Functional Genomics
Professor S Ganesh
Department of Biological Sciences & Bioengineering
Indian Institute of Technology Kanpur
Lecture No 17
Comparative Genomics Outcome of Genomics

Welcome back to this functional genomics course where we are discussing the topic what you call as comparative genomics how comparing the genome helps us to understand how the genome functions, so in the previous lecture we looked into how you know comparing the genomics sequence help us in identifying regions that possible could function as a regulatory elements It could be enhancer elements on which some proteins come and bind and regulate the gene transcription and so on, therefore if you have changes there then the gene function may have would been affected.

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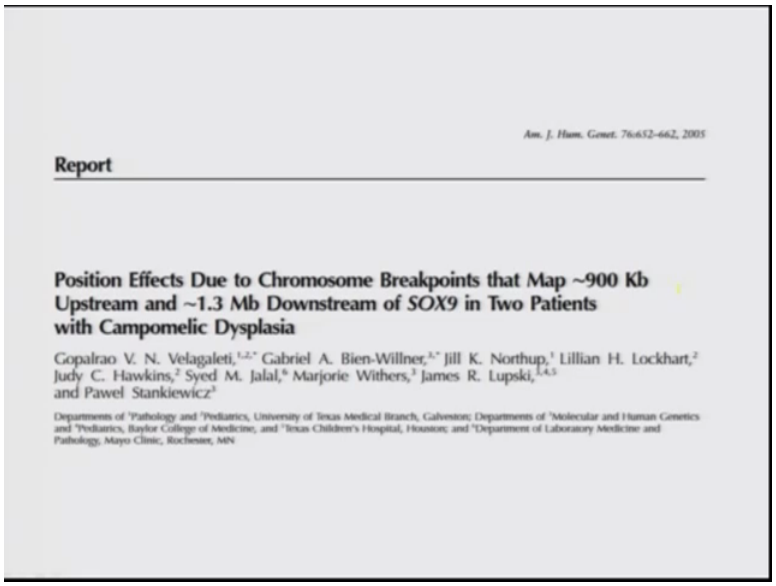

So we are going to look into one such example here it is disorder caused in the human because of changes in the genomic region that are several mega bases way from the gene yet it affected the gene function and you have a condition. So what is show on the screen is a paper and this paper talks about position effect due to chromosome break points that map our 900 kb upstream and 1 point 3 mega base downstream of a gene what is called as SOX9 in patients with campomelic dysplasia.

So this gene SOX9 is involved in two different pathways one off course its involved in the bone formation cartilage formation so it is very very important for the bone to form but this gene also is involved in the formation and function of testis, so in other words it male it has got two function for the testis formation and in the bone. The female it has got only one function that is for the bone formation. Now if you have defects then you would expect two things one if that individual is XY chromosomally and SOX9 gene is affected then they will have to anomalies one they become XY female meaning they could not develop testis as a result they become phenotypically female these are called as sex reversed female and they will have condition wherein the bone deformity are same.

But if they are XX you know the testis any way will not develop, they remain female but they will show what you call as the bone abnormalities. What is interesting is that a majority of the patients off course show mutation in the coding sequence of the gene therefore the protein either it is not made or you know made in abnormal way therefore the gene is not functional as a result you have the defect but there are patients in which like that is discussed in this paper where the translocation or structural changes happen about 1 mega base upstream or downstream of the gene, still it had affected gene function resulting in identical you know condition like sex reversal and and campomelic dysplasia.

So one of the hypothesis one can put for this that these regions were the deletions or structural changes happen far away from the gene, yet you have the condition. Could have affected certain elements that normally regulate the function of the gene so this and couple of other papers I am going to discuss is to show how comparative genomics approach can be used to decipher the mechanism and test the possibility right, so this is one.

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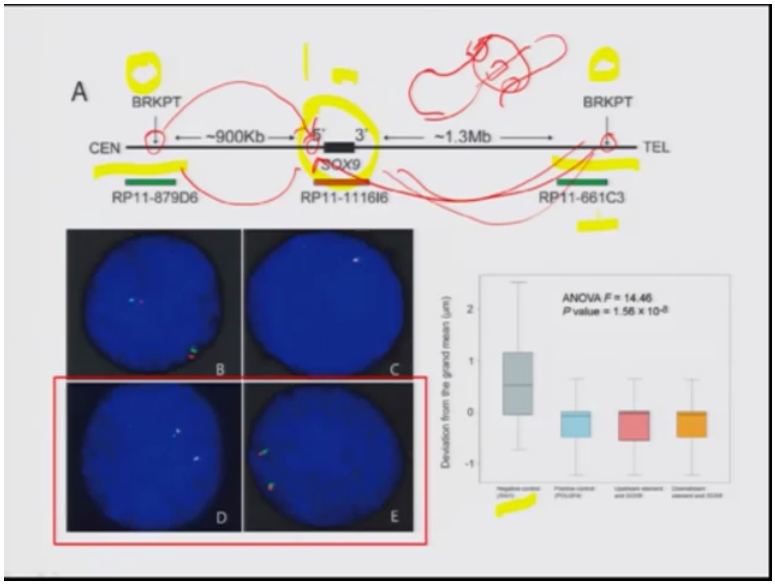

So what they have shown here is that you know these are the regions you know this region and this region is where they break point took place chromosome got translocated and you know it led to possibly you know affecting the function of the SOX9 gene here, so what they have the hypothesis for there could be a region here right which are elements onto which some transcription factors can come and bind and regulate the gene expression. If that is the case if indeed that is the case that these are the segments that are present certain transfiction factors coming and binding what you expect is that you have the promoter here right and then, so you have the promoter here and that the elements are here and here so how these elements can you know communicate with the promoters that is present over here.

So what is believed and of course as been shown in other gene segment is that this is your promoter and if possibly this DNA can loop out and bring the elements for example the upstream element and the downstream element something like this and you have the you know complex of proteins coming and binding and regulating the gene expressions. This is one of the hypothesis, if indeed it happens then if you look for the distance between this and this segment in a cell that is normally expected to function and the SOX9 being expressed then the distance should be much less as compared to similar region in some other gene where there are no you know elements like this right.

So that is what tested in this particular study what they have done is that they have looked at for example a gene they have taken a gene which do not seem to have any such control elements and then they looked at the distance between the gene and probes that are falling about 1 mega base away from the gene right and that is what is shown here you can see here in this blue circle nothing but a nucleus right of a cell in which they have used a red colour probe for the gene and a green colour probe for a region of the chromosome about one mega base either upstream or downstream ok.

And you can see the distance between the green and red is far apart this are two copies that you can see here and then they are looked at another gene which gene is known to have such regulatory element meaning it has a regulatory element about 1 mega base upstream of it and they looked at the distance you can see that they are almost present close to each other that is because of this particular model that I am proposing that they come together as a complex of protein bind and activate the genes so the distance is almost you know negligible.

Although they are separated you know the distance between these two segments is about 1 mega base but you know they loop out to form a structure wherein these two elements come together. Now they tested whether it is same true for this case where SOX9 is you know either the break point here and here affecting certain element and that is what its shown here for example here.

In both these conditions right whether you are using a probe for a downstream of the SOX9 gene or upstream of the SOX9 gene you will find the distance between the two signal that is red and green is almost similar to what has been shown for another gene which is established to have an control element about 1 mega base right. So it clearly tell that there could be certain element functional elements present far away from the gene and if that is disrupted the gene will not function right this is the paper that proposed that possibility.

