Functional Genomics
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Lecture No 01
Introduction to Functional Genomics

So, welcome to the first lecture of the first week of the course a functional genomics.

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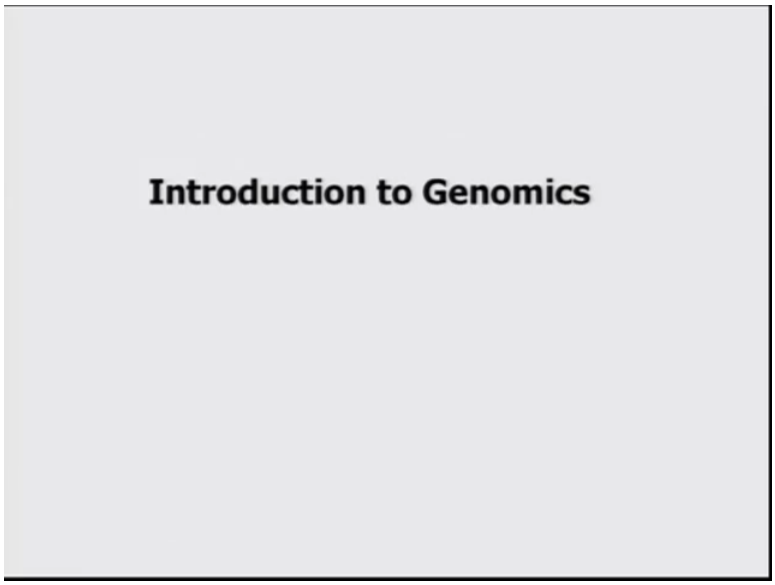

So, in today's lecture we are have going to look into the growth of a field called genomics. How did really this particular field came into existence and what the main people who contributed to the growth of this course or whether the field and so, this can be bit history but very important and interesting. So, I thought I would share with you.

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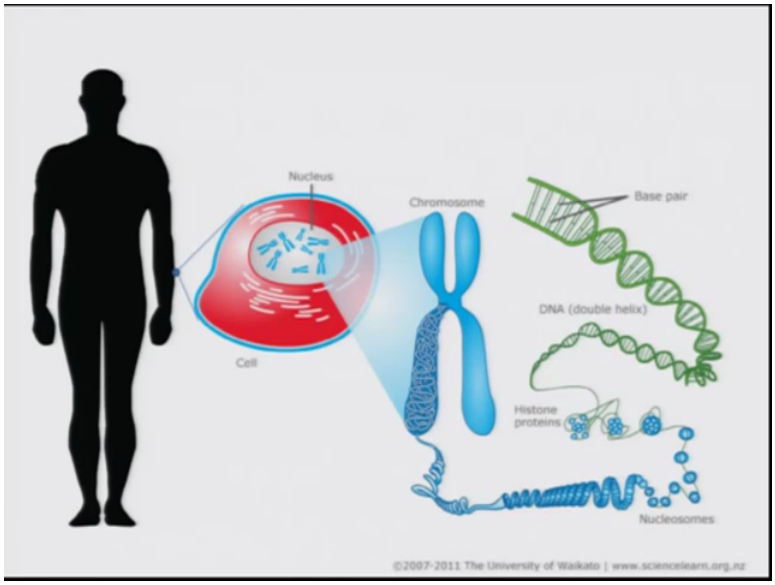

If you look into our you know, human body then you know that the smallest unit , in terms of functionality you can call it as a cell and cell as all of you know, has got chromosomes, which has got DNA and that is what the genetic material which has all the signal as to how the cell as to function specific to that tissue that it is present in and how that tissue contributes to the function of the system that it has, the skin beat digestive tract and then how all the system gets integrated in terms of function to be successful organism.

So, the basic information that a cell needs or the tissue requires or organism requires is present in your DNA that is our belief but we do not know really, how and what way the sequence information is understood and the cell is able to perform its function. So, one of the major question is that most the scientist have been asking since, centuries back is to understand how the genetic material (())(2:00) or what is fundamental you know, information that is present in the cell and how that information is retrieved and executed. So, that you can go back in history and we will look into some landmark discovery is as to how we understood.

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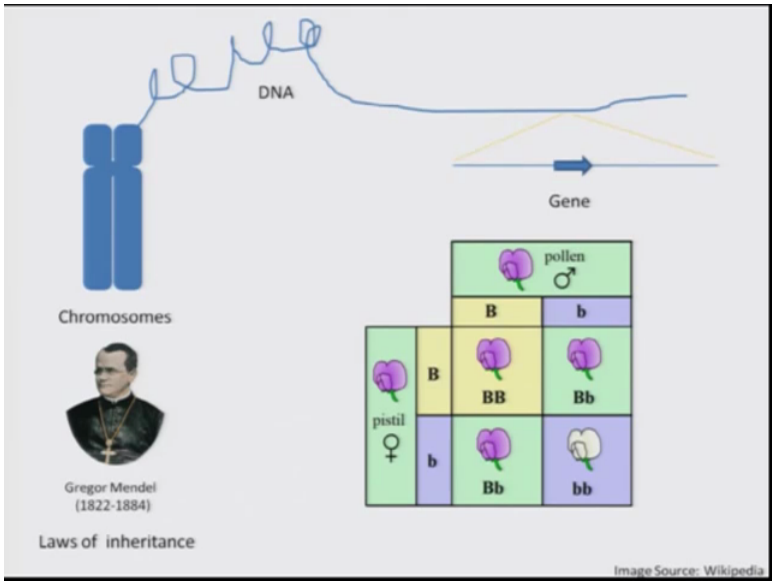

So, if you look into the chromosome as shown in the slide, you can pull out the DNA from the chromosome, you know there from the top to the bottom what you call the telomeres (())(2:25) the two ends of the chromosome. Inner is (())(2:28) one double helix (())(2:30) run all the way. So, that is what you call is a DNA. And of course, a small segment of the DNA constitutes a functional part of a gene. So, this gene has all the sequences that that constitute the the gene in terms of its function. It includes for example, the region gives you the , signal as to where the transcription should begin where it should stop and and which sequence the RNA should be translated meaning copy it for making, amino acids to form peptide and so on.

