Human Molecular Genetics
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Module - 02
Lecture - 05
Pedigree Analysis

Welcome to the second week of the lectures for the course human molecular genetics. In the previous week we looked into the concept of central dogma of molecular biology, where we looked in the genetic material, how, what are the experiments that led to understanding as to how the genetic material functions, how the information is processed and how defects in your genetic material can have an effect on the cell, system and organism. So, today what we are going to look into is how we look into the human population, or the family and understand the phenotype that you see which is resulting from the defect in the DNA; we can track them as to what kind of inheritance that is running through the family, the characters that run through the family; what kind of inheritance is there and how that information can be used to predict the onset of such diseases in the future generation and also to identify the chromosomes that could have the defect and eventually the gene characterization and so on.

So, we will start with a concept called as pedigree analysis wherein we talk to individuals that are affected with a given disease or at times it could may not be a disease, but a phenotype that is very different from a normal population and then see how it segregates in the family. So, this is typically called as pedigree analysis and that is the concept. So, let us look into one simple concept, what do you mean by phenotype?

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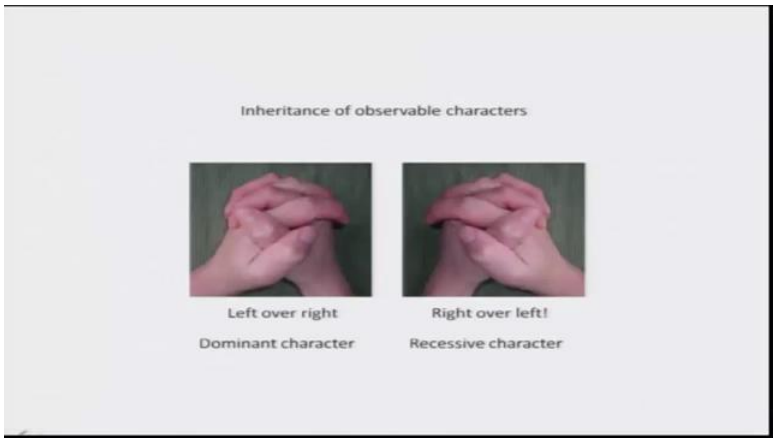

A phenotype could be any character that distinguishes certain individuals from the rest of the population. One classic example is hand clasping; when you close your eye and you clasp your hands, you would find always majority of us we will have the left thumb going over the right thumb. This is considered to be wild type, meaning the majority in the population would have such clasping behavior. But if you do it in alternate way, you will find it is difficult. You try it out; you close your eyes and try to close it, you will find putting your right over left, you will feel it is uncomfortable. So, that is what is shown in this slide here. The left over right is considered to be a dominant character, whereas the right over left is a recessive character, but still you see there are a good number of individuals in that population, who have this you know, character. That is again we believe that there could be genes that are underlying such character. So, this is one such character that you have seen. So, this perhaps you can even trace it in a family and that is how you call it as dominant or recessive, because you can trace it in the family and that is being inherited. That is with regard to a character which may not necessarily affect your normal life it doesn't really matter, the left comes over the right or the right thumb comes over the left. If you are alright you can play cricket, you can, you know cook food, you can do your studies, absolutely it doesn't affect.

But at times there could be other characters which could affect your survival. For example you are blind and that could be because of some genetic defect that are there in your, DNA and that would affect your survival or you may not be able to hear, hearing impairment or you could have other problems which again run in the family, because the defects originates from a defect in the

DNA. Therefore the DNA is transmitted from one generation to the other; you could trace it in the family. So, how you really do that? Let us look into the classic way. So, whatever probably you have studied in your text book, so far we talk about the Mendelian genetics and more often you call also some of the disorders in human as Mendelian characters because, whatever laws that Mender proposed, it applies even to many of the genes that and the phenotype that you see in the human.

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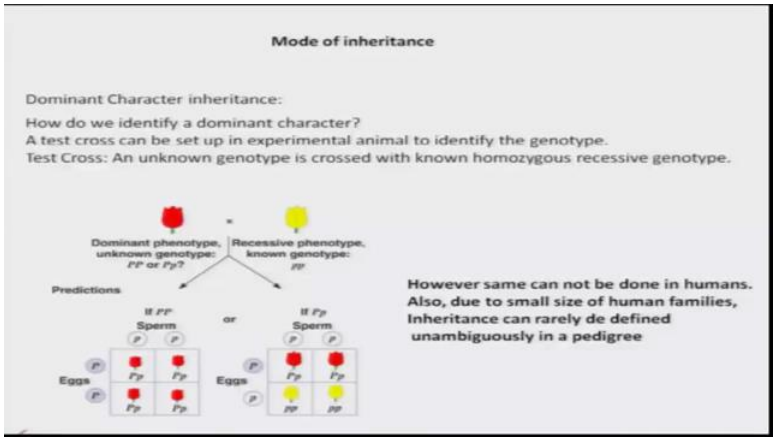

One of them of course is the law of dominance, wherein he suggests that one particular trait is dominant over the other and if you could remember that he has used certain plants and certain characters for proving that hypothesis and we call it as a law, because now majority of the genes obey that and for example what is shown here is the flower colour. Let us assume that the orange or red colour flower is dominant over the yellow and, we can, pretty much test whether the dominant phenotype that you see, the orange colour is because of a particular genotype. For example, whether that colour is because of a heterozygous condition, only one allele is dominant, other one is recessive or it is a homozygous for the dominant allele. That is both the alleles are for the dominant phenotype. We can test that by doing what is called as a test cross, which is a classic example; you must have studied in your genetics.

You cross the plant with a plant that gives you the yellow colour flower, which is a recessive phenotype. Therefore you would expect that genotype to be having an allele which is homozygous for the recessive phenotype. So, if you cross we can see what would be the resulting

F1, what would be the resulting phenotype. You could have two different scenarios. Assuming the dominant phenotype is because of a heterozygous condition or a homozygous condition for the wild type you could expect as shown here. See, it will be all F1's either or displaying the dominant phenotype that you would expect if the plant that you have chosen is homozygous for the dominant allele. But, you would expect for example 50-50 of the progeny showing both the dominant phenotype and recessive phenotype if, that plant, the dominant plant having a genotype which is heterozygous for the dominant allele. So, these are, likewise we can do it for animals and many other species. But, it is practically not possible in case of humans, because here this is; the marriage is what you call otherwise as mating it depends on many other factors, not necessarily for testing anything. So, here normally what we do is we infer from what has happened; you cannot test anything, but infer from what has happened in the normal course of marriages and mating and so on. So, that is called as pedigree analysis.