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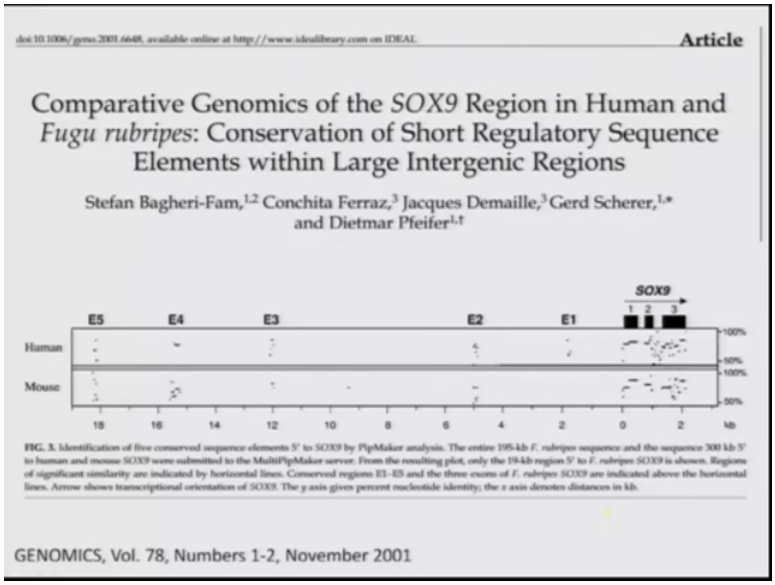

Can you use functional genomics or approach you know test this possibility. This is one of the earliest paper where they have looked at such possibilities and what they have done is first they have compared the sequence of the human with the mouse ok. This is the SOX9 gene exon 1, 2, 3 and possibly this is where you know the upstream regions are there and you can see that this is 50 to 100 percent similarity and you can see that there are segments right that are highly conserved you can see that you know this is compared with human and mouse sequence compared with puffer fish ok.

A fish you know which has got again SOX9 gene and you know separated by millions of years from the mammalian species. They compared the puffer fish genome with mouse and human genome and they are showing that exactly at the same about 18 mega base and what a kilo bases and you have segments that are highly conserved right. So which suggests that these are the regions possibly there are elements that regulate the SOX9 gene expression. They are conserved because change is possibly not permitted otherwise the gene you know activity may be lost ok.

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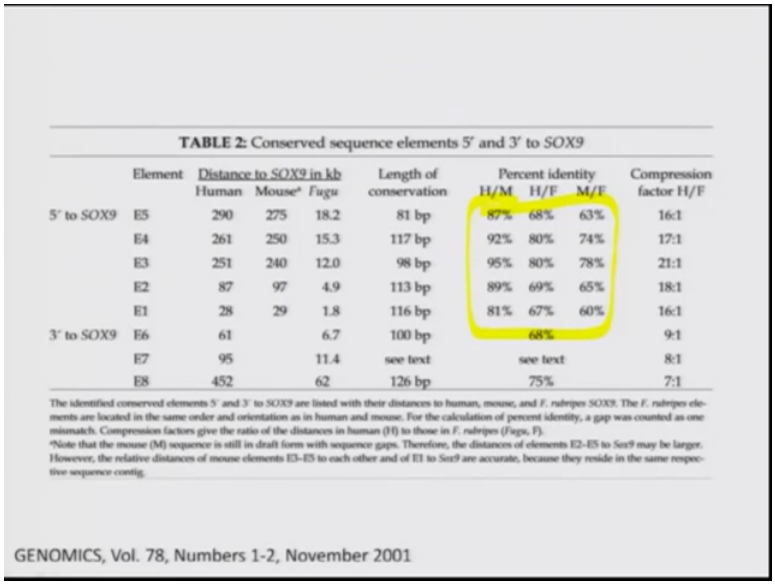

TABLE 2: Conserved sequence elements 5′ and 3′ to *SOX9*

	Element	Distance to *SOX9* in kb: Human	Mouse[a]	*Fugu*	Length of conservation	Percent identity: H/M	H/F	M/F	Compression factor H/F
5′ to *SOX9*	E5	290	275	18.2	81 bp	87%	68%	63%	16:1
	E4	261	250	15.3	117 bp	92%	80%	74%	17:1
	E3	251	240	12.0	98 bp	95%	80%	78%	21:1
	E2	87	97	4.9	113 bp	89%	69%	65%	18:1
	E1	28	29	1.8	116 bp	81%	67%	60%	16:1
3′ to *SOX9*	E6	61		6.7	100 bp		68%		9:1
	E7	95		11.4	see text		see text		8:1
	E8	452		62	126 bp		75%		7:1

The identified conserved elements 5′ and 3′ to *SOX9* are listed with their distances to human, mouse, and *F. rubripes SOX9*. The *F. rubripes* elements are located in the same order and orientation as in human and mouse. For the calculation of percent identity, a gap was counted as one mismatch. Compression factors give the ratio of the distances in human (H) to those in *F. rubripes* (Fugu, F).

[a]Note that the mouse (M) sequence is still in draft form with sequence gaps. Therefore, the distances of elements E2–E5 to *Sox9* may be larger. However, the relative distances of mouse elements E3–E5 to each other and of E1 to *Sox9* are accurate, because they reside in the same respective sequence contig.

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Now this is simply to show that there are you know comparisons like percent identity between for example the puffer fish and the mouse like what I have shown earlier.

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But now this paper which came out more recently is that tested that. Whatever I was shown conservation meaning higher sequence similarity so this thing these are control elements. Do they really regulate the gene expression in the human so how will you test that so they have created what you call as transgenic models ok. You take the promoter and other control elements

of the SOX9 gene like shown here, SOX9 gene you have you have elements here here, here here and here here right there are 7 different elements that are known highly conserved likely regulate the gene expression.

What you do is that you take these elements you know make transgenics in each one what you do you delete one of the elements and see what happens to the expression of the gene. So now this what that has been done so you have this SOX9 promoter you know tag to a coding sequence called LAXY which is exactly like what you guys use in bacterial blue white colour selection. So it is an enzyme beta galactus as you give a substrate it will give you a blue colour. So this is a way to essay where the gene is expressed you do not need to worry about SOX9 here because you are using the promoter which if you get a LAXY loose staining that is a readout for the promoters function.

So this is what it is now if you use just the [promoter ok this region alone with a LAXY and if you look into where the LAXY is expressed we can see that it is the hyne brain and spinal cord this is what I am showing here. This is embryo the embryo we can put in a substrate having the beta gall it works on that and converts into a product which gives you colour and you can score nowhere it is expressed but if you take SOX9 promoter with E1 like what is shown here if you make a construct and you find that it is in addition to the hyne brain.

It is also expressed in another tissues like monocot, gut and others like you can go and see like this as you add for example E2 then we do not see any difference but E3, E4, E5 you find that it started expressing in crane or neural crest you know and other so you can see that they are you know how in development you know the different elements control the expressions of these genes in different segment and what you are doing is you are taken the genome of the human and you are putting it in the mouse. Still it is able to drive the message as to where it should express.

So it is the power of the comparative genomics you go and compare the genome, you identify the signatures predict it could be elements and create transgenic models to test your hypothesis. So this all doable only if you are able to compare the sequence and that tells you how powerful the comparative genomics approach is, so let us look into the genome so if you compare the different genome what is that one thing that strikes you the most with regard to the human genome what you find is that the gene density goes down.

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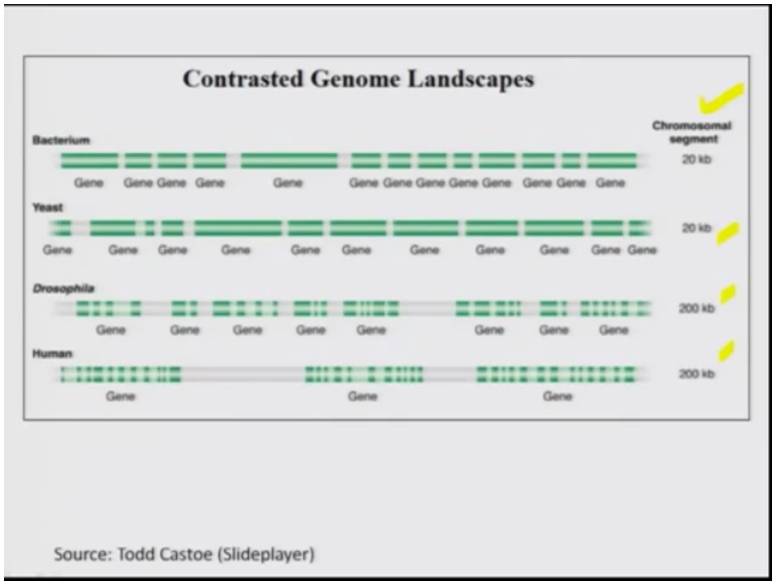

So this is the bacterium for example there are chromosomal segment of 20 kb of bacterium yeast, drosophila and human compared and you will find that for the same segment you are going to have a large number of genes in other species whereas in humans for example you have only three genes but here these are multi exonic so spread out right whereas in others you will find these are much more clustered and and packed ok in other words you know the number of genes did not change really dramatically across species but it is this the other DNA that so called noncoding DNA that is there in the genome that is normalcy increased therefore you know that possibly have got some strong control over how the genome functions.