But if you look in the history that the first time somebody really talked about that there are , certain factors that are there in your cell, that gives you a particular phenotype. When I say phenotype, it could be any of the , changes that you see in a body, for example, whether you are able to roll tongue or you are unable to roll tongue or the way your hair, structure is whether the straight or curly or for example, you have free ear lobe or it is fused, sometimes it could be your height and there are many other such phenotypes that are regulated by your DNA.

So, what is that in your gene genetic material that really regulates. This understanding comes from one of the pioneering studies done by this monk called Gregor Mendel, he looked at plants as most of you would have studied, on to some of such contrasting characters like height of the plant, the the color of the flower, this the size or the shape of the seed and so on and try to

understand whether whatever factor that determine as to what should be the phenotype be the height of the plant or color of the flower or the shape of the seed whether these are transmitted from one generation to the other and how they are transmitted.

He looked at, he did some really amazing experiments, you have to go back and study the original literature you can understand, how beautifully he selected the plant. How beautifully, he selected the phenotype and came up with hypothesis then he called as there are three hypothesis, we talks about segregation, dominance and what is called as independent assortment which we call them as a laws now because every gene obeys, whatever hypothesis that he proposed therefore, he call them as laws.

So, in that was the birth of genetics. Generally, people consider because that is a one that really give the fundamental understanding as to how the genes can regulate without you know Mendel of course did not know that there is a DNA, there is a gene but he said these are some factors and beautifully as shown and still if you look into the human population or animal or plant and this is what you see. They you know all the genes and their phenotype obey, the three hypothesis that Mendel proposed and that is why we call them as laws. So, that is the pioneering discovery and that let to, a kind of a concept that there is something there in your cell that is transmitted to the next generation that governs your character.

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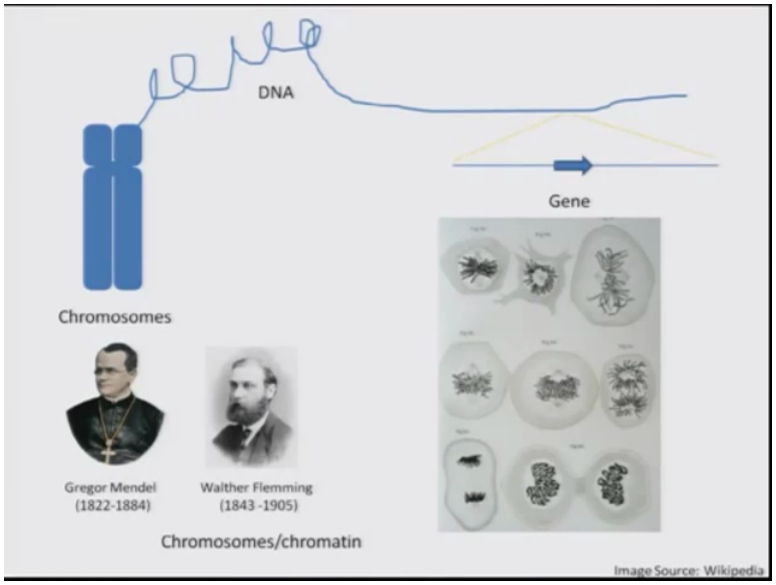

Almost to the same time somewhat overlapping is another person who came called flemming. Flemming again you know he looked at plants but not like Gregor Mendel. Mendel looked at plants as a phenotype; the he looked at how the plants look like, what is height? What is a color? What is seed and he really did wonderful experiments. He crossed them looked at the second generation, (())(6:32) generation came up with the last but this gentleman Flemming, he did phenomenal work. He looked at, the cells of the plants. Okay. These cells as to how do they divide. So, (you) what you see on the right side, in the in the power point slide is one of the drawing that he made after looking at the cells that are dividing.

So, you can for example, those who have done biology in their school you must of used the onion root tip to look at, you know how the cells divide mainly the mitosis. So, basically he also did very similar kind of, you know he is one proudly started with such kind of analysis and drew all these different stages and you can see beautifully the chromosome that are forming in the meta phase and how the cell is about to divide and you have this, cells about to divide and so on and he came up with, you know the theory as to we call them as you know, the concept that you are talking about now, chromosome and chromatin, meaning you know the chromosome is a distinct entity which is different from the other.

Chromatin is you know what you call as a DNA with the protein that forms the compact structure. Now, this is what he drew and he called them as chromosome and chromatin. The very concept that you have something like this, which becomes compact and when the cell divides they are sorted as come from this gentleman Flemming. So, that is his phenomenal contribution, we can see when, you know possibly it could have done.