By talking to an individual of a family and trying to understand who are the other members of the family and who are the members who have a particular phenotype and their history, medical history and so on, who marries to whom, how many children and this kind of information you put together to construct what is called as a pedigree. So, how does that really help?

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Let us look into this picture which represents the very famous family in India, the Nehru-Gandhi family. So, you have here two Prime Ministers, ministers and politicians, everyone in this

particular photograph. So, what it, this picture shows is that you do have important members of the family, but it doesn't really explain how they are related to each other.

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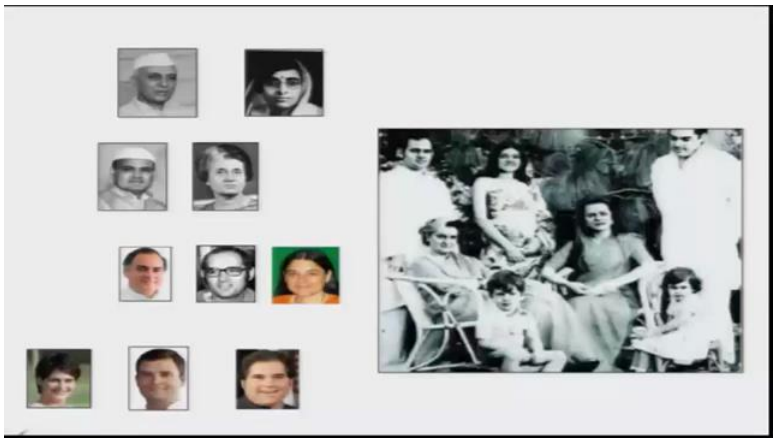

If you expand the family they are, these are the very prominent members of the family; starts from the first Prime Minister of the country, Nehru and his wife and next generation, again the most powerful Prime Minister Indira Gandhi, her husband Feroze Gandhi and in the next generation of course you have Rajiv Gandhi who was then a Prime Minister, Sanjay Gandhi and his wife and so on. So, this easily you can see that there are members, but how do you really see in which way they are connected? So, this we do, by way of connecting them, we will be able to make a pedigree.

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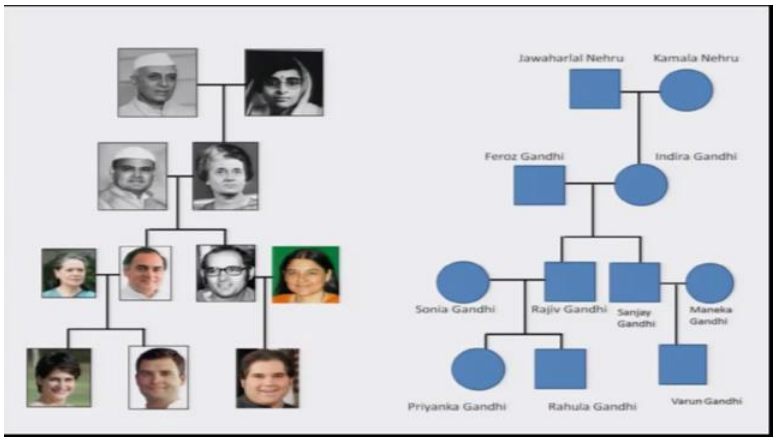

So, for example here, the biological father for Rahul and Priyanka Gandhi are Sonia Gandhi and Rajiv Gandhi. Likewise we can go up and so on; we can go up in the hierarchy, in the generation and you will be able to tell how each one is related to the other. So this is, this is one way of connecting the family and explaining how they are related to each other. The same thing is done, by using certain symbols we try to represent the different members of the family, their generation, in what way they are related and so on and this is what is shown on the right side. So, you have symbols; we have replaced the symbols with the photographs. Again it represents pretty much the same family and we can show. So, this is one way of depicting what is called as a pedigree.

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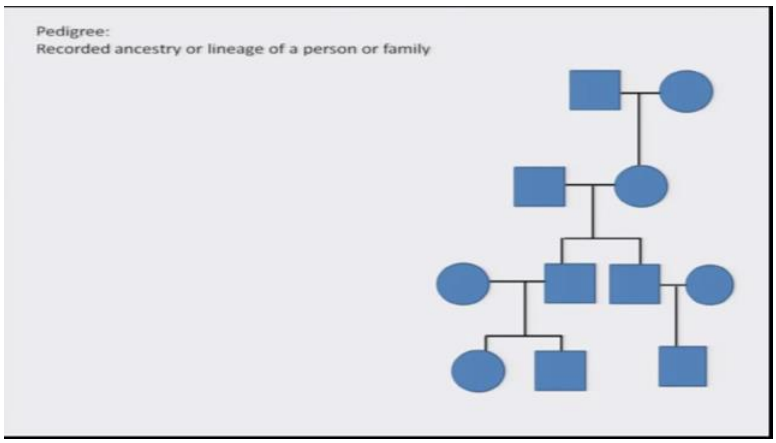

Let us see how do you really do that? So, you talk to individuals and construct the pedigree, because you may not be interacting with every member of the, the previous generation. For

example the great grand-parent may not be living now. But still, you will be able to talk to their children or other relatives and still you will be able to understand what kind of phenotype they had; whether they were normal, what are the other conditions they had that really helps in constructing a pedigree. So, let us see how you really do this kind of recording. So, there are symbols as I said; some of them are already shown.

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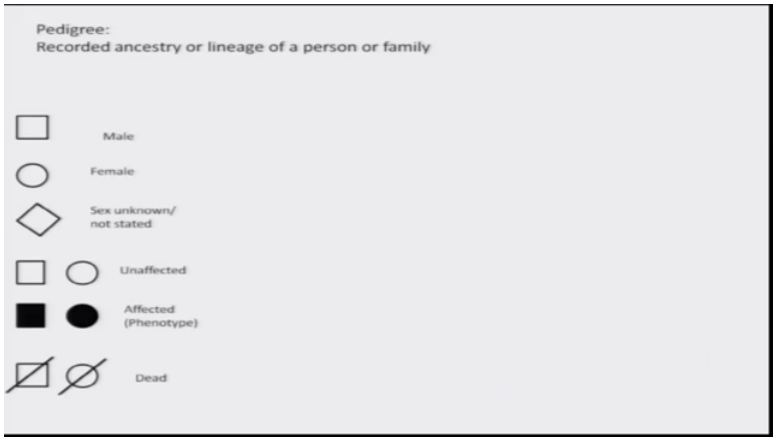

I am going to tell you some of the very important ones. For example, the square is a symbol for male and, another individual if you make a circle that individual represent a female. So, these are the two sex that we represent using symbols; square - male, a circle represents a female. At times you don't want to reveal the identity of an individual or, when, someone passed away even when they were developing in the, inside mother, so you don't know the sex. So, when you do not know about the sex or when you don't want to reveal the sex of an individual you can use this particular symbol; so that really doesn't denote as to what is the sex of that individual.