So one of the important components of your genome is the transposable elements or there are what you call as jumping genes there are segments near genome which are called as transposons because they do not they are more like parasites in the sense they are not there to help us for genome but they are there for their own survival because they have to survive right because they are parasites.

They do not do harm to us often but at times they can harm us at times they can help us both happens without any direction. I will say why it is so these are transposons nothing but they have a small segment of the DNA which has a coding potential for a reverser transcript or other nucleus. What it does is that it makes copy of itself and goes and you know get integrated somewhere in the genome so they keep on moving within with in the genome leaving a copy

therefore over the time what happen you have accumulated large amount of such sequence in your genome as increased genome size has increased and you know and they are all in between genes.

The reason is if they have landing in part of a gene then it is going to affect the gene function and that may affect the survival of the individual therefore it is not selected but wherever they are integrated in the region that are not having in a gene your genome tolerates, so that is what shown here.

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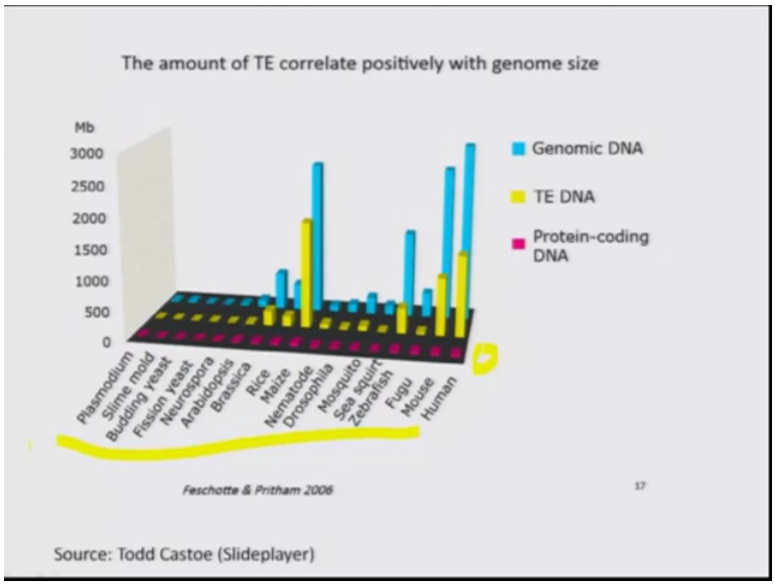

So if you look into the protein coding sequence between human to you know yeast and others it is not a big difference almost you know similar. And then if you look into the genomics you know size the entire DNA and obviously in the human, mouse and you know you zebra fish you can see there this is like a tower because the genome size is very large and so is the case with plants. They have as big as the human genome size and in addition what you have is that a good proportion of almost 50 percent of the genome is made up of these kind of transposable elements in other words that transposable elements contributed to the genome diversity also the increased genome size and there are elements that are unique to species.

Some of the transposable elements that we have are unique to humans for example ALU transcript I know the repeats that we have these are unique to humans you do not have in other

species and so on right. So that really you know changed so as I told you the transposable elements can see it some evolution ok.

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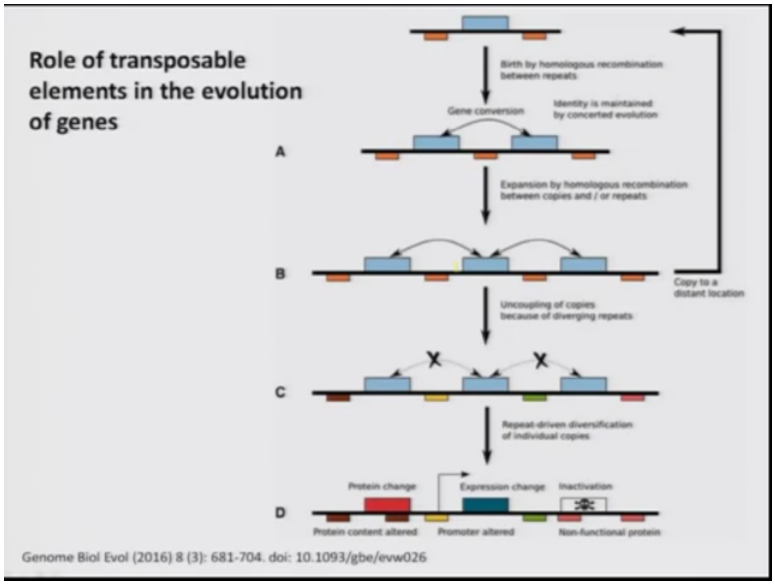

So evolution could be at times it can land as I told you in a gene and affecting the with gene function that can result in a disease or the individual not surviving but it can also help the genome to survive. One of the ways by which it can help the genome to evolve is by facilitating a process what is called as gene duplication ok. So what happens in this case is that you could have for example the element landing on either side of a gene right. You have identical sequence present on either side of the gene it happened, so what happens during meiosis it could so happen that there is a process called recombination that happens in recombination.

So in the meiosis and the recombination normally looks for identical DNA sequence and then brings the homologs together. There is a double strand break therefore there is a cross over happens, so since the elements the transpose elements have identical DNA sequence at times what happens is that you could if you know if you have two such elements nearby the system may get fooled because it may identify these two as homologous segment and then you would have a recombination you know going through this as a result one of the two recombinant chromosome would have two copies of the genes others would have lost the gene right.

So now if you have any two copies of the gene you have the luxury, the luxury is that instead of having one copy in a chromosome you have two so one is doing the function of original function, the other one is free to evolve because it changes its not compromising the gene function because the other one is taking care, so now if the changes can result in such a way that the gene becomes dead. Meaning accumulate mutation no longer functional or it can give a new function to the genome or the gene.

Therefore it evolves into a new gene right so this is a possibility that is what shown here is that at the end of the day you could have for example there is a protein change this sequence is changed dramatically that is become almost a different protein or the expression changes where the gene is expressed that could change or it can completely lose its function. So what I am showing you is that how such elements you know help in the genome.

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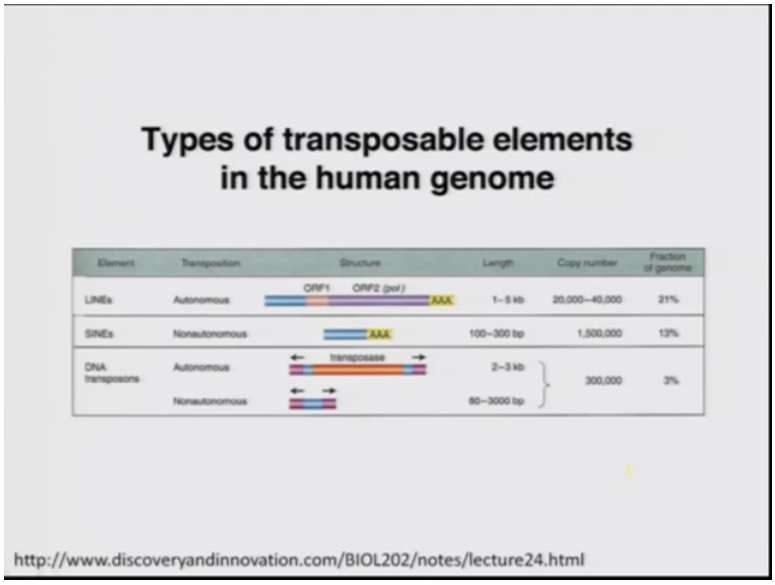

Now there are large number of transposable elements in your human genome some are shown here lines.