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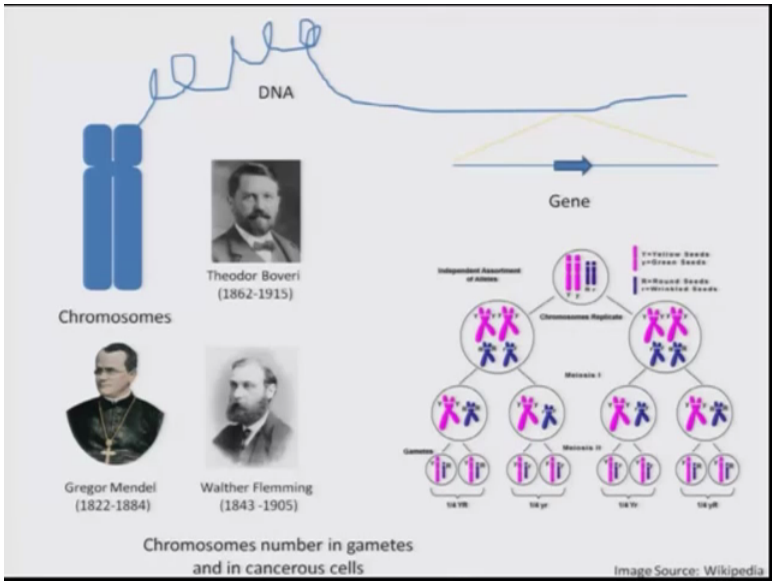

And then came another person, Boveri. You can again phenomenal, he basically looked into the chromosomes and he looked into what is called as meiosis. How cells divide in the germ cells that makes gametes. So, he looked into the reductional division whereas Flemming looked at your mitosis synomal cell division. So, Boveri really gave a kind of explanation as to what Mendel has proposed that is that you have different forms of the genes what you called as a alleles, for example, a gene could determine your height. So, you may have two variants of the gene, one that gives you tall phenotype, the other one gives you somewhat short phenotype and these two, you know get separated during what is called as gametogenesis.

Therefore, if you cross a plant that is tall but having one allele that is, you know when giving the phenotype that is note that tall and cross it with another plant which is not tall then you would expect in the next generation 40 percent of them not being so tall, right. So, that means that chromosomes you know the two alleles are sorted into two gametes when the cell undergo meiosis and basically, he looked into the meiotic process and he has shown that you know this chromosomes gets sorted and they become you know kind of reductional division happens and that is something that his contribution, again it is very very major contribution in terms of understanding how the genetic material then they do not know that it was genetic material but whatever, it is he get sorted in the self.

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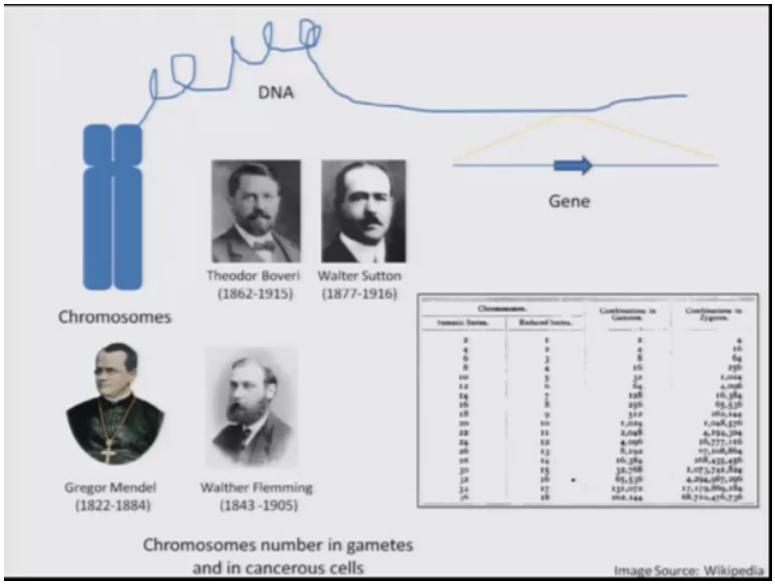

But almost at the same time these all three people Mendel, Flemming and the Boveri all from European origin and they were working from the Europe, but at the same time Walter Sutton he is an American, who also was looking at the same phenomenon as to how the chromosomes are sorted in meiotic cell and what is shown on the right side, this is one observation. He basically has shown that a cell, which is undergoing meiosis at the end of cell division, the number of chromosomes become half. So, we can see that what he call as a somatic series, the chromosomes he named by then and then you say somatic series if it is 2 in the reduce series it will be half of it.

So, he has basically shown that how the reductional division takes place and then he spoke about combination in gametes and combination in zygote when you know this , 2 gametes the sperm and worm and when fuse together to form what you call as zygote. How they again restored the original number that was seen there. So, basically if you know looked at all these things and that is how we as shown that there is meiotic cells undergo what is called as reductional division that is an amazing discovery. So, these all , you know independent Boveri and Sutton have done independent observation that eventually turn out to be the same.

