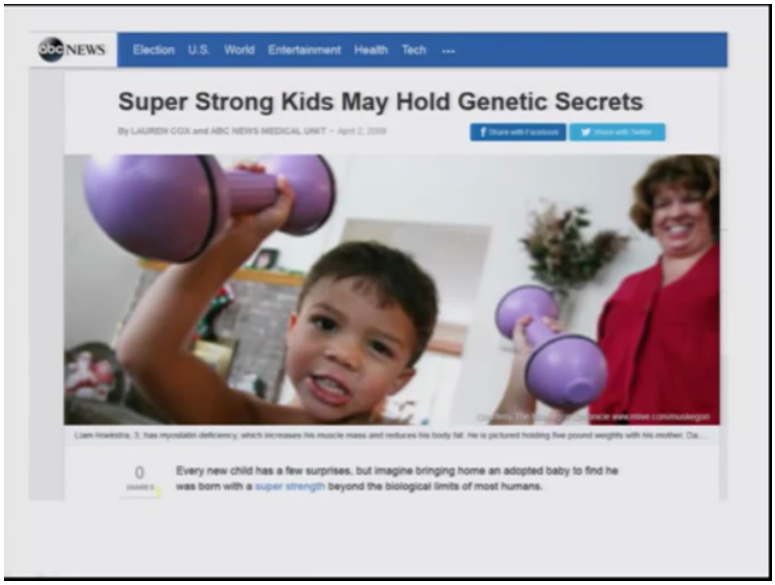

And there are you know if you can look into the you can Google search you will find many such babies one of them I am just showing super strong kids may hold genetic secret and this kid who just three years old he is deficient for the myostatin deficiency but he can really he has a increased muscle mass therefore he shows lot more you know he is more powerful than his peers that really you know makes it interesting for at least the kids that are around that guy.

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It has also important clinical significance for example you know what we know is that this protein myostatin you lose it then you put on large muscle mass right. So if if you know how this protein function itself alright and if you are able to identify certain molecules that can partially block the function of this protein myostatin or its path way where its working on then you can you know use that as intervention strategy to increase the muscle mass. So this is one paper which talks about such kind of applications at least using cell models. How possibly you know this can be achieved and this is engineering.

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Now I am going to go one more example and show it. So recent example happened just couple of months back in China. You remember we discussed a condition wherein you can crispr cas9 model wherein you can edit the genome remember like we said that the abused egg you know guide RNA with that you have this endonic layers which can go on cut and edit you know and then make whatever changes you want.

A group in China what they have done is normal breed of dog they have taken alright the cells embryonic stem cells, they edited the gene mytostatin in that embryonic stem cell such that now it has you know they have introduced the mutation and they made a cymera and they produced a dog which is like the hero now muscular dog you can create. So we can create you know for example a breed a given breed you know which is for example which is extremely good in detecting for example you know there are different breeds of dogs which have unique capacity.

For example smell you know you must have seen the police use the dog to sniff around and find is there any explosives right, they trained but it is not that any dog strain can be train further because there are certain phenotype that are selected and these breeds are very good with smell right and they can be trained and but if you if assume a dog strain is there it is able to sniff well but it cannot run right alright.

So therefore this dog can sniff somebody having an explosive that guy runs away with that explosive then the dog cannot chase on other hand you can make that particular dog to run faster by putting more muscle that you are able to create a new breed which has the desirable characteristics that is we are able to you know smell what you know exposing other at the same time you make them to run faster make it stronger, so that is an advantage. So these are some of the applications now people are trying to introduce in in a domesticated animals so it is possible could have some desirable affect so this is how the comparative genomics really helps.