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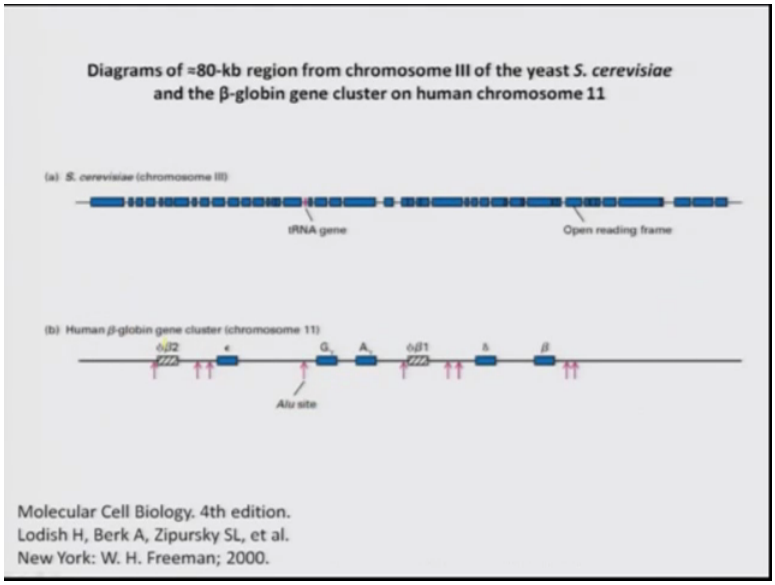

Signs and other transposons but what I am showing you is a classic example which you must have studied in your textbook. This is a diagram schematic which compares the yeast genome with the human genome right, so the human genome that is compared here is from chromosome11 having the beta globin gene cluster because this is one of the gene dense region, even then you can see the number of boxes which represents the gene or few other in case of the human obviously you have more in a space elements. These arrows or nothing but the repeat elements remember I told you that there is a transposon called A-live you know repeats and these are repeats. Now there are present here.

So what we believe is that these A-live repeats helped in the evolution of beta globin genes multiple you know forms of the beta globin that you see could have happened because of gene duplication, each one now selected into new function and somehow them would have lost the function like what you see here so that is one way and the same kind of you know hypothesis is given for haemoglobin as well. So you have the adult haemoglobin and foetal haemoglobin, the difference between these two is the foetal haemoglobin the haemoglobin express when we are the embryo growing inside our mother is a haemoglobin that has a higher affinity for oxygen.

Therefore it is able to capture the oxygen from the mother whereas the adult haemoglobin as you know lower affinity because you know now you are able to capture oxygen from the you know atmosphere. So this also people believed could have evolved because of gene duplication and the

duplicated gene acquired something new function right. So how do you really study right when you talk about transposons right transposable elements one of the model systems or one of the species that has got very few transposable elements is the puffer fish that is something that is shown here.

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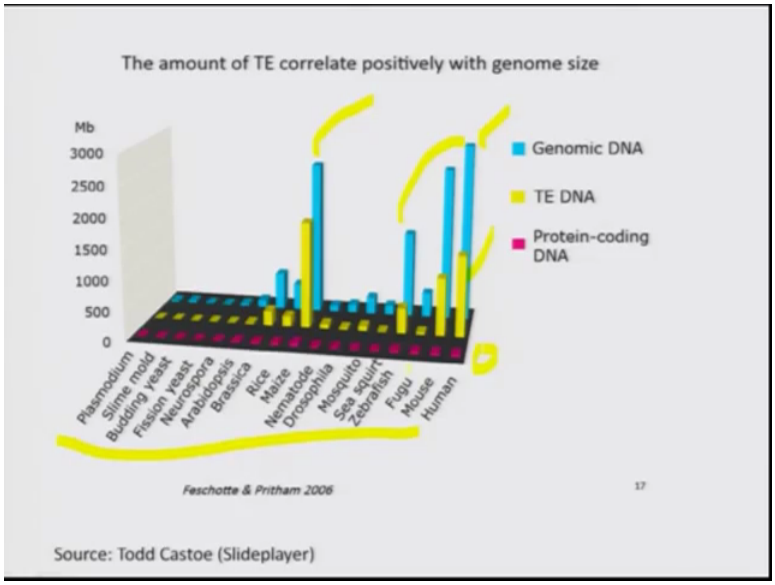

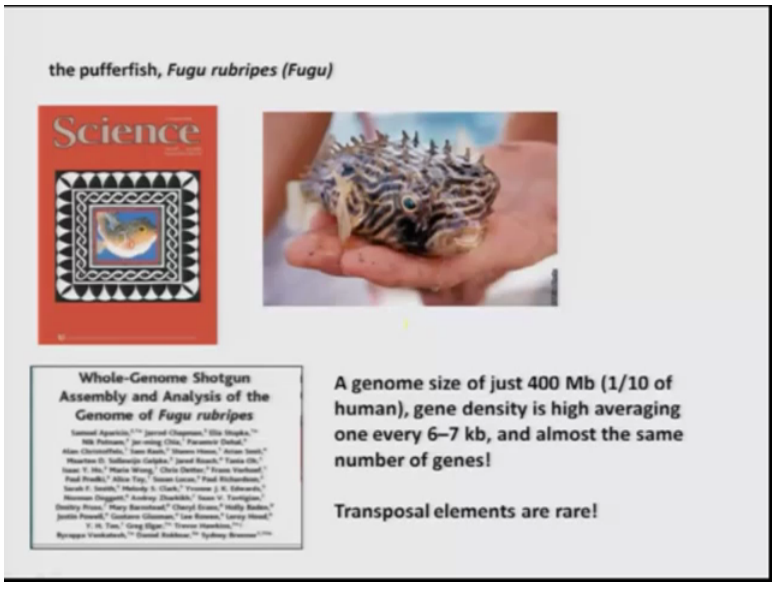

You can see that this fish called Fugu you know has got negligible you know amount of transposable element and and the genome is so small it is just 400 mega base one tenth of the human genome but it is got as many genes that human has almost all number of genes and and

the size of the gene is 6 to 7 kb pretty smart. In other way it is like a you know miniature genome which is got all the genes act in a very small you know segment so that has really you know made people to wonder what is so unique about this fish why it is got such a small genome and if you can sequence the genome understand you can what are the essential genes what are the essential DNA elements that are required for a successful species right.

So that led to this whole genome sequence of this fish Fugu (())(20:48) and this is a you know fish that is normally found in Japan and this one of the delicacy people eat this fish and you know this was developed by the person Sydney Brenner who received noble price for his work on C elegans ok. So as i told you this fish has got you know very few transposable elements in the genome and probably that is that could be one of the reasons why it is able to keep the gene density very high ok.

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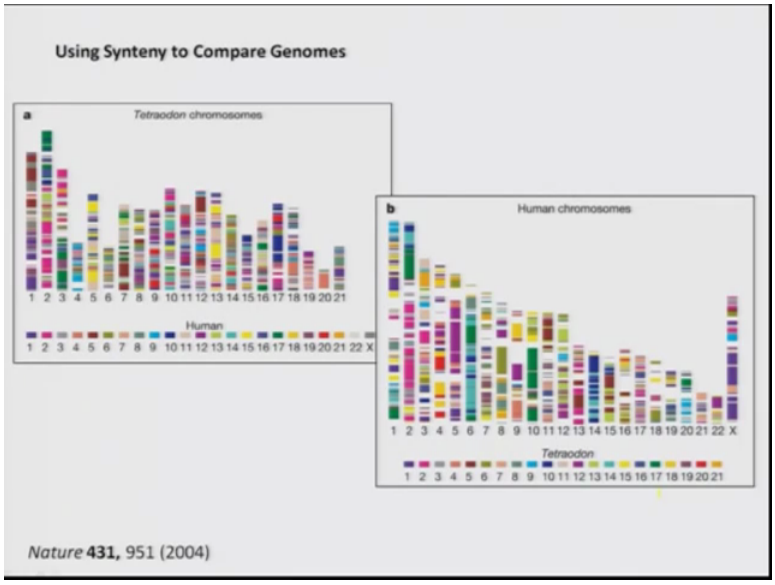

So what has been done is there are many studies one can look into we can I have given you another example how this puffer fish helped in understanding SOX9 control elements, so what we are going to discuss today in this section is to see how the fish genome can be used to understand what possibly or the first vertebrate genome so when vertebrates come in the first species of fish evolved or could have been the chromosome, how many chromosome how it could have been. So what people do is they make synteny maps meaning you look into the chromosomes of humans and look into the chromosomes of other species and see which segment

of human chromosome represented in which region of the chromosome of the species you are studying because the chromosome number is not same.