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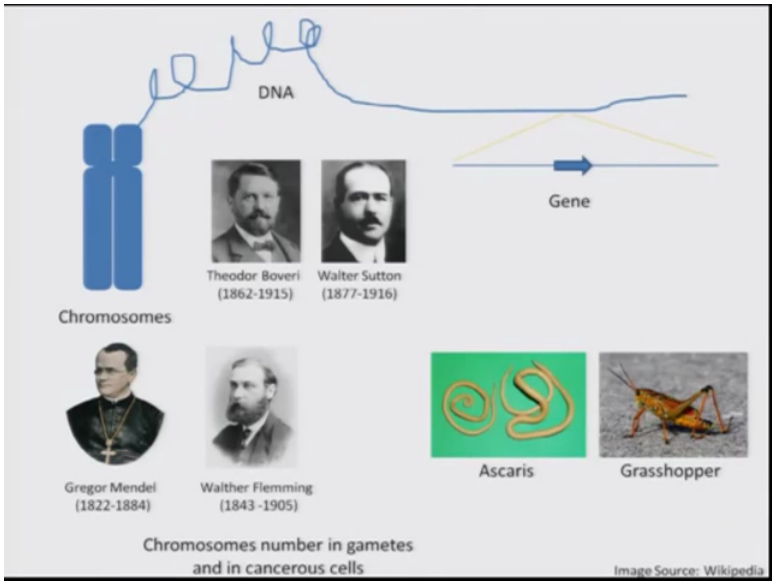

What is interesting here is that what kind of organisms they have used to understand this , phenomenon whether it is mitosis or meiosis, which pretty much you know universal. So, you know whether it is the plant, animal, human you find the cell divide to grow or to repair the damaged part by mitosis, right. So, there then you know DNA replicates meaning makes another copy and then eventually cell divides (())(11:47) what is normal number of chromosomes, but it is was very difficult you know note not until 1960s, people have not really looked into the human system because it is very difficult.

So, they have used a variety of different organisms to understand like, for example, Flemming I said he looked into plants and because easily one can do the preparation and see the chromosome, that is why he named it as chromosome and chromatin, but Boveri and Sutton, they looked at meiosis which is very difficult. So, they went and looked at animal system. So, much of our understanding in the early years for mitosis have come from plants whereas for meiosis have come from animals.

Although, such cell division do happen in the plants as well when they you know make the sperm. Boveri used here worm call Ascaris you know, he looked into the looked into that and then and looked at the meiosis process whereas Sutton looked into Grasshopper a obviously insect, American insect and in these spices you know the tissue that form the gamete (())(12:54) , the is this the soft one can dissect and looked at make you know make it , thin layer under a

microscope and then we can stay in for the chromosome and look at and that is how they have really came up with these discoveries right.

So, what is generally you know spoken as a descriptive science in biology? How come from such kind of observation that is nothing but looked at in on different snap shots of event that to plays when you fix a cell and observed them and try to correlate as to what could possibly the sequence and they came up with the discovery which is amazing. So, so in science this is nothing called descriptive or analytical experimental sciences science that you guys should remember whenever study anything. So, this is the system like Ascaris and grasshopper really contributed to the understanding of the concept that even talk about in the humans today whether, it is disorder or reproduction or normal growth whatever observation they have made in any of the system, really helped us in understanding what goes on in our body as well.

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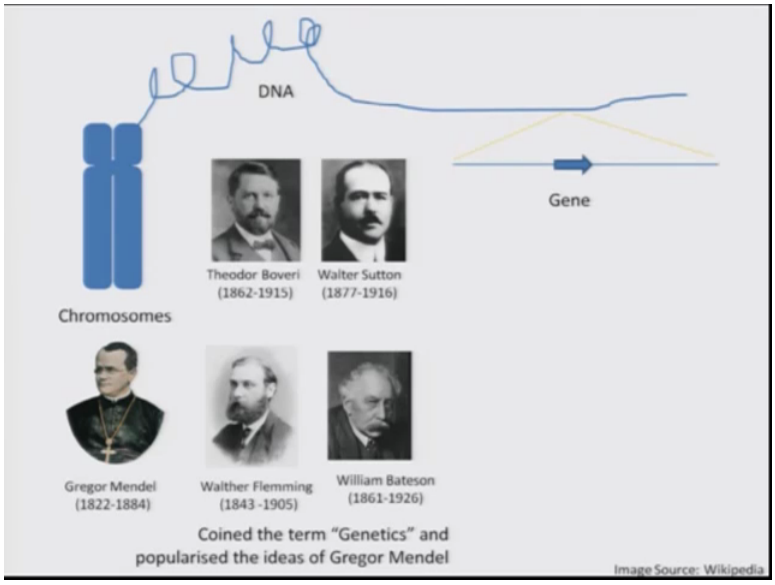

So, the fifth person I am going to introduce is a Bateson. So, he is again the one who made or term the the field called genetics is one who gave this term and he is one really understood what Gregor Mendel has done. By then until then Mendel's contribution was not known. He has done that and he recorded and left but nobody really looked into the implications, some of them who looked into felt like what he was done is observed is not explaining anything, it may not be applicable to humans and animals and so on but it was Bateson who really looked into Mendel's data and then he develop the field, he coined the field called term called genetics and then he

said what Mendel did applicable to each and every organisms. So, if pretty much popular as what Mendel has done then people took note of Mendel's contribution. When Mendel was no longer living. So, that is a legendary work that he was done.