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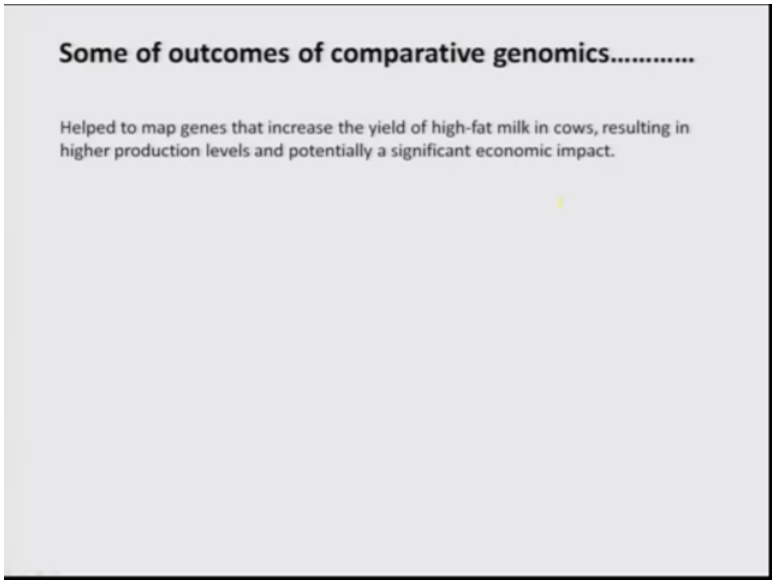

The other example you know such approach also helped us to map genes that increase the yield of high fat milk in cows you know it increases because milk you know is one of the essential commodities really all of us need and if we can produce cows that have high fat contain milk then possibly you can could be off great help. So it results in higher production level and potentially significant economic impact you know it is going to really help.

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So again people have used you know genomic approach people have sequenced different groups of sequence the genome of various cow species that produce the high either a high for example a volume of milk or a high fat content and if we can bring this together obviously it is going to be much desirable end result because you are going to have more milk with high fat content is really helpful and there are approaches people are used at identified for example the gene which which impact you know which help in the high yield right and and now now they have identified these genes. If you can likewise you know manipulate or engineer the genome probably you would be able to have you know cow breeds that could really produce large amount of large volume of milk.

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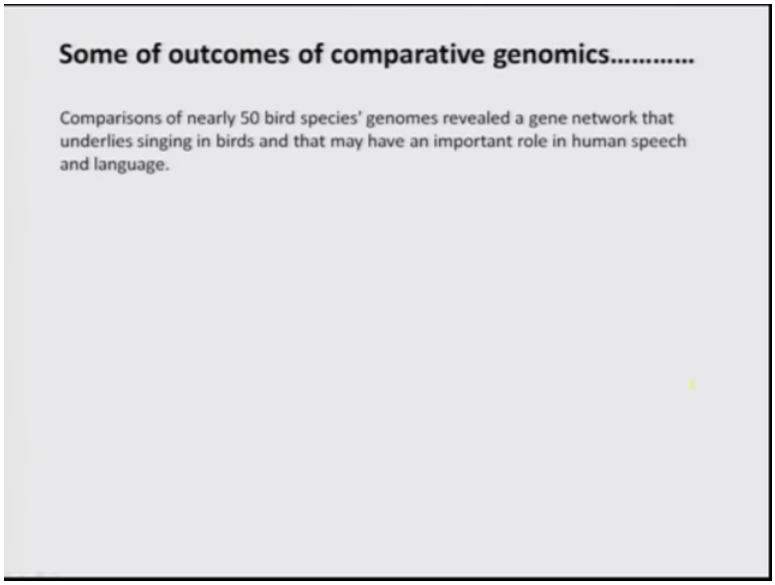

Another example is how even birds can help us to understand how we are able to speak right this is a landmark study again. Comparison of nearly 50 birds species genomes revealed a gene network that underlies singing in birds that may have an important role in human speech and language so the language is not limited to humans. All the species communicate they communicate in different ways we do not understand always. But one of the fascinating research field that had come from the birds is this birds sing right and this is the way they communicate.