So we have 23 pairs but there are some species who has got only 6 pairs mammals same amount of DNA, some has got 100 plus you know chromosome which clearly tells there is the genome has undergone large number of fission and fusion process meaning a chromosome cut into multiple pieces and joined independently from new chromosome, that is the fusion process right. So you can now look into the genomes where the genes are and the clusters and then go on map in the genome.

So this what shown here for example that the the for example the fish genome first you know mapped to the human genome, so this the human chromosome is colour coded here and for example chromosome1 is mapped to you know you can see that where they all present. Its present somewhere here present somewhere here there are large number of segments in which chromosome1 is present likewise you know every other segment

One can do the reverse they can take the chromosomes of the tetra hydron, the fish chromosome21 pair and then look at which are the segment that in which it is present right. So this is the way you can analyse and when you compare a fish with a human it looks like scattered right but if you compare a mouse with a human you find that there are many regions that are present in in a larger segment like this.

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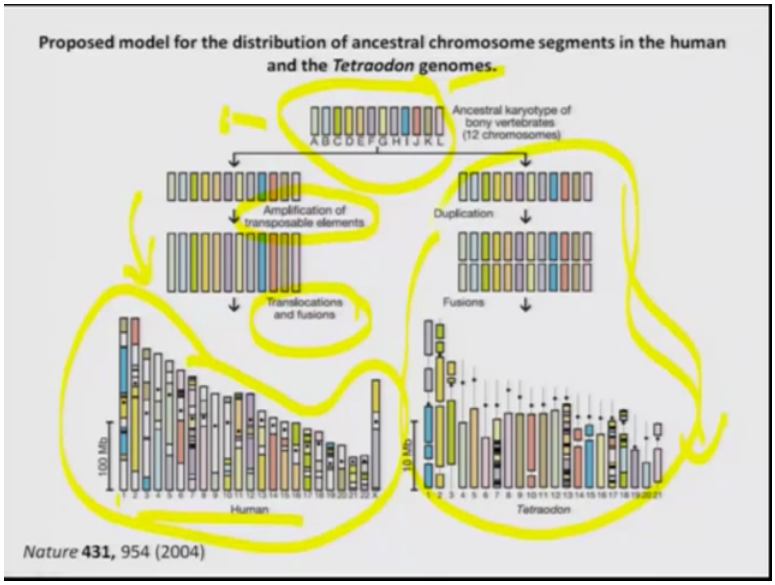

And based on that kind of a comparison what has been done is that this is a human chromosome, they went on to sort of propose access set of what is called as ancestor karyotype you know chromosome set for the bony vertebrate because that one you know the bony vertebrates are the one that evolved you know from the the soft body fishes and that led to you know massive genome duplication leading to a kind of fishes that you see ok. So this is ancestral karyotype they believe that there could be 12 chromosomes right which is numbered from A to L and you know what would happen was that the genome you know obviously this genome was much smaller as compared to human but what could have possibly happened is there is amplification of the genome not because of the duplication the whole genome duplication but because of transposable elements you know they came into the genome kept on living a copy and making a new entrance so on.

So the translocation and you know the the genome size has increased and then what happened is that you have you know chromosome fused together or broke with each other resulting in the kind of chromosome that you see so this is an hypothesis based on such kind of analysis but what is interesting here is in the fish you know the genome evolved in different way. What happened is the entire genome got duplicated so for a given gene now it is become two in number and then again you have process which led to the fission, chromosome broke and joined together and to see what kind of chromosome exactly have.

So we can really understand how the genome has evolved by comparing the genome sequence that is what we spoke about how for example the puffer fish helped us to understand you know the evolution of the genome with little amount of what you call as the transposable elements right so by tracing the evolution we can now look at some of the major events that are happened.

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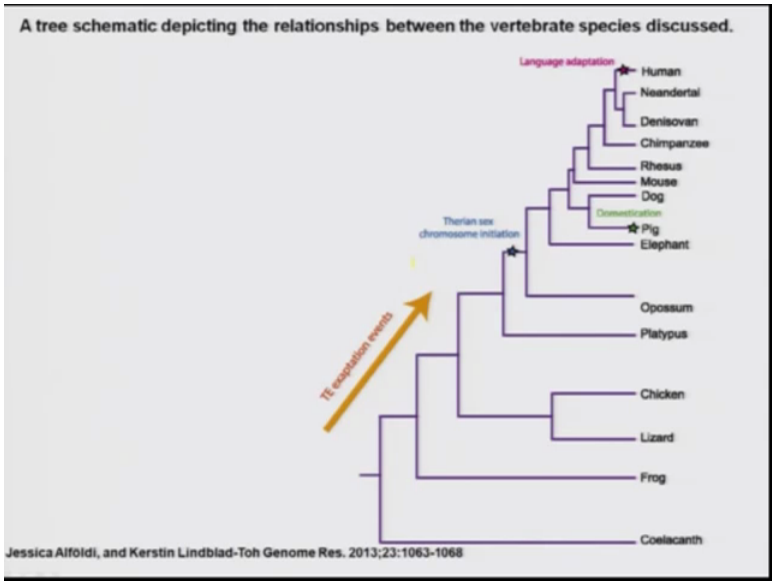

One of them is that the you know the mammals the evolution of X and Y chromosome so if you talk about sex determination you have X chromosome and Y chromosome, that determine the sex of the individual if it is a XX it is a female, XY it is a male. It is common to all the true mammals right including for example the kangaroos right so what we believe is that that happens sometime at this point of the evolution that a given chromosome was identified to become the future sex chromosome and they were identical in size but over the time point when the evolution progressed it became such that the Y has become very small X has become very large and Y in variably had the gene that determines the testis.

So now we have very good leads which suggests that indeed that could be the case. The other important element that people have dissected is domestication for example the pigs were domesticated there are a very good number of studies which tell you how the genome has changed while domesticating the pigs because you have selected for certain quality in the domesticated pig because you are looking at certain quality how the genome has changed then and then off course the language adaptation right in the humans.

So for these two I will you know give you some links in the in the course portal you can read more on that we will not discuss more but we are going to slightly touch upon the language adaptation in the human. How your genome probably helped us to develop the language that you speak.

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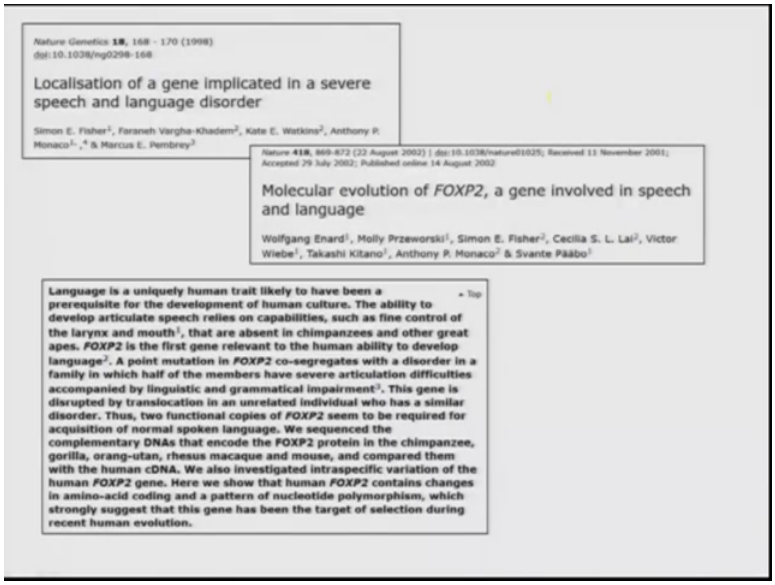

So we know that there are individuals in the human population who are unable to speak the way the majority of us speaks, so that is called as speech or language disorder they are unable to comprehend you know understand the language or unable to put together words to express themselves right. We are talking about not a non-native language we are talking about the mother tongue language we are not talking about which language. So looking at such families there was a study which identified a gene a defect in that gene you know led to such kind of disorder. Obviously genes regulate you know your cognitive abilities one of them being the language right.

So if you know that gives you key as to you know how genes can regulate your brain right, so if that gene is so critical for language you know then then we can go on look at the gene sequence and ask whether the sequence that you see in the human that made us to speak the language develop the language, understand the language. These signatures are present in the other animals which do not use the kind of languages that we use that gives us like glimpse as to how it could have evolved.