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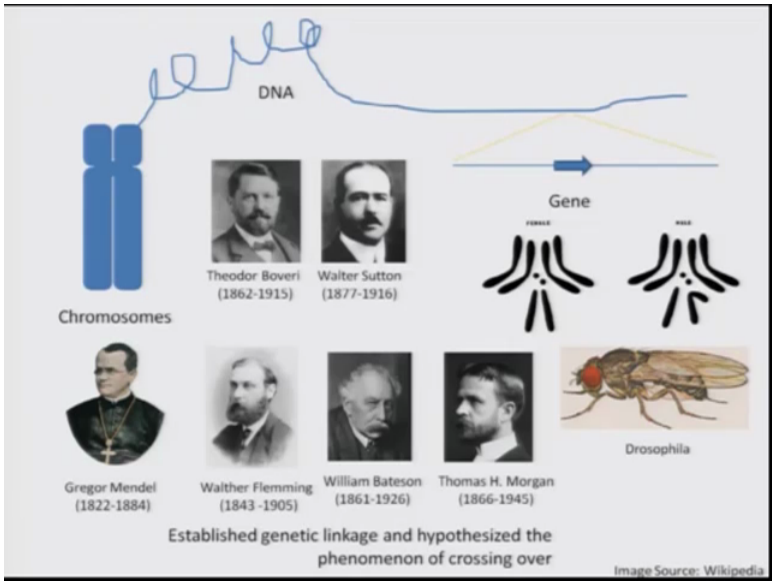

So, then there are people who really try to look into variety of model system to understand because depending on what question you are asking, you need to have appropriate model system to understand that is when a Morgan came an American geneticist and he started using the most famous model system that we have on drosophila. So, he basically went with what Sutton did using insects as a model but you found drosophila to be much much better for simple reason, one it has a shorter life span so you can cross them to have the next generation and so on because genetics cannot be, you know done without looking into the generations and two the organism has got fewer number of chromosome.

So, basically he wanted you know organism that has fewer number of chromosome. Therefore, in a wherever character that are linked to the chromosome or fewer therefore will be able to understand better. So, what is shown on the top here, in the in the slide on your right side is chromosome schematic of the chromosome from a female and the male drosophila, which you know of course you have this like human, you have (())(16:28) that are depicted on either side and then you have the sex chromosome which is XX or XY.

So, he has used this you know drosophila to understand the chromosomes and he is one who really established what you call as a genetic linkage meaning, there are different segments of a chromosomes and these segments represent a character like what Mendel's, you know said it could be a gene that determines your height or it could be a gene that determines, you know your any other phenotype, for example, in plants it could be, the color of the plant, it could be the shape of the seed and so on and he said that they are physically connected each other and then he also said in though, they are physically connected when you have a pair of chromosome which are homologous meaning identical but about to be separated during the formation of the gametes, each of the homologous could have what is called as say variant of the gene.

The other form of a given gene what you call as allele and there could be shuffling takes place meaning there could be exchange of DNA material from one homologue to the other and that we call as crossing over. So, he hypothesized everything by only looking at the chromosomes in the fly and then during different (seg) you know generations and then looking at what (we) how the fly look likes.

So, like Mendel he also selected flies that have variants in terms of how do we look like, for example, it could be the color of the eye, it could be the shape of the of the wing, it could be the size of the fly itself, their color, body color and there are many different , pattern that we will discuss little later. So, he has used that to show that all these phenotype just like Mendel did can run through in families meaning different generations and they are linked to the chromosome, some of them the same chromosome. Therefore, you can show that more often they are you know transmitted together, right.

So, this is the major difference between Mendel and Morgan because mendel whatever character he took, it so happen or he has selected those character that are present on different chromosome that is why his law, the third law what you called as independent assortment applies because that law applies to genes who govern you know characters, the genes are present in during chromosome that is why they are sorted independent of each other. So, this law does not apply two genes present on the same chromosome. There are because they would if they are closer to each other they going to go together often or separated there may be cross over but it cannot obey the law that he has given 9 is to 3 is to 3 is to 1 that applies only if they are present on different chromosomes.

So, that is where morgan has really contributed to show the linkage and he gave what is called as a say genetic distance between genes by looking into the recombination frequency and so on and this model what he developed become very famous model and most of the genetic, concepts and developmental biology what you call how the genes regulate development how come from this beautiful in a system that is a contribution of Morgan.

So, they not only contributed in terms of developing model but they also trained their students to ask more deeper fundamental questions, some of them which they could not test. One of his students Morgan's students you know later on to look at some other aspect but the concept the very concept what is called as chromosome theory of inheritance meaning your cells do have a genetic material which we call as chromosome and these you know chromosomes are transmitted to the next generation and chromosomes have certain segments which dictate what would you be your phenotype, we call as chromosome theory of in a written and this is called as theory then because it is purely observational.

There is evidence to show indeed that is the case because they did not know what the chromosomes are made up of and what to really dictates as to which phenotype should be there, they were not you know how clear about that, but they made this theory but now you know certainly, the chromosomes are the basic material and these people that that you see in the screen are the major contributors. There are many other who I did not discuss but these people are the major contributors for our understanding as to how the chromosomes contribute in terms of you know your phenotype that goes from one generation to the other so that is a major a contribution.