Likewise if you have this symbol, whether it is square or circle and if they are unfilled, open, that suggests that they represent the wild type, meaning they are normal. They don't express the phenotype that you are trying to show in that particular pedigree. But on the other hand if you have filled like this, that represent that these are the individuals who developed or who display the phenotype. The phenotype could be something like what I said. It is closing your, you know clasping your hands the left thumb over right. That is a phenotype that you are looking at or it could be a disease; the affected individual. So, it depends on what you are trying to show in a

particular pedigree with regard to how it is being inherited. As I said there could be multi generation family; you may have four generations in a family and not all the members of that four generation family may be alive today. But you want to even display that in your pedigree. So, you can show that by putting a cross, across either the male or female that particular individual that would denote that they are no longer alive when you made the recording of the pedigree. So, this how you do it.

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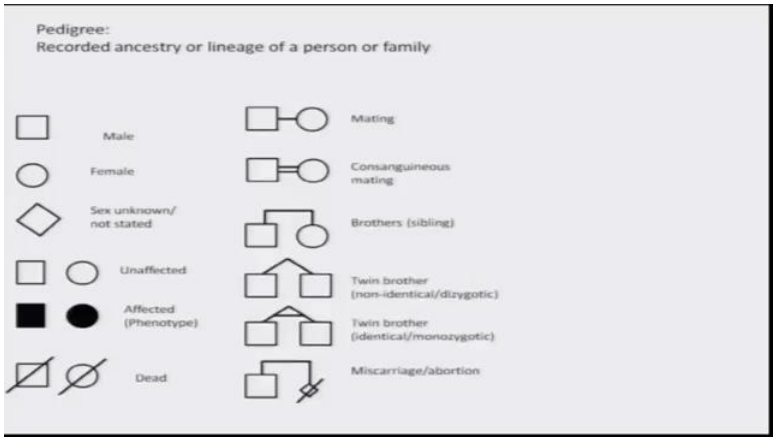

There are more symbols. So far what we have discussed on the left side is individuals and their status, but now we are going to show how they are related to each other. Normally when you draw a line between two individuals, obviously it would be between a male and a female, that represents the mating; that they are the biological parents. At times there could be two lines like this that would denote that these two individuals are related. For example marriage between cousin; for example I am marrying, you know married to my aunt's daughter for example; know that represents what is called consanguinity. So that represents consanguinity suggesting that they are genetically more closer; this is a marriage within relatives.

Now, how do you represent the second generation? So, if you have a line on the top and they are connected on the top that represents that these two individuals are siblings. It could be brothers, it could be sisters or it could be brother and sister, like what is shown here. You could also have individuals that are twins, they are born at the same time and they could be of two types. Either they are twin brothers, but not identical. They are, pretty much like your otherwise brother; 50%

you have shared similarity and that results because of two different embryos growing at the same time. That's why they are different from each other. So that is denoted by this kind of line, suggesting at the same birth you have two individuals or it could be what you call as twin brother that are identical resulting from the same embryo; the same embryo was growing, split into two and each half has developed into two new individuals. They are genetically identical, look alike and so on and that is identical brothers or sisters and that is denoted by a line here, as you see here. Now,, there are conditions wherein an embryo is aborted or it is a miscarriage; so that you denote by a small symbol and cross, because they did not survive. So, these are some of the symbols that we use to identify the pedigree.

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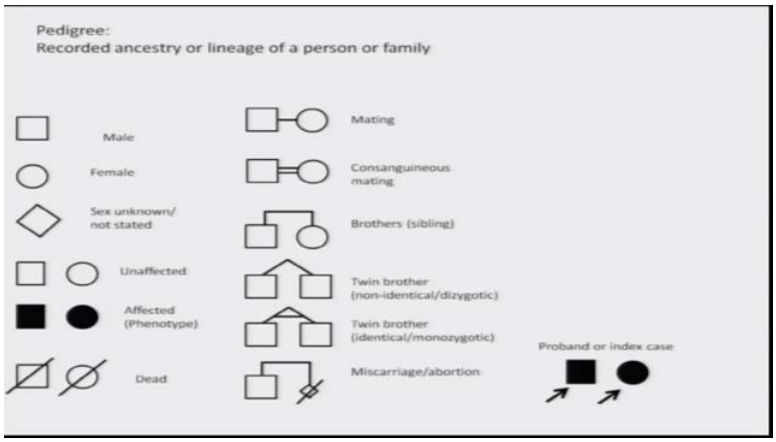

Two more, this is very important. This you call as index case or proband, because, assuming that you are a genetic counselor and there is a family that comes to you to take some input on, on the disorder that may set in the family, so you get to know of this family because of a particular individual who may have a phenotype. So, you talk to that individual, their parents, their brothers, sisters and grand-parents and so on. So, you get to know of the entire family because of one particular person.