So now what they have done is similar study was done was they have there is a paper and 2002 where they looked at this gene FOXP2 gene which is involved in this severe speech and language disorder. They looked at the evolution of the FOXP2 gene across different species and I am just putting this you know paragraph here you can read that, so what it said language is uniquely human trait because the kind of language that we have you know no other animal has likely to have been pre-requisite for the development of human culture because you know you have what we call as inheritance you are reading about somebody Mahatma Gandhi or Shivaji and so on. We are able to read because there is a language so you do not nobody need to tell us we can open a book and read and understand what it is about.

So you can leave the history because of the language otherwise you would have forgotten it would have been just like our epic like Ramayana, Mahabharata which was you know told by the parents to their kids that is very own but but that is now the information has grown now everything cannot be told verbally, so you need to have a language even for verbally telling there is a language right so everywhere there is a language. So the ability to develop articulate speech relays on capabilities not only the cognitive functions such as fine control of the larynx and the mouth basically the sound that you create is nothing but the sound you are able to control and produce using your mouth because you are closing, your tongue because you are twisting the tongue and you are able to a larynx because that is where you make the noise or the signal is what you call as the language.

This ability is absent in chimpanzee and other great apes ok, so the FOXP2 is a first gene relevant to the human ability to develop language because you have a defect there you are unable to speak. The point mutation (())(30:25) me to co-segregated with a disorder in a family in which half of the members have severe articulation difficulties accompanied by linguistic grammatical impairment. They cannot speak and they cannot comprehend or put together even a sentence.

This gene is disrupted by translocation in a unrelated individual who has a similar disorder. So in more than one family the same gene defect you know resulted in a phenotype which is you are unable to speak. So the functional copies of FOX seems to be required that is you are to have two copies to require for acquisition of normal spoken language this is very important. So what they have done is they have sequenced the complimentary DNA that code for this gene FOXP2 protein.

In chimpanzee, gorilla, orang-utan and other monkeys apes and others which do not have the ability like us to articulate ok and compared with the human cDNA and to see what happens what they have found is that we also investigated the interspecific variation of the human FOXP2 genes and what they have shown is that the FOXP2 contains changes in amino acids coding and a pattern of nuclear polymorphism which strongly suggest that this gene has been the target of selection during human recent human evolution that means the ability that we got to speak is because of this gene and some changes happen and the changes could be not really meant for this gift that we are able to speak but so happened that that gave us this ability and we picked up and this was selected now you find it in humans right.

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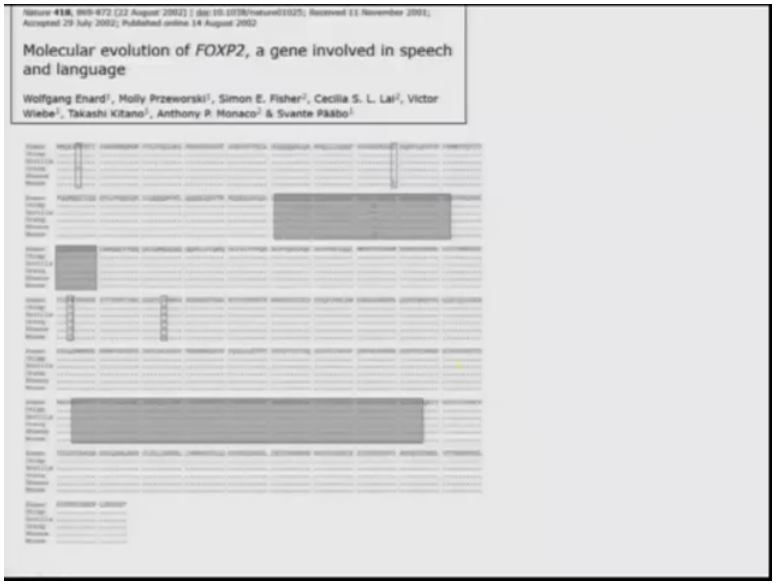

This this just to show you that signatures we can see that there are you know variants right and and you know these are the variant that are unique you can see that these S you know amino acid is unique to human and likewise here is an amino acid is unique to human and there are segments that are multiple queues people believe that these are the residues that has given you that end ability to speak ok whereas other animals do not have the ability possibly that is the signal that led to the you know a language.

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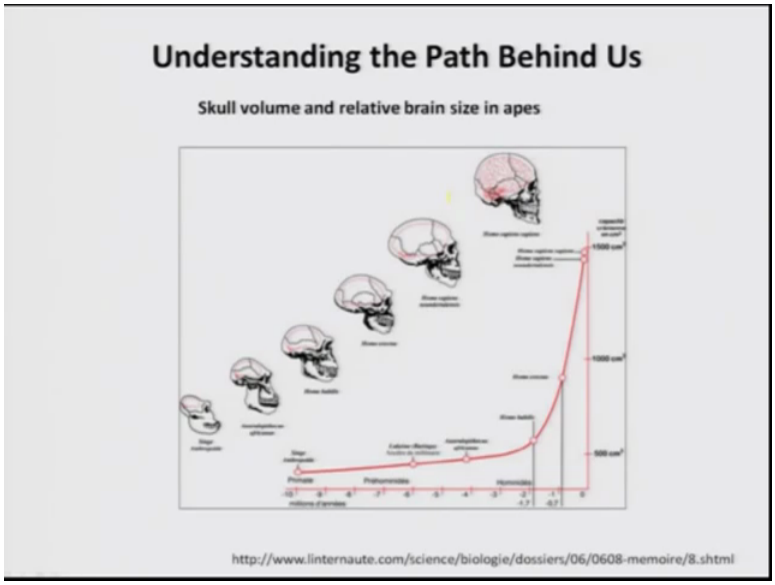

It could be very subtle small change but you can have greater impact another example is that our brain itself so what you can see here is that although the orangutan are the apes have much large head but their skull has got small cavity for holding brain so if you look into the skull volume versus relative brain size, we have got the larger you know brain you know size in the skull right.

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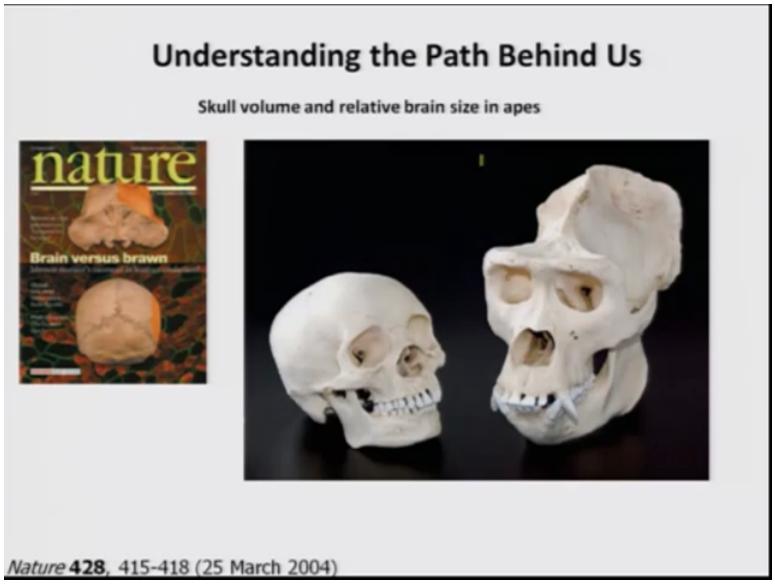

So what led to this you know evolution and we do not know for sure but what we believe is that it is the ability to use your hands as a tool could possibly one gift so what is seen here is that

skull of a human and skull of one the apes and we can see here the although the head is so big it is there is a huge cavity there and it is it is there because the lower jaw of the apes are so strong right because they can they have the muscle connecting from here to here and fore the muscle to connect you need a huge cavity there.

So if you do not have the cavity then muscles cannot connect to lower jaw as a result what happens the lower jaw become less powerful so they can cut open anything with their lower jaw and possibly there was a mutation that happened with the loss of the muscle strength which led to a condition wherein you do not really need that huge pocket therefore the skull now is allowed a larger brain to occupy now it comes with a cost the cost is so you do have a bigger brain the same size as skull but your lower jaw is not as powerful as it was.