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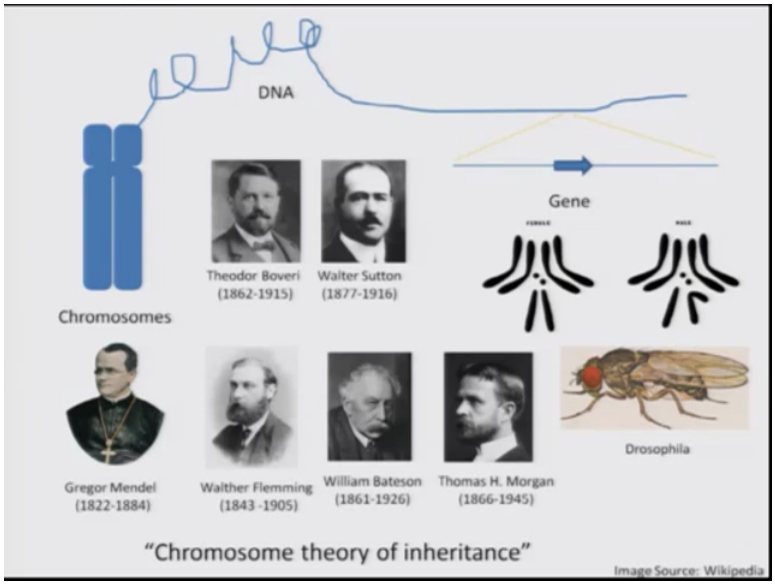

As I told you these contributions are not only in the science but they also trained the people so that is the that is where Morgan's legacy even today you see him because you know, he has trained students who took up newer challenges and develop new model depending on what kind of question they are asking and that let to discovery of genes and DNA and so on. So, let us look in here, for example, what is shown here in the cartoon is so for we spoke about the chromosome. The chromosome theory of when inheritance but you have pull out the DNA that DNA as I said as we know now has got segments which are the functional unit what is called as gene say, a chromosome could have thousands and thousands of genes.

Now, the question is how did we really know that the chromosome is made up of DNA because whatever , the previous section that we have seen whether is Boveri or Sutton or Morgan. They looked at something that are they are inside the cell that gives you particular straining property which becomes compact you know segregating to the daughters to cell, there are dividing but they name it has chromosome without knowing what it is, it is like you are seeing something but without knowing what it is. Similar way you know (())(22:36) really, there are many scientist who looked into what is this chromosome? What is a chemical composition of the chromosome and how that chemical moiety or biomolecule that is present there really gives the information as to what phenotype you should have.

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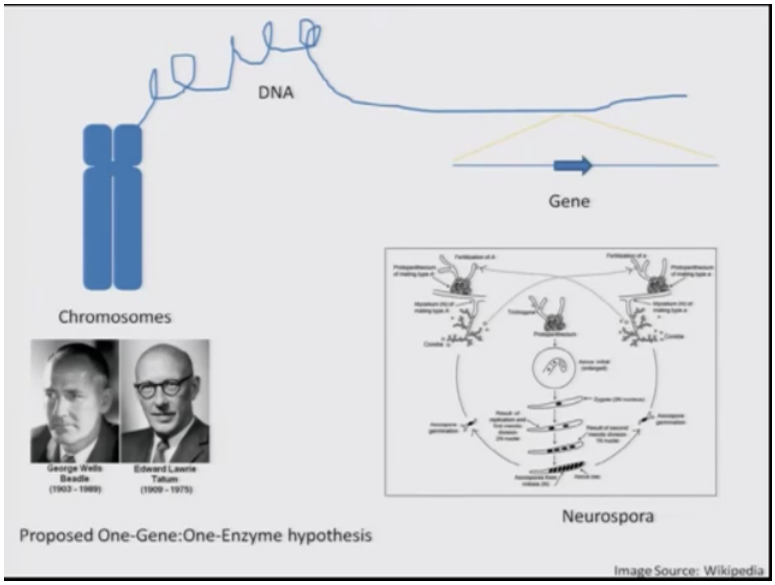

So, that has come from again you know several scientist who came after morgan, two of them are these people George wells and Edward Fleury. These are the people who gave the theory called one gene one enzyme hypothesis. This you look into the text book even in biochemistry textbook or genetics, this how it will be called and is very very (())(23:19) because they said that there are certain segments in the chromosome that gives an information as to what protein should be made and so happen here you know obviously, that protein in an enzyme that the looked at.

Both of them are students of morgan, both of them were trained in drosophila and and then all the genetics that we discussed sometime back but they felt you know the how to go deeper, deeper than looking into just chromosomes and looking at you know next generation what is phenotype? we have understand how whatever that is there in the chromosome that dictates as to how the organism, the fly for example behave or what phenotype it has. So, they found that system the model system is good for genetics meaning looking at the chromosome on segregation pattern but is not so good in terms of you know understanding what kind of information that the chromosomes gives. So, with that available tools that they had they could number go deeper. So, they looked at some system where they can go and study for example, you know proteins meaning enzymes, their functions and so on.

At the same time they use the same technique that Morgan used that is creating you know mutations. What he did was he looked into different flies where in there was natural variation

that variation resulted in different phenotype whether, it is eye color or the body structure or the wing shape and so on. So, they went for a system which of course can be you know (which we) which you can create certain changes whatever the genetic material and then look at the phenotype and then now go at the protein and study the protein. So, they selected system called neurospora, it is a it is a fungus mold and there are forms what you call as a applied meaning just like a gamete like just one copy of the genome or deployed which is two copies of the genome and so on and you can create mutations and then look into isolate for exam you can grow them and you can extract protein from there and understand the function of the protein.