They have variety of expressions that really tell whether they are happy they are predators. They communicate with other and it is so for most of the animals but bird is something which is unique in that because they have much more sophistication the way they communicate with each other and that is how they have you know try to understand as to how what are the genes that helped them you know make this kind of sounds which convey certain information and how the brain is able to process the information and store and to get the information out of it because it also as to be a memory because it is not one time event. So how does the brain is able to store receive this information store it and process and and then get the meaning out of it.

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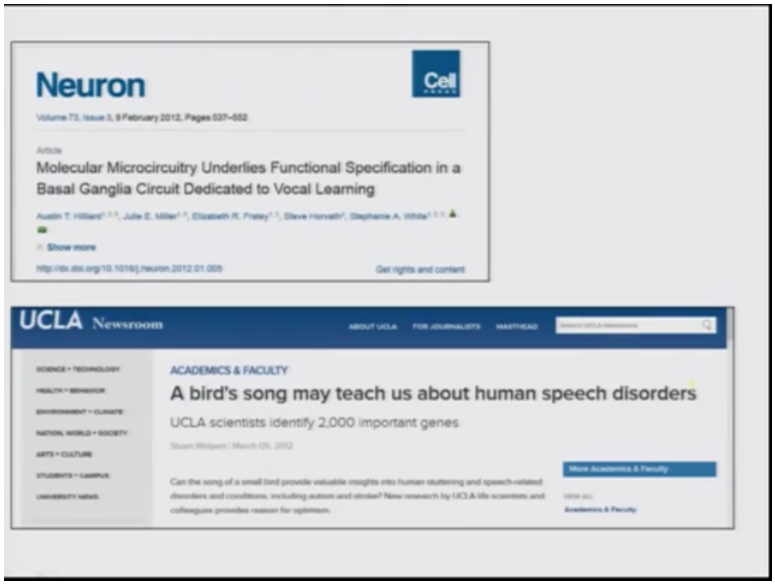

This paper came in neuron in year 2012 where they have really look into a large number of genes and the networks how different genes you know function together and that is what called as molecular microcircuitry and and that pretty much you know it helps you to understand how at the neuron level the information is processed and and stored right. So that is kind of you know learning ability and then once they these birds the young ones learn from their adults then they are able to practice it and give it to next generation and so on, so that is the way they communicate with each other.

And this is not only you know that whatever you understood you understood only birds but he processing is also the understanding how the brain process the information might help us even humans because there are kids who have inability meaning they have there are challenged to speak or to comprehend what people are saying so these are called as speech disorders. So either they are unable to put together words and communicate or they are unable to understand was has been told right, so this is because the way the brain is able to process information somewhere there is a problem right.

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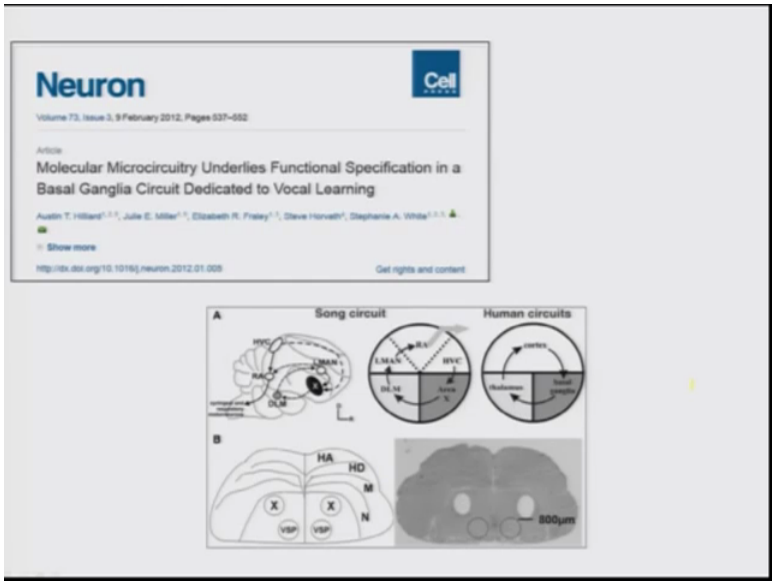

So what goes wrong in these kids is going to be very extremely difficult to understand but the birds might you know the study from the birds might help because what we know now is that the song circuits right. So what has been compared here is you know kind of human brain mammalian brain with the bird brain and so on and what you are seeing is the way the birds brain process this information seems to be very similar to how the human brain process information especially the language.