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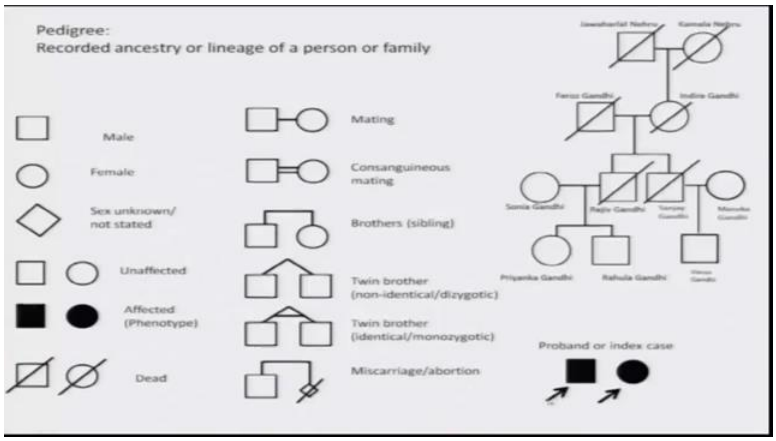

So that is denoted by an arrow here. So, that is called as the index case, or the proband. So, these are the symbols that we use to show the pedigree or to construct a pedigree. Let's do it now. So,, I have shown here now the same Gandhi-Nehru family with all the symbols that have been used here; we are showing that you have Jawaharlal Nehru, Kamala Nehru, no longer alive; next generation is Feroze Gandhi and Indira Gandhi; Indira Gandhi being daughter of Nehru and Kamala Nehru and again they are not alive now and you have next generation Rajiv Gandhi, Sanjay Gandhi, married to Sonia and Menaka Gandhi and you have the next generation. So, easily you can depict and you could perhaps in your free time you can draw a pedigree for your own family; as big as possible you can combine papers and try to practice. That would really help you even to understand how possibly some of the phenotype that you may see in your family is segregated which would help in some of the exercise that we are going to do little later.

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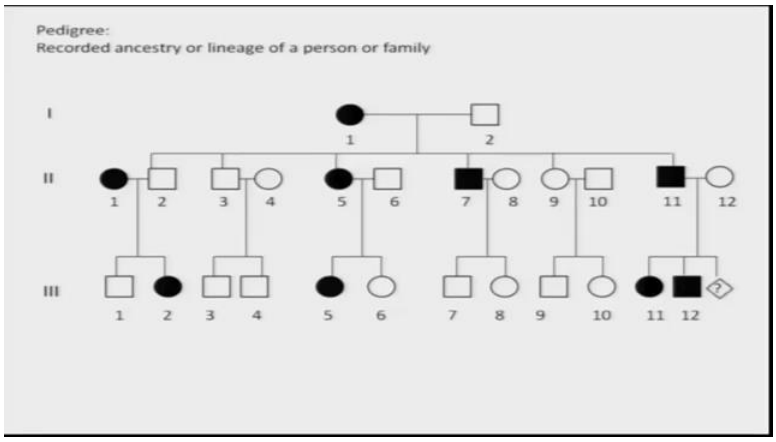

So, why should you spend time in making this kind of you know diagrams; circles and lines and squares and filling them and crossing them and so on? So, this is the way to represent the family. Otherwise, in one go you can understand how each one is related and you will be able to show a particular phenotype how it is segregated. So, in any pedigree when you draw like this, when you have for example, the filled one or unfilled one, in a given pedigree you are going to show only one particular phenotype. Say for example, you are talking about the handedness, like when you clasp your hands the left thumb comes over right. So, this is a phenotype. So in a, in a given pedigree you are going to only show that particular trait. You cannot talk about whether, in the same pedigree you cannot talk about whether they are able to roll their tongue or not; that becomes complicated. So, you may want to use another sheet that represents the phenotype, but for the same pedigree you can do that. But, traditionally in one pedigree chart you are going to show only one phenotype, because that makes it easier for us to understand how that phenotype is segregating.

So, how do you really record ancestry? We spoke about the symbols, other symbol that really explains the relatedness; in what way they are related. But, we also have to identify an individual. So, you cannot say again using relation. So one, you know simple way to show it is on the left side, use Roman numerals to identify the generation and use Arabic numerals to identify the individuals. Like for example second generation individual 3, 4 and so on; third generation and so on. So, it is easy for you to refer to which individual you are talking about. So, in each of these you can see that this individual, you call this as married in, because she is not related, genetically with this, the family. But, she is married to this individual who is related to

the previous generation. Likewise here, likewise here, but you denote that. So, that is how you do it. So, you really build the pedigree this way. So, these are thumb rules because you follow it, because anyone else again can look into your pedigree, can understand what really you are trying to explain. So these are standard symbols.

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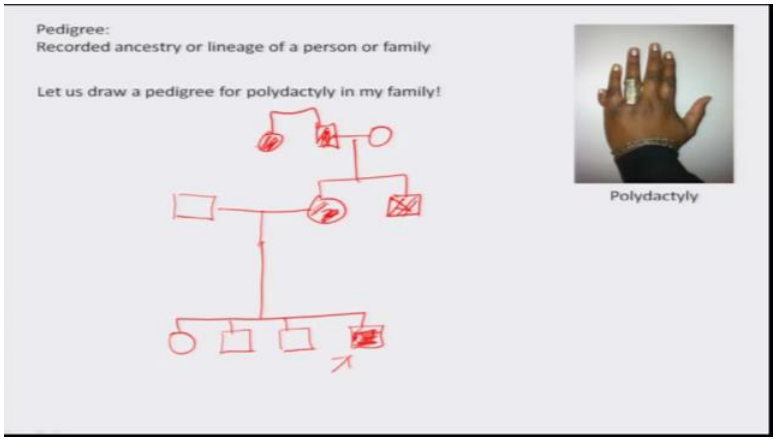

Let's try to draw a pedigree for a phenotype that we have already discussed that is polydactyly. We said it is a dominant disorder, meaning you may have a sixth finger. It is because of a defect in one of the genes and it is a dominant phenotype. If I have the defect I am going to have a sixth finger. So, but it is abnormal because it is not seen in the wild type. All of us, majority of us have five fingers in our hand, but certain individuals extremely rare condition, you do have sixth finger. So, how do you draw? Assuming that I am, I am an individual who have got sixth finger, I am going to draw my pedigree. So, what I will do? I will interview myself. Let us assume that I am here, this is me and I am starting the entire family with myself, being the index or proband. So I have, the six fingers, so I am the individual who is affected. I have expressed the phenotype. So, how do I really build my family? I first ask how many brothers I have. So, I am fourth in my family; I have two brothers, one sister. So, I construct. None of them have; they are all normal with five fingers, and of course I am talking about my parents. So, it is a dominant disorder.

Obviously I should have gotten the bad gene from one of my parents. So, assuming my mother is also having six fingers. So, I would talk to my mother whether in her family anyone else had this and I understand and her brother also had six fingers. Then I asked whether her parents had. It

looks like my grandfather also had six fingers, and his sister, that is my two generations back, you know you can talk about that way, she had. So, you can go on building a pedigree like this by talking to people. So, this would explain as to how from where possibly the gene that gave you this particular phenotype that is having sixth finger came in. So that is one way to construct the family.