So what you need to do so you need to use your larger brain to compensate the loss of the power that is to make tools what you can cut with your mouth, you can cut with a tool, so that larger brain help you to come up with tools so you compensated but it really helped you to way the way the humans have evolved.

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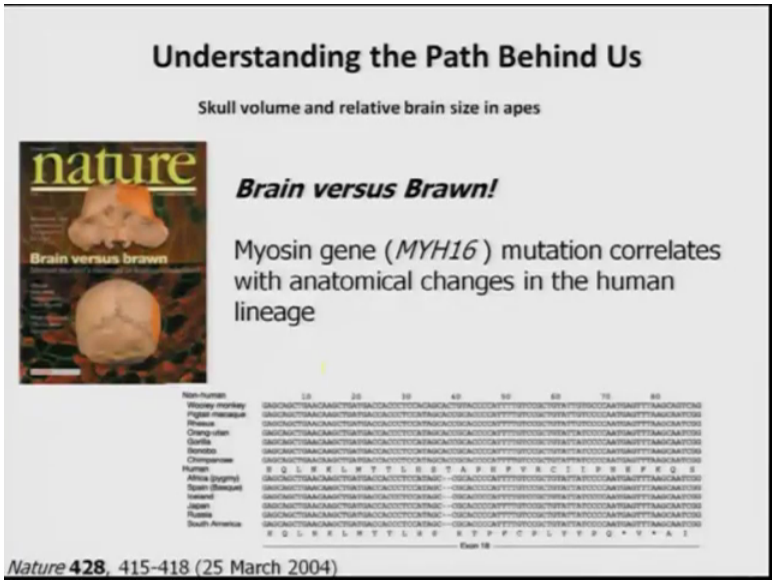

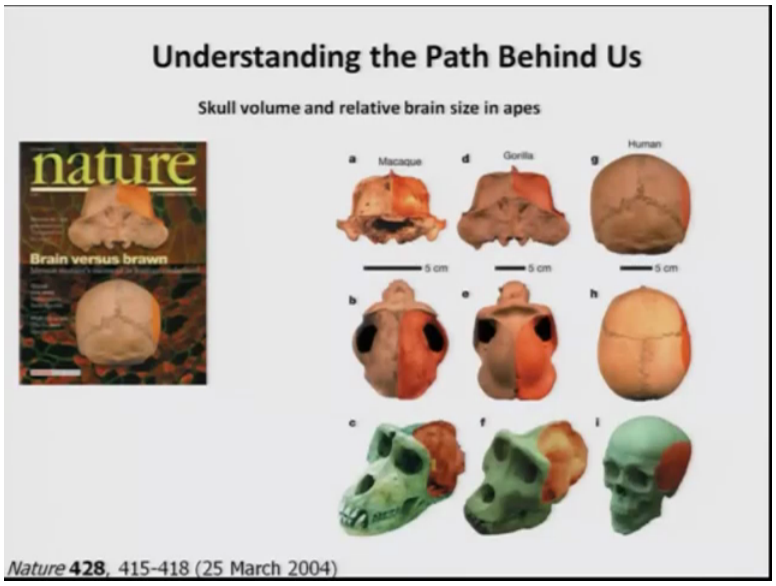

So its its an hypothesis based on the sequence analysis what is shown here is a sequence analysis we can see there are again unique residue that are present in case of humans but not in other species of gene that codes for the myosin one of the protein that helped the muscle and ;people think that that could possibly be the one of the reasons why your skull is able to accommodate4 much larger you know brain ok.

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So that about how the humans evolved now I am going to talk about some unique species the species that have power to live beyond what the human can imagine, so I am going to talk about

one ugly animal looks ugly but the phenomenal animal in terms of its ability. This is this animal that is shown here is called as the naked mole rat rat it does not have the skin is open it does not have these you know you know have so its its naked, it is called as a mole rat because they live in barrows and mostly in dark conditions.

They do not have that kind of eyes that we have they can sense light but cannot really you know see beautifully but they are amazing animals, they live in barrows like this you can see that all these are small you know litter that that is a mammals this is like size of a mouse or rat and they are unique to this eastern part of Africa ok. So what is so great about it therefore people went and sequenced the entire genome of the naked mole rat.

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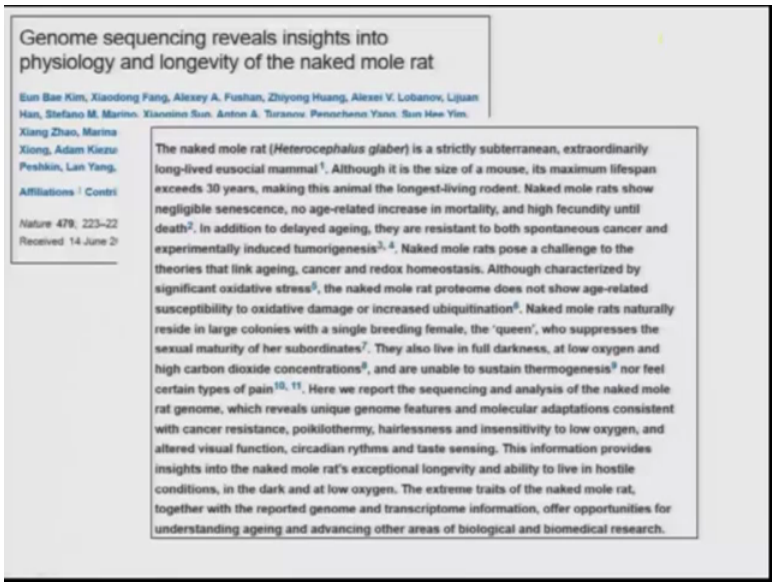

I am just putting you one paragraph again to appreciate what is so unique about this naked mole rat ok, it strictly subterranean meaning it lives on the surface of their extra ordinarily long lived mammals. They although the size of the mouse its maximum life span exceeds 30 years, making this animal the longest living rodent, naked mole rat shows negligible senescence they do not age at all they look perfectly normal. No age related increase in mortality it is not they die or at later part of their growth. High frequent ready because they can keep on breeding until death so they reproductively active until they die. So they do not age they live longer they are absolutely alright even at the time of death otherwise.

In addition to delayed aging they are resistant to both spontaneous cancer and experimental induced tumorigenesis so their genome has got something which make them resistant to cancer. So we are able to somehow control the bad genes from going you know on and inducing cancer even you experimentally induced. These rats pose a challenge to theories like aging because we normally say aging is inbuilt in your genome. You age because the system want you to die, you have done your job of reproduction you no longer compete with your you know of springs, you have done your duty that is the concept but it defies that even theories.

And then cancer they say happens because the death has to happen and redox homeostasis because even your ability to cope up with stress cellular stress goes down with the aging but nothing happens in this animal although characterized by significant (())(38:17) stress the naked mole rat protium does not show age related susceptibility auxiliary damage, no damage happens. There is no increased ubiquitination saying that proteins are damaged nothing happens here.

Naked mole rat natural resides in large colonies with a single breeding female the Queen very similar to what you see in honey bees who suppresses the sexual maturity of per subordinate therefore she remains the main female who is reproducing. They also live in full darkness at low oxygen and high carbon-di-oxide concentration because they live in faros and are unable to sustain thermogenesis nor feel certain types of pain.

It all gives because when you when you feel cold you shiver, the shivering is an you know physiological response to increase body temperature, they do not show that kind of shivering when you bring down the temperature and they do not feel pain either so it is a gifted organism which has sort of whatever we think of they should get it off, they could get it off you know what is there in the genome. So what they have done is they have sequenced the genome and analyse the genome of the mole rat which reveals unique genome features and molecular adaptations consistent with cancer resistance.

Quite low thermy you can survive in different temperature gene hairlessness you know you have fur for protection they do not need that in sensitive to low oxygen. They live in hypoxic condition very little oxygen there are survive better and altered visual function which cannot see but still they function. (())(39:58) and test and sense all are compromised because you do not

have the you know day light so the (())(40:05) what you normally see in mammals is all altered here.

So this information provides insight into the naked mole rats exceptional longevity ability to live in hostile conditions the dark oxygen, low oxygen level right so we can understand how the genome functions what do they really mean how this animal become so successful possibly it could help us in advancing our own biomedical research.