So if you can gain deeper understanding as to what other genes that are involved in this possibly can go back and look into human population wherein you have the speech disorder and then see whether the genes have any changes that possibly explain why you have this disadvantage so so we can see again how studies from one species can really help us to understand the other species including human.

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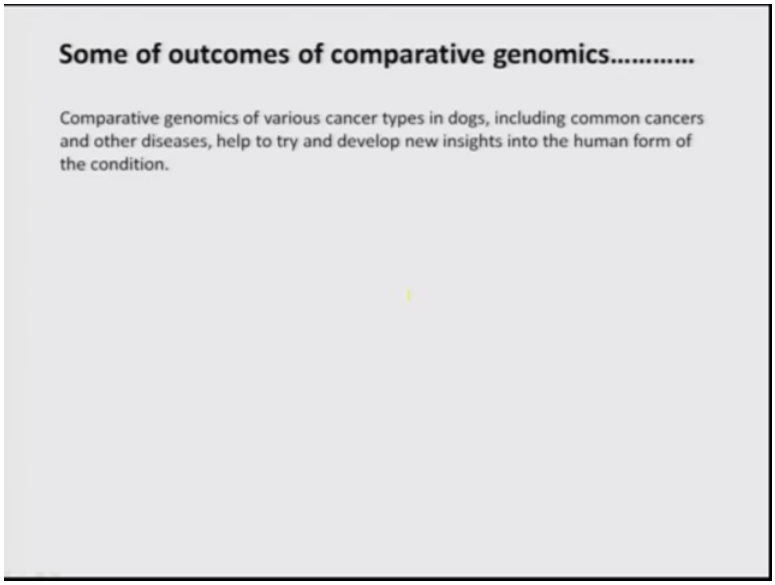

Again example of dog here that you know as I told you the huge number of breeds available of dogs. There are many dogs that also you know have cancers right whether they are more prone for cancer or they are very good model for cancer and spontaneously they develop cancer so thats you know they are being higher mammals. You can study them and that would help us to understand the genetics of cancer in human as well.

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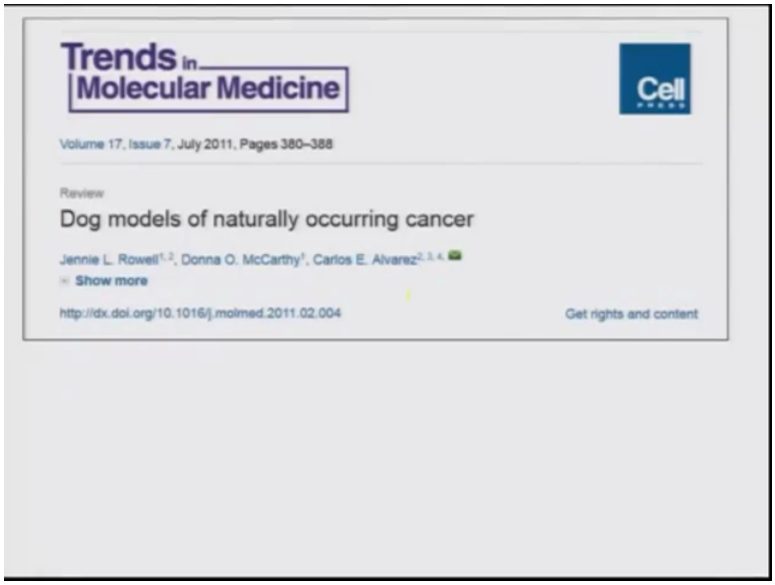