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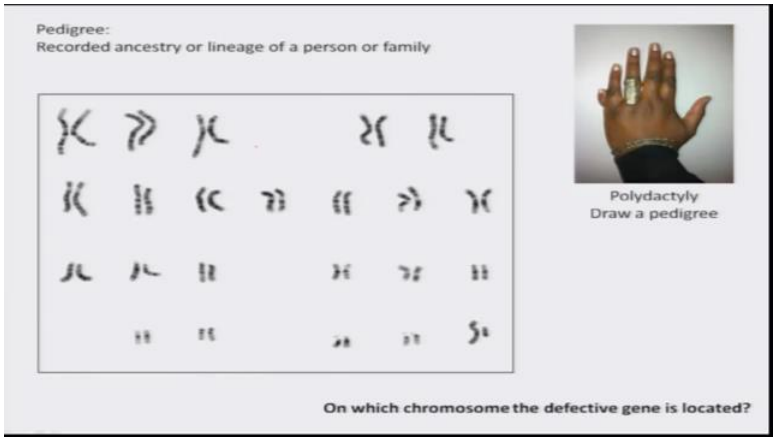

The question is by doing this, how does it help you? So, one of the benefits of this pedigree analysis is that you would understand as to from which of the chromosome you have the defect that results in for example the sixth finger. The pedigree analysis really helps you to start with this gene hunt as to where it is.

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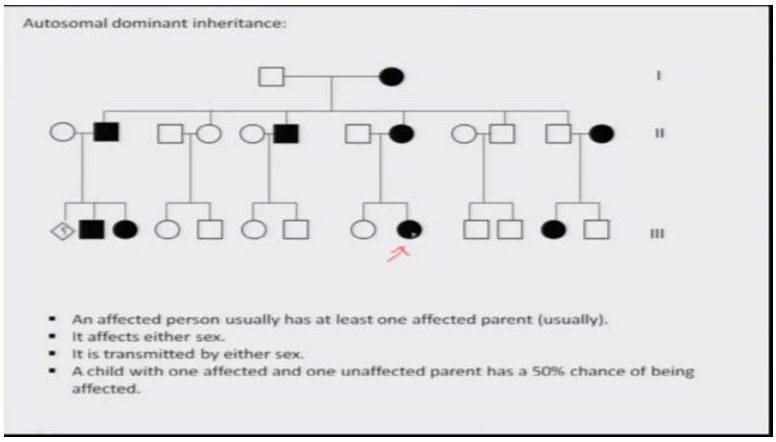

Let us see. So, how does it really help? Let's assume that this is one of the families that you are talking about and this inheritance here you call it as autosomal dominant. You call it as autosome because you assume the defect in a gene that results in this phenotype is present in one of the chromosome that is autosome meaning every other chromosome other than X and Y, the 22 pairs and you call it as dominant because you would, in the model you would anticipate even if one of the two copies of the gene that you have is defective, you would have the phenotype. That is why you call it as a dominant phenotype.

Let's see; this is the pedigree that is shown. Let's see how does it really help us to tell whether, the defect is on a autosome and the phenotype that you see is dominant. Because you really don't know where the gene is, you don't know where the mutation is, you don't know what kind of mutation, nothing. You only spoke to that individual and let's assume that individual happened to be somebody here, let's say your friend and that's how you came to know about the entire family and you sort of plotted this and you want to ask what the mode of inheritance is. In an autosomal dominant inheritance what you would see is that an affected person usually has at least one affected parent; go with the model, you should have inherited at least one defective allele from one of the parents; even one is good enough to show the phenotype. Therefore, you can see here that her mother is affected. Likewise you take any individual, for example his or her father is affected, likewise her mother is affected and so on and likewise if you look into this, each one of that here also you find that one of the parents of each one of the affected individual here is also affected. That is what you are showing. Affected person usually has at least one affected parent.

Affects either sex, because autosomes are present in both male and female and likewise it is transmitted by either sex. You can see that male, female both are affected; transmitted by either by a female or by a male; both are possible, because it is autosome and what is the probability. If a child with one affected and one unaffected parent has for the next child it is 50% chance for being affected simple because, of the two parents one is having mutant allele in a heterozygous condition. So, there is 50% probability each gamete of that individual carrying the affected allele. That is why it is 50% probability of having the affected phenotype. So, this is for autosomal dominant inheritance. Let's look into how the genotype would look like.

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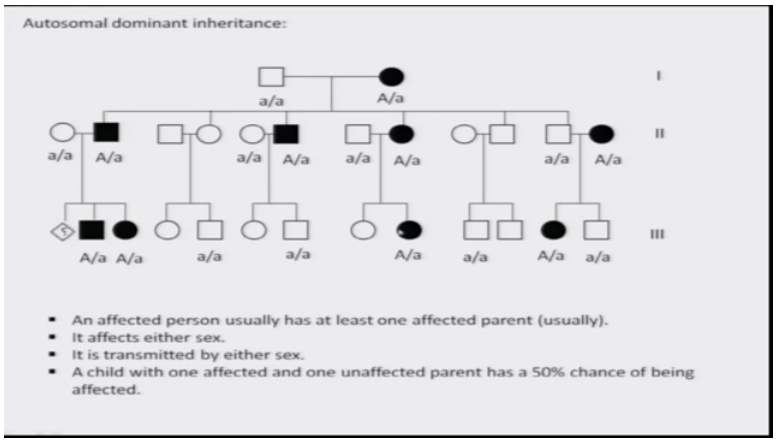

This I just try to plot it over there. You can see here, you say dominant, because you know this individual would express the phenotype even if one of the allele is mutated and likewise you can see everyone here are having an allele which is the dominant, which is shown here with a capital A and that is that allele is present in every affected individual and you can show that that dominant allele with capital A has come from the affected parent. So that is, that is how you can really trace it. So, this is the model that you can use it to identify or even predict that a given phenotype is dominant phenotype.