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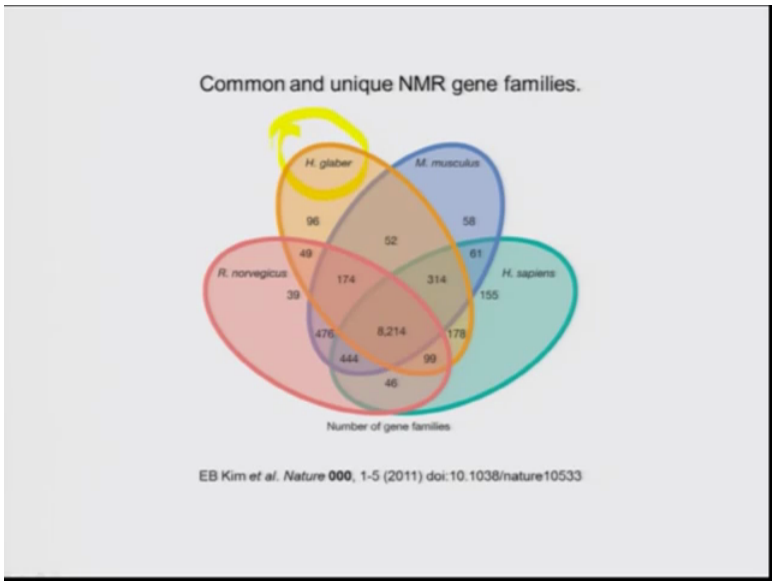

So this is just one diagram I am showing to show that how this particular species you know has got genes that are so unique very different from mouse or human or rat but unique to this species, if you can understand the function of these gene that are unique to this mole rat and what function they do in the cell system, tissue system at organism level probably you will get some understanding as to how we can control cancer how we can live in condition that are hypoxic and many of their advancement that otherwise off very very challenge to the human being so this being investigated.

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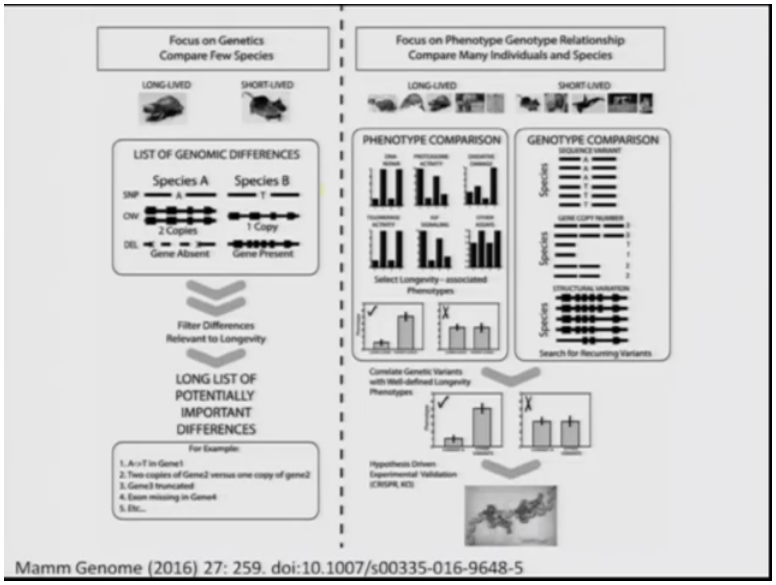

These are some of flow chart people are trying to understand for example long lived and short lived you know animals compare the transcription genome decipher what is the difference and go hide and understand the function of the gene in the physiology, that is just to summarize some unique species how they can give you some insight into some of the physiological condition that otherwise are extremely lethal to the human.

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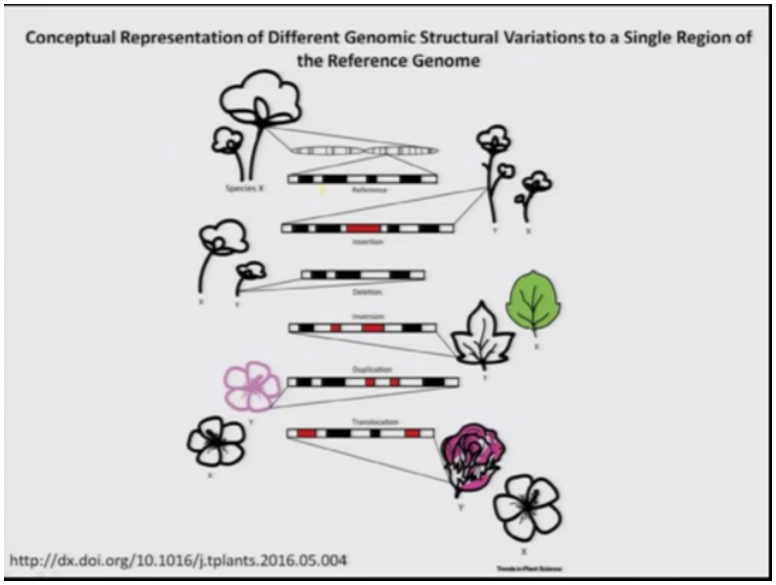

There similar approach have been applied to plants as well so you can for example we can look into species right A and species B you know some are large or small and compare the genome and understand what genomic changes gives you particular trite for example you talked about cabbage right it is a flower like thing that we eat if they can make much larger somewhere it makes smaller so if you can understand what is the genomic signature that gives you the larger cabbage possibly you can engineer plants or the leaves for example spinach leaves again so you know a variety that makes huge leaves if there are signatures you identify you can get it.

Like ways for tea plant, coffee plant we can go on for flower and so on, so this another you know line of investigation one can study plants for their unique phenotype that could be of advantage to the humans and also the parasites for example. The parasites have evolved from free living species right so you have species that are parasites there are you know there are close related species that are free living.

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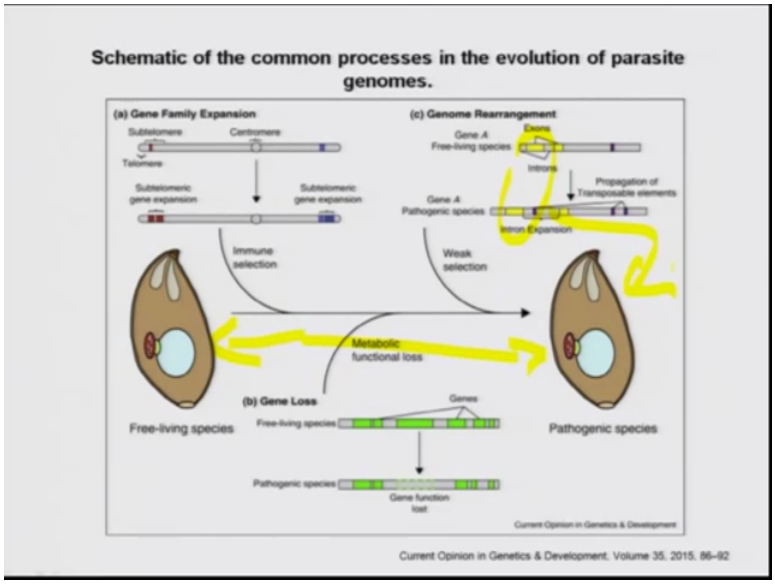

They do not infect any organism, so if you can compare the genome of a parasitic species with a nonparasitic closed living species and compare the genome you can understand as to what are the genes that has given that ability to become parasite, so then you can target those genes or the gene products to control the parasitic infection right so there is another advantage directly to the human that you do. So the the approach is what we discussed or just gives you an idea as to how

one can approach. The outcome is endless, it all depends on what you are looking at how you want to do, what are the technologies developed.

So it is you know unimaginable in next 10 to 20 years you are going to see you know a revolution in in functional genomics because this just the beginning where we are trying to understand genome at large how it functions. It regulates the gene expression, protein expression. How the cell functions, tissue functions and organisms functions and if you can understand likewise for a variety of species possibly you will get more insight and help us in either you know preventing disease or controlling the disease or increasing the desired phenotype in in the plants and animals that that we are directly depending on.

So you are here to witness such changes in next time years it is going to be very dramatic and if you want to look into any field that is going to really make a huge impact on the human society it is the functional genomics and thanks for joining us in this course I hope you enjoyed.