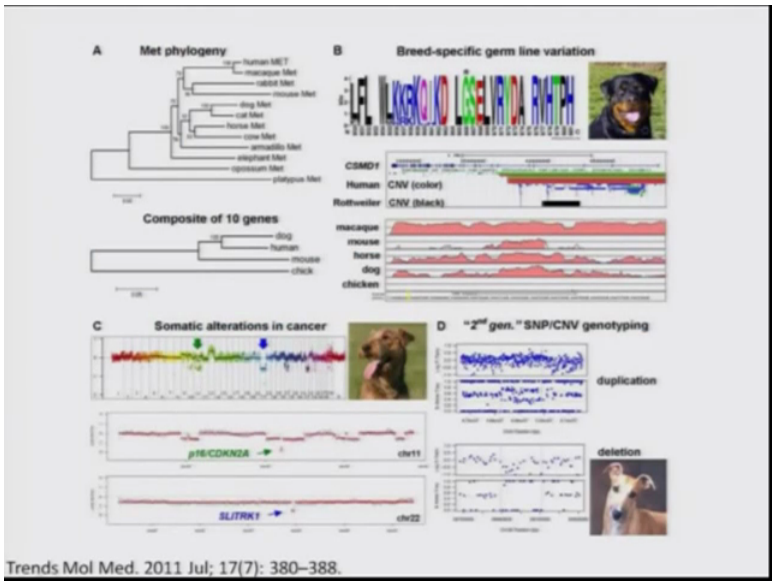

And there is again a paper which talks about how the dog models of naturally occurring cancer. These are not induced cancer these are naturally occurring you know dog models and how this study can help us to understand the genetic defects behind such cancer form and and one way is to look at you know for example the (())(30:42) you know it is one of the genes which you know when its activated then it leads to cancer we can study that you know for example in in dog or there are breeds specific germline variants you know there are variants that happen variation that happens the genome which makes the animal more at higher risk of developing cancer later you know certain breeds right then one can go back and look into what are the variations that are there in the dog genome that made it you know at a higher risk of developing cancer.

And then we can go and compare for example other species human and other you know animals that will help us to understand the genomic signature that can predispose to a given cancer and like what you see in human there are somatic alteration meaning only in certain cells of a given tissue you have changes in the DNA which results in cancer. So we can we can do that kind of a high throughput genomic analysis in cell that are present cancerous state and compare it with cell that are normal and try to understand what genomic alteration happen and you can in fact you can co-relate with humans as well it gives you insight as to which possible region in the human can have very similar effect if altered right. So there are huge numbers of advantage including for example genomic instability.

There are regions that are duplicated meaning two copies or there are regions that are deleted any of them copy number variation again is one of the major triggers for cancer and then there are dog models which really help us to understand that, so this is again a very very powerful model system to understand if you know the genome you can do.

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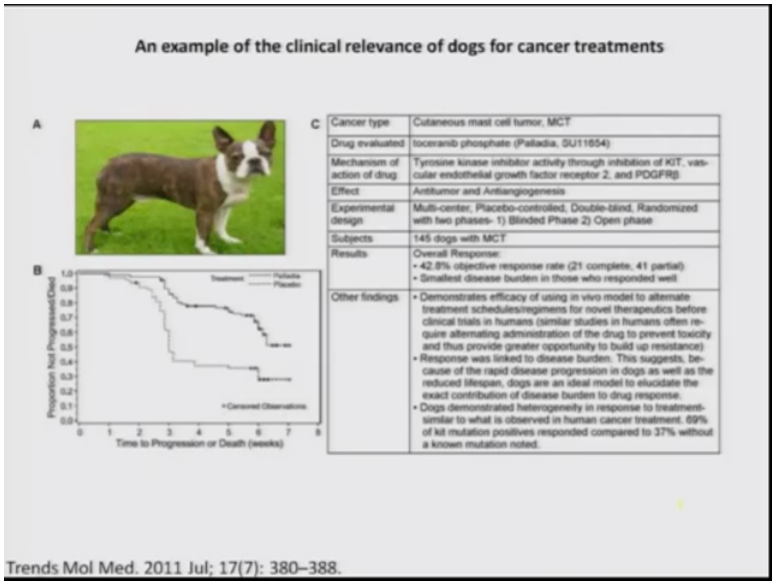