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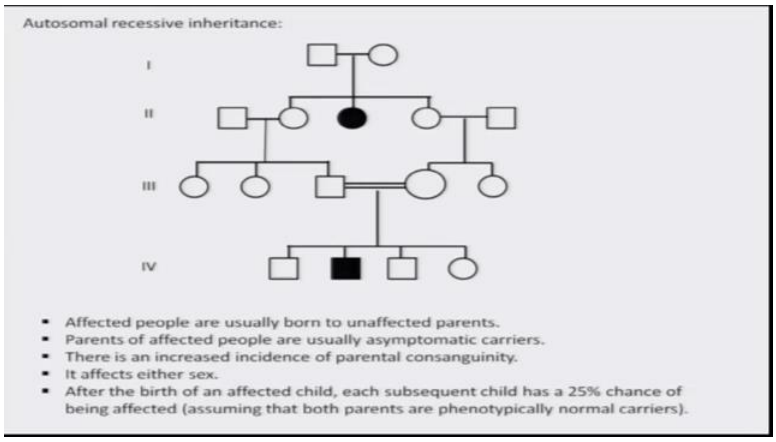

Let's look into an example of how autosomal recessive inheritance might look like. Here is a pedigree that represents a phenotype resulting from autosomal recessive condition and as compared to the dominant condition you may have a generation in which the individual may not have the phenotype, the reason being given here. So, usually if you look into a pedigree that is autosomal recessive character being inherited, you will find that affected people are usually born to unaffected parents and more often you would find consanguinity in parents like for example here you are showing two lines, because they are related because they share the same ancestry, as you can see here. So, that's what is shown here and parents of the affected people are usually asymptomatic. Likewise you see here, this is the affected individual; their parents don't show, but in the previous generation you may have an individual who is showing the phenotype.

There is increased incidence of parental consanguinity as depicted here. Again it would affect either sex, because it is autosomal. The gene that is causing the disorder or defect in the gene causing the disorder is located on one of the 22 autosomes. After the birth, you are talking about say, suppose this individual had the phenotype and if they are planning for one more child what is the probability that that child, the fifth one for example would have the same phenotype. So, after the birth of an affected child, each subsequent child has 25% chance, because, for you to have the phenotype you have to have both alleles carrying the mutant forms of the gene. Then only you would show and if you could recollect the Mendelian Punnett square, like if you plot it then you would find it is 1:3. So,, that is why it is 25%. We will come back to that little later. So, that's the example of, how autosomal recessive condition would be transmitted in a disease.

Just you plot the genotype. Therefore you can more easily understand and we talk about consanguinity. Here you see that, this is the consanguinity between, this is the mating or marriage between relatives and both the individuals here are heterozygous for the mutant allele. Let's assume the small 'a' resulting in the phenotype and this small 'a' – allele, is contributed by both the parent. Therefore you have homozygosity. The individual is showing the phenotype and if you go back to the parents, their parents too were heterozygous for the mutant allele and this mutant allele actually came from their parents. Both of them are heterozygous and you can see in this individual unfortunately the mutant allele contributed to the phenotype. So from here on the mutant allele co-segregates in the family and given a chance they may have the phenotype. So, that is an example of autosomal recessive condition.

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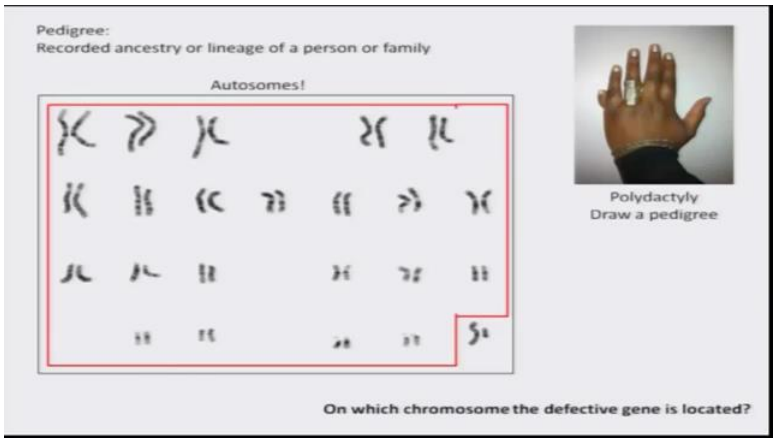

So let's go beyond the autosomes. So, with this kind of pedigree analysis, you will be able to tell whether a gene or defect in a given gene results in a dominant or recessive condition and the gene is located on one of the 22 chromosomes which you call as autosomes. But, how would a phenotype look if the gene, defective gene is located on this particular pair which you call as sex chromosomes. So, their distribution or their segregation or their expression is very, very different.

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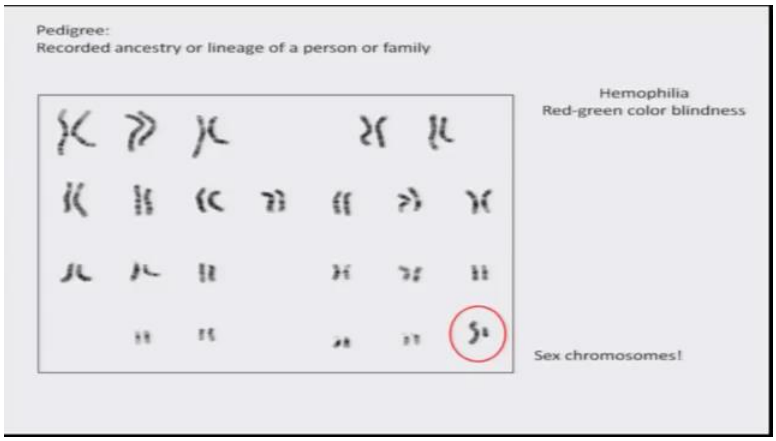

There are disorders as well associated with the sex chromosomes. For example hemophilia, the blood clotting disease and red-green colour blindness, the genes for this particular phenotype is located on the X chromosome. So, let's look into how a phenotype linked to X chromosome segregates in a family.