So, they went and looked at the biochemistry enzyme activity and so on combining genetics with bio-chemistry and they came up with clear understanding that there are certain phenotype that are caused due to enzyme deficiency and these are linked just it could be one gene which thus by then they have given this term called gene, a segment which possibly gives information as to what function you should do here, it is a protein that as an enzyme activity. So, they develop this particular model system to understand the protein. So, protein became much easier for people to handle still DNA is for a way.

So, they started studying protein fat enough we will talking about little later, we were able to sequence the protein much earlier we will that than we could sequence the DNA. So, much of our understanding and the protein have come much before the DNA sequence, DNA structure was not even the RNA years old know structure or if sequence was sort solved. In that way they were pioneering, in terms of connecting the protein with a gene.

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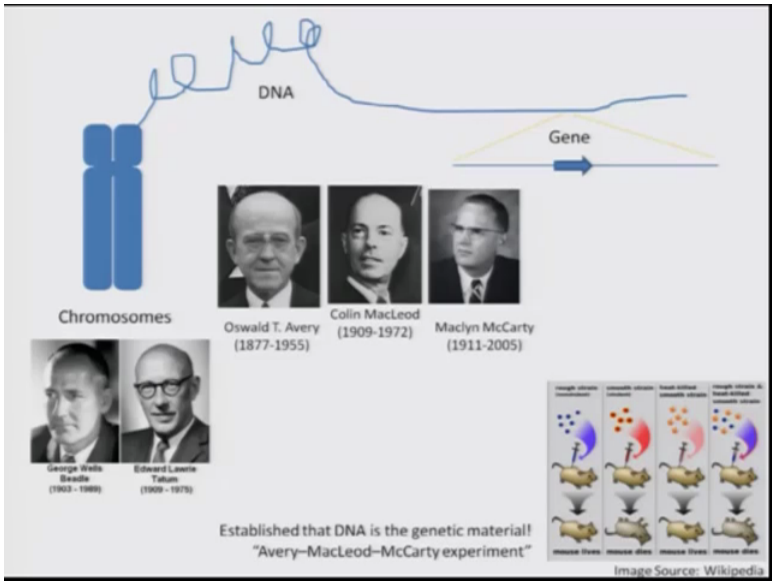

Then we have (())(26:48) people, again must have studied this in the text book, this is Avery, MacLeod and McCarty, these three gentle man together in a proven that the DNA is the genetic material. Although, the protein Wells and Laurie did say that protein connects to the DNA or gene without knowing what is the gene is but these are the three gentleman who really, you know established that DNA is a genetic material. By then we know that you know all the living system that as cells have got three major biomolecules the protein, nucleic acid and the lipid and they are able to carbohydrate and so on and there were able to show that it is not the protein but it is the DNA that gives the phenotypes.

So, you must have studied about how they have used the microbes that are virulent which can kill the animal and they are able to separate the protein or labels protein and DNA mixture them and then able to show that DNA is a one that that that gives the phenotype the virulence right. So, you can look into that. I am not going to the detail but most of the textbooks really talk about it.

So, what you will see now there is a shift. So, in the in the when the theory was about the chromosome we looked that there mostly plant and insects being used to understand how the chromosome functions but now you will find all of a sudden people are going to the new system because the question that you ask is very very different you find that neurosporal fungus was used and there you will find again quickly that these are microbes that are coming in fact from

the the concept called as molecular biology where you really look into the molecule whether it is you know whether it is DNA or RNA or protein all these understanding are come from microbes because they are much easier to handle and grow them in the culture and then the complexity is less. So, you find now that you know really the understanding of the microbes let to the field what si called as molecular biology that led to the genomic cell comeback little later.

Of course, this is considered to be the landmark discovery. There are controversies as well that it is Watson and Crick in 1953 who proposed model for the DNA. So, although the Avery, MacLeod, McCarty they did say the DNA is a genetic material. The structure and how we that particular molecule can function genetic material was not understood until Watson and Crick solved not solved a propose his model that is what shown here. This is on the right side of the screen what you see is that seminal paper published in nature just page, in a proposed model for the DNA double helix, it is model now you know that it is no longer model that that is indeed the structure and that basically gave an understanding has to how the DNA has a genetic material can function because it is double helix.

It is anti-parallel, complement, reverse complementarity all these things help the DNA to function as genetic material because one of the strands can serve as a template to make a new strand and likewise the new strand can be a DNA or RNA. If it is RNA, it is perfect copy of what sequence is there and that can go on give the signal as to what protein it has to make. So, in that way it was you know considered to be a land mark discovery and and in all the textbook describe as to how important that discovery. So, that is the birth if what you call as molecular biology. So, the moment we know that there are four basis and they complementary to each other and base pair and form a structure like this anti-parallel and then people just started studying into how the DNA is copied into another copy of the DNA or to RNA and how really that functions as a biomolecule.