And there are also examples of what is called as clinical relevance of dog for cancer treatment because they spontaneously develop cancers. Now you can try out different chemicals teraputics to see how effective these chemicals are in controlling the cancers so you can see here this is one that is you know what is called as triggered with a given drug and what is shown here is the survival right then percent animal survived over the time and this line represent the one that is treated with vehicle meaning untreated and you can see that over the time you will find that in about 7 weeks you know almost 70 percent of the dogs have already that had cancer already you know died down whereas the one that is treated they are able to live longer which gives you very good model to even for drugs screening platform and so on.

So this is one another implication because you know what is the genomic change is happen in this particular cancer in this dog and you are trying to use a drug. So once you know that the drug is able to control the tumor growth in this model then you know this can be easily applied to human those who have got you know same kind of alteration so that really helps us to model cancer as well.

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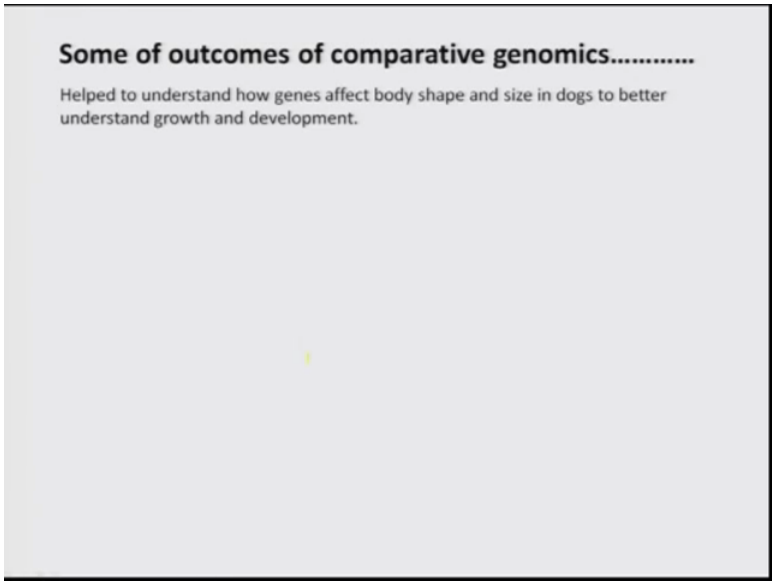

The other example is you can also you know understand how gene affect body shape, size again dogs are good example and how really it it affects to better understand growth and development you know you have to you can relate everything.

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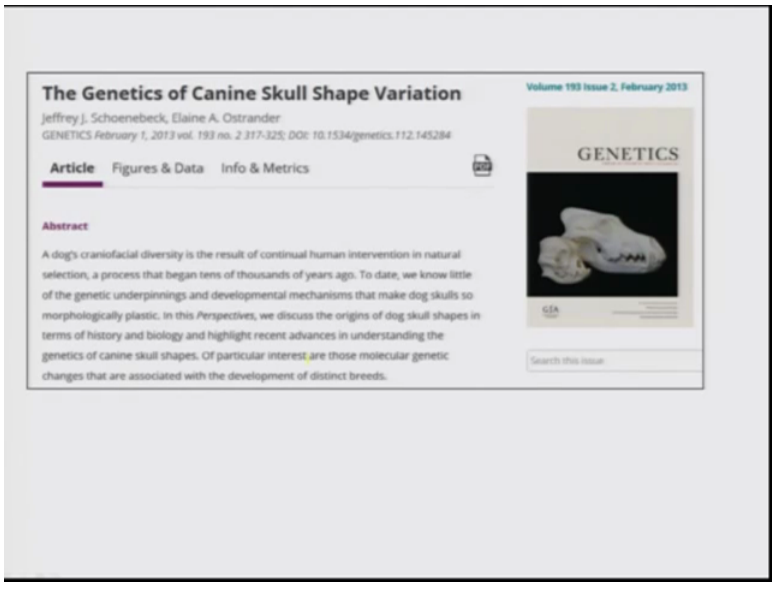

For example your skull size right it is very important, the face features and you know your ratio between the skull to the body and so on. There are many constraints because if that constraints are altered then it is going to have a problems even in birth because if if the baby skull size is

much larger than desired then there cannot be a normal birth because you know the baby has to come through the pelvic bone and there is a small window for the baby to come through so it is going to be a limitation.

So there are strict control over the genes and how they regulate the skull function and this is one example as to how there are different breeds of dogs which have got you know different shapes of skull again the each one can be linked to a particular gene signature.

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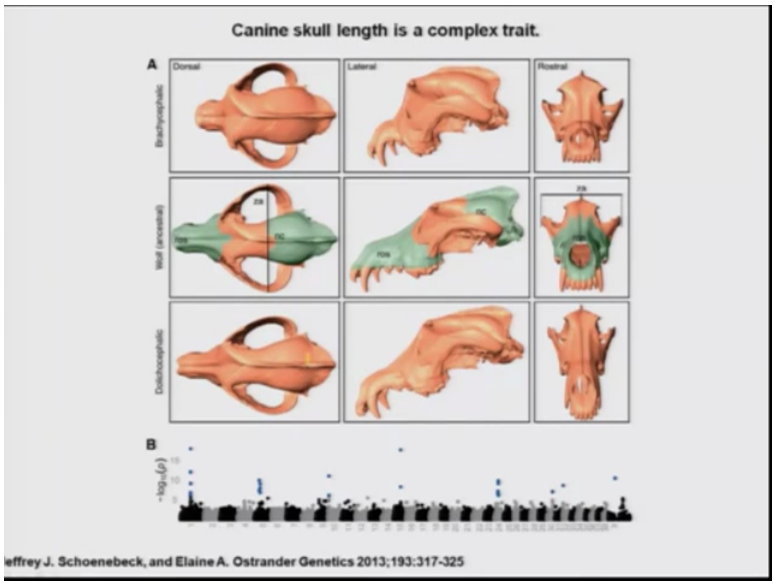

And that is what shown here there are you know you can look into and people have mapped it. These are regions for example chromosome1, chromosome5, chromosome9 and so on. There are different regions different chromosomes, people have mapped genes that regulate the skull size and skull length and in the complexity right which again is a very good way of understanding the gene and what are the set of the genes that are involved in the governing the body shape right.

Now what you do is you basically sequence a particular species of a dog and compare with the genome sequence of another dog these two have difference the way the skull structure is, then you look into what are genes that are different and try to understand their function and which would help us to map the gene for this particular phenotype right. So this is again a powerful tool which really really helped us.

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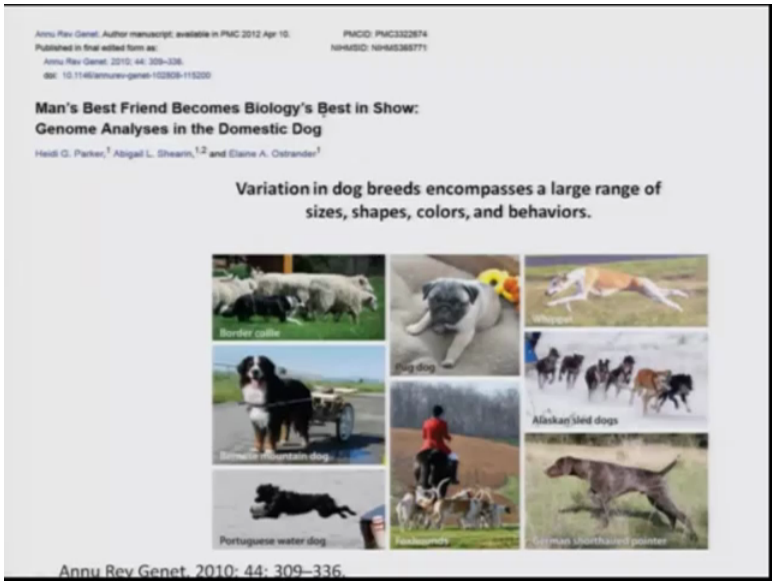

So the man's best friend becomes biology best in show meaning you know we can look at you know the dogs have been you know domesticated long time back and they have been living with the the man they call it as the best friend because they only is the help you know unlike other species like whether it is a pig or cow or cattle or a horse they have a specific function right mostly horse for transport. You have pig mostly for you know food like ways chicken and so on or cattle for either you know work hard or for the milk.

The dogs have variety of you know vitality for the humans right from being a good you know pet right to being a ferocious defender of your land or your house to in in in snow fields for example they can sledge for example they pull the cart and and and there are variety of you know help that the dog breed gives as a result for each one of the specific functions people have you know over the time they have selected breeds identified them. They breed and they have pure in-breads strains which have a different you know phenotype.

So this variation in the dog breed because of the selective breeding encompasses a large range of size, shapes, colour and behaviour, as I told you the behaviour you know sniffing around because they have been selected for this particular quality over and again by breeding selective breeding. So they have the extremely versatile way of you know identifying different smell you know you must have seen in movies you know where there is a victim whose dead and you want to see and there is a in the crime scene there is a cloth that are left not probably belong to the victim but

could be because of the person who possibly killed him and then they show the you know cloth piece to the dog and dog you know goes around and find the person who culprit who you know killed this person.

So this you must have seen but it is because they are able to distinguish the smell and they have a beautiful well order interceptor which is able to distinguish various smell types and able to map the mass well so that is a you know an important aspects in dog which really have that is why the dog species have been extensively studied and that has led to a large number of discoveries which could have a implications even on human.

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For example one of the landmark study identified a sleep disorder and this disorder affects the dog and later the same gene a mutation is known to cause the same disorder in the human, so really it helps.

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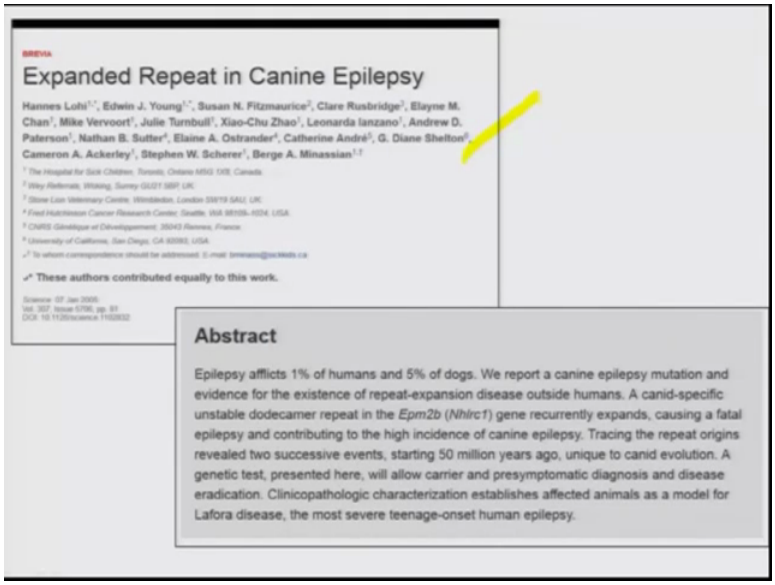

The other example is you know another dog model developed very fettle form of epilepsy because of the genetic change that is there in the same epilepsy cost by the same gene mutation is known in the human right. Now in addition to understanding the conserved functions of the genes and the mutation process these dogs model really helps us to even understand the pathophysiology so that way the dog you know has been one of the best studied example and really helps us to understand various process of genome evolution and that is pretty much brings the you know end of this particular lecture and will see again in the next lecture.