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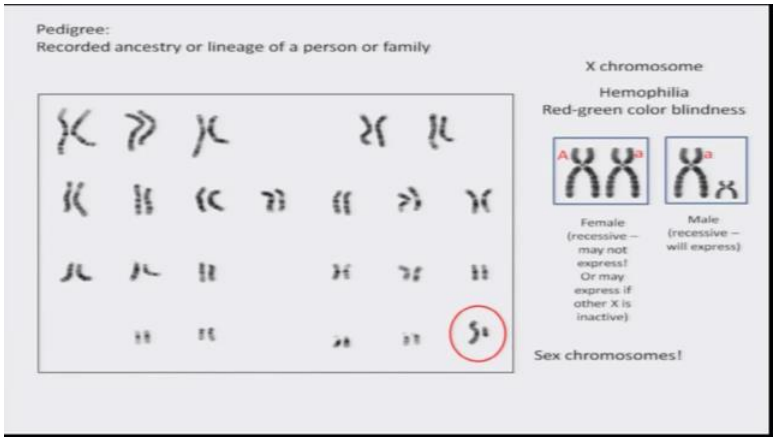

There is a complication when you talk about X chromosomes and their expression of the phenotype. As we discussed in the central dogma and also about the chromosomes, we have male and female. The sex chromosome composition is unique to each sex. In female for example here you have two X chromosomes, there is no Y; whereas male have got one X chromosome and one Y chromosome. So depending on whether a mutant allele is present on XY individual that is male or XX individual that is female, you may or may not show a phenotype. That is what is denoted here. For example, let us assume that you are looking at a phenotype resulting from a

recessive condition, meaning both the allele should carry the mutant allele. Then only you would have the phenotype; both copies of the chromosome should carry the mutant allele, then only you will have the phenotype.

In case of female you may have a condition wherein you have one X chromosome which has got normal wild type allele, other one is having a mutant allele and the female may not express the phenotype, because she carries the normal allele there. But in case of male, because you have only one X chromosome, if that X chromosome carries the mutant allele, invariably the male would express the phenotype, even if only one allele is present. There is one more complication. The female who is carrying only one mutant allele at times may express a phenotype, because of the phenomenon called as X inactivation. Because there are two X chromosomes in female, the copies of the gene that are there in a female also is twice as the number of gene copies that are there in the male.

To compensate the dosage, one of the two X chromosomes gets silenced and this silencing is random. So, in certain cells, for example X chromosome 2 gets inactive, in certain cells X chromosome 1 gets inactive. So, it may be a chance that in majority it could be X chromosome 2 which carries the wild type allele may be inactive; as a result you express a mutant allele and you may end up having the phenotype, even though you are heterozygous and even though the phenotype is recessive. So this could happen; so that is the complication that comes along with X chromosome. Even then, since the inactivation is random you assume that in 50% of the cells it could be inactive and so on, still you will be able to trace whether the phenotype expression of an X - linked gene is recessive or dominant; still you will be able to do it.

So, let’s look into recessive condition. So, that’s what is shown here.

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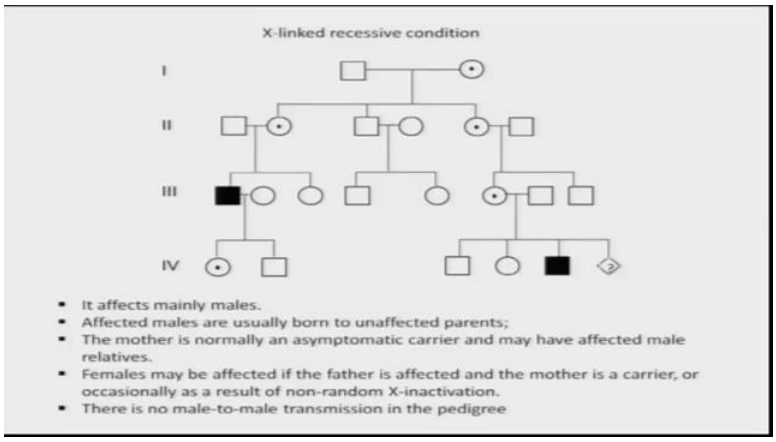

This pedigree represents an autosomal X-linked recessive phenotype and you can see here that you have introduced a new symbol that is you have a dot inside an individual like either a circle or at times it could be a square. That denotes what is called as carrier. So that means that these are asymptomatic individuals, but do carry the defective alleles. So, that is what it denotes. Why do you say that? Because of this model that is, it is X-linked recessive condition. Let's see that. So, if you have a recessive condition for X-linked disease more often it would affect the male, because in female the other X would have a normal copy of the gene, therefore it may not express. But, invariably in case of male if that individual somehow received the X chromosome which has got the defective allele he would end up showing the phenotype, because there is only Y chromosome that doesn't really complement the X. So therefore, in majority of the times in such families it is the male who is affected.

The second is that affected males are usually born to unaffected parents, because the X has come from mother; father will not transmit X chromosome to son, then that individual becomes daughter. Because, you know if son has to be born, then father should have given the Y chromosome, so it doesn't come. It comes through mother and the mother has got the other X chromosome which could be normal, therefore she may not show a symptom, but she is a carrier and you can see it here. For example, here the son is affected. His mother is a carrier, but asymptomatic, not showing. Likewise her mother is asymptomatic, but carrying the defective allele; likewise her mother is a carrier not showing symptoms.

The mother is normally an asymptomatic carrier and may have affected male relatives. So, likewise you can see here, you can go back in the family you would find some of the males are affected, who are related to the mother because if that X chromosome results in a male, then certainly he would show a phenotype. He doesn't have the other copy, wild type copy. Females may be affected if the father is affected and the mother is a carrier. It can be transmitted by a father to a daughter. That is like what you can see here; but, if the mother also contributes to this X chromosome and if she is a carrier, then the daughter also can be affected. Occasionally, that happens and as I told you there is a phenomenon called, X-inactivation. At times it could be skewed, it could be non-random, meaning in majority of the cells, the allele that is having, the wild type allele, that chromosome may be inactive. Therefore you would, even though it is a recessive condition if you are heterozygous still you would, you would show the phenotype, because of the abnormal X-inactivation.

So, what is important here is that in this kind of inheritance you will not find a male to male transmission. In any of the generation you will not find a male transmitting the phenotype to a male in the next generation. That is not possible because, it is there in the X chromosome. So, if you look into the phenotype, it doesn't segregate. Then you can call that, whatever the phenotype that you are looking at could be X-linked recessive. So, you use these thumb rules to understand whether the phenotype could be X-linked or autosomal, whether it is dominant, recessive. So, you sort of come up with a hypothesis and if you can apply that in multiple families having the same genotype, it becomes more and more clear that this is indeed the mode of inheritance. That is how you do it.

Let's look into the other condition that is X-linked dominant condition. Even if one allele is defective, so you would show the phenotype in case of female.

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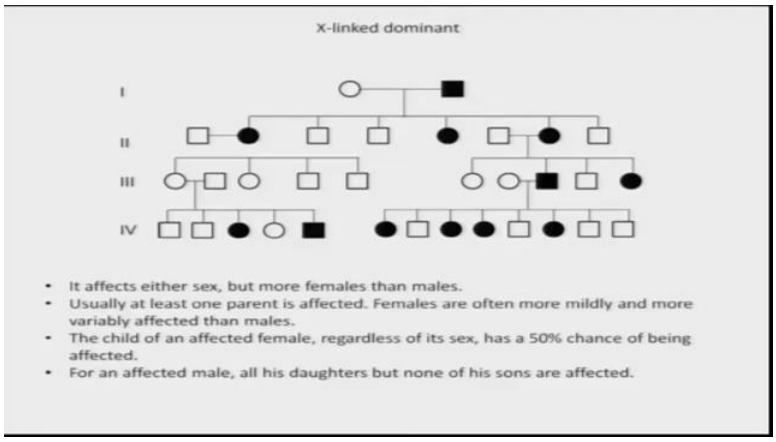

So here, it affects either sex, but more females than males. Why? Obviously you know, if it is a female, then she is going to give this X chromosome to two individuals in the next generation. So therefore, from female it will go to more number of individuals. Therefore you would have more of them and more often it would be females. So, that's what it is. Usually at least one parent is affected because in the dominant condition you would expect either father or mother or both of them could show the phenotype. But, females are often more mildly or more variably affected than males, because of a difference that is the number of cells in which a given X is inactive. So, because again there is X-inactivation condition, so you will have variability in terms of how severe the phenotype is if it is a disease.

The child of an affected female, regardless of its sex, has 50% chance of being affected, because she has got two X chromosome in her meiosis, she is going to gift if she is a carrier or heterozygous, 50% of her germ cells would have the affected chromosome. Therefore, it is 50% chance. So an affected male, all his daughters, but none of his sons are affected, because the moment he contributes sex chromosome in his sperm, that sperm, whichever egg it fertilizes that would result in a daughter not in son. So therefore, the daughter will be affected if it is X-linked. So this is how you really look into the family and come up with a hypothesis or a suggestion that the phenotype that you are seeing is a dominant, recessive and what it is.

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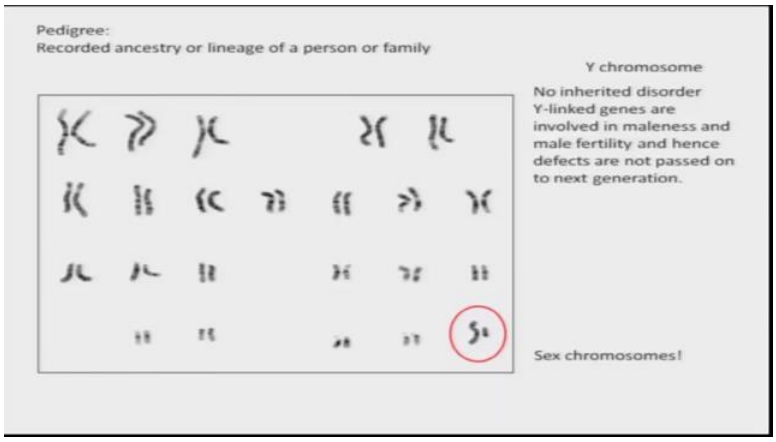

So, let's look into the other chromosome, sex chromosome that is Y chromosome. It is very, very interesting because the Y chromosome is the smallest chromosome in your cell and it doesn't carry all the essential genes for a normal which is the function that are required for both male and female. Because the female don't have the Y chromosome, still they are normal. So, it has genes that contribute to the maleness like developing into a male, the behavior, the fertility, the sperm functions and so on. Therefore, really you don't see any disorder that is linked to Y chromosome that runs in the family, because if there are defects in Y chromosome, then the male embryo will not form or if there is defect in Y chromosome the fertility will be affected. So, it doesn't run in the family. So therefore you don't see disorder that is linked to Y chromosome. So, it is a hypothetical family, if there is a phenotype linked to Y chromosome this is how it will look like.

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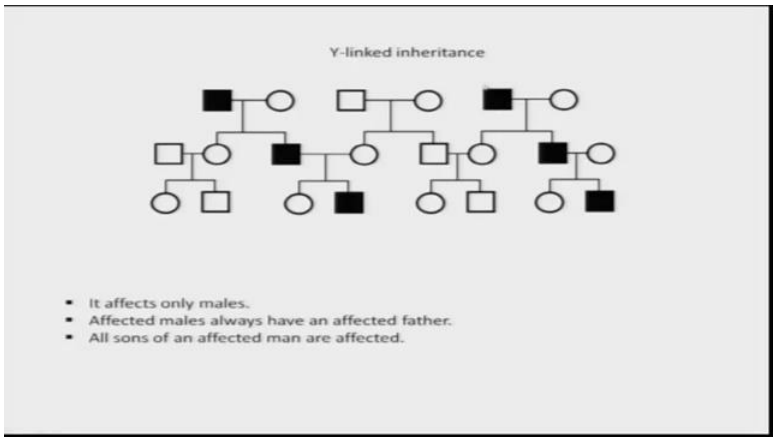

So, it would be always from a male to male to male. It doesn't go the other way. It affects, it would affect only the males. There is always an unaffected father, because they have gotten their

Y from their father. All sons of an affected man are affected. So, these are the thumb rules you would use, but hardly there are any conditions that runs in the family, which are linked to the Y chromosome.

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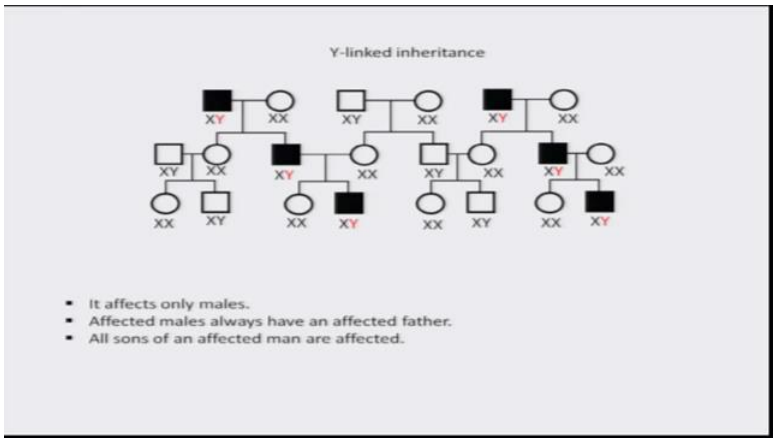

So that's pretty much the condition. This is what is shown here, like we have Y which is