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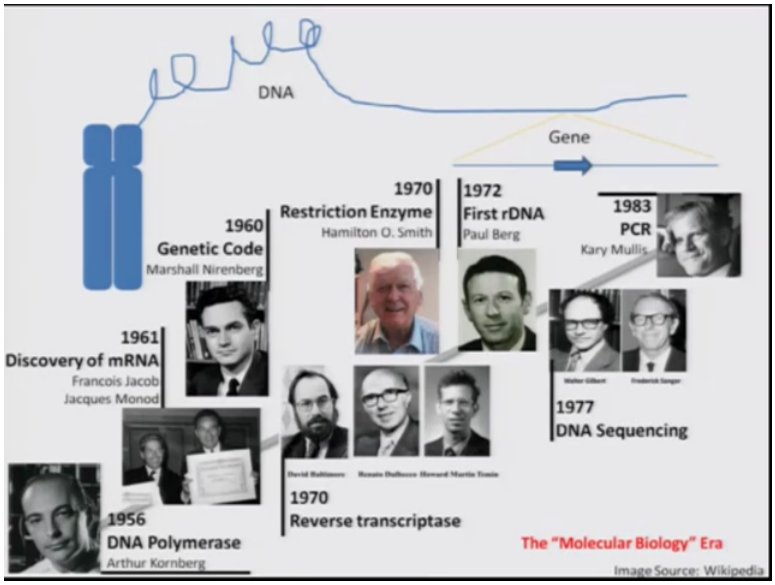

So, we are going to discuss now is about, 40 years of history where what you call as molecular biology era, so that basically plate the foundation for what you call as genomics now, so without this revolution of what is called as molecular biology we would not have reached what you see as a genomics. Let us see how this journey begins. It all started with Kornberg who looked at again, this whatever you are talking about from 1946 to 1990 is going to be most of them are studies based on microbes whether it is microbes whether is a phage, bacteria and so on e coli and so on, yeast and so on.

So, Kornberg is a one who really looked into the process of DNA being copied. So, he looked at an enzyme which reach one of the strands and then makes a copy of it. It is seminal discovery again you we know because in terms of how the DNA may can be copied because that is important for the cell to divide. The cell has to divided as to make a copy of the entire genome and then you know, put them into two daughter cells that is how we grow. So, that is fundamental for any living system whether you are multi-cellular or unicellular. So, it is a seminal discovery that started with that.

Then we came Jacob and Monod because there are the people, who really you know shown how DNA is copied into what is called as messenger RNA or mRNA and what you study in textbook what is called as Jocob-Monod pathway, the Lac operon and so on are the discoveries which talks about even how the gene is organized? What are the different elements that control the

function of the gene and how mRNA is made, copied and how the RNA is important for whatever phenotype you see. So that is very seminal discovery that came in 1961.

Then we have this gentleman Marshall Nirenberg again an American scientist, who desified the genetic code the triplet, the there three basis together gives a code as to what amino acid should be made when the RNA translated meaning decoded and later of course we have our scientist of Indian origin, Khurana really helped in, in a solving all the you know that different codes code on that you have in the table, they are the people who solved it and but but the siminal contribution that that three basis together form a (())(33:55) come from the study of Nirenberg.

In 1970, there is a another landmark. Here, they looked at another enzyme which copies the RNA into DNA what you called as reverse transcriptase. This reverse transcriptase came from, the group Baltimore, Delbanco and Temin they contributed in understanding a special polymerase which you know copies the RNA into DNA that really helped us to understand you know how the virus functions and how they are able to infect other cells the virus that have only RNA as a genome and that is the discovery part but that really helped us to make several tools, for example, we understand now what are the RNA that we have we convert them into DNA that is doable only by this particular enzyme called reverse transcriptase in that way that is seminal.

Then came in a 70, Hamilton Smith discovered another enzyme again from microbe. These are called as restriction enzymes you know now that these are the enzyme that can identify a unique set of sequence in the DNA and make a cut tab and regardless how much enzyme you add these enzymes would cut only if subsequence is present not otherwise. So, that really revolutionized you know the way we understand DNA because the so called recombinant DNA meaning, combining to you know DNA from two different source is possible because of this enzyme because now, we can cut the enzyme and join them sticks them together so that again is a fantastic achievement and that let to you know for the first time Paul Berg made a DNA from two different source what you called as rDNA or recombinant DNA that is again a seminal discovery that you can sticks the DNA together and form a new synthetic DNA having different source is something amazing because that is what we use every day now in recombinant DNA technology or molecular biology genomics and so on.

In 77 as again a landmark , Gilbert and Sanger came together and proposed a method or a established method to sequence the DNA until then we are talking about DNA as a nucleic acid without really having no tool to understand what is a sequence, much of the protein sequence are known from protein sequence but these are the people came up with the method that we call as dideoxy sequencing which is very efficient tool for sequencing the DNA. They proposed and they establish, they are shown that can be used and that let to you know enormous data because then every lab started sequencing DNA and RNA because now, you have reverse transcriptase. So, we can convert the RNA into DNA and sequence the DNA.

So, basically you can understand the sequence of RNA from from DNA using the same method that again is a seminal contribution and last but not the least is the contribution from Kary Mullis, we used all this principle right from the 1956 or Arthur Kornberg principal that there are enzyme that copy the DNA to the double helix concept and so on. What he came up with his simple approach to make millions of copies of a small segment of the DNA using an enzyme DNA polymerase and the four basis of the DNA and we can make in a tube quickly in 5-6 hours in enormous copies that that is these method has really changed the way you look at, the DNA because earlier tube used to put the DNA inside a host for most often E coli and allow e coli to grow and make copies on its own way, so that is you know removed all this botel naxen and you are able to make millions of copies of a small segment so which is now being used every day, in clinic, in labs for diagnosis, for any other such kind of approach.

So, in that way the contribution that we have talked about from 1956 to nearly 1980s is something which you call as molecular biology era because they are able to, understand, analyse and manipulate the DNA and that led to the field what is called as genomics and that we will see in our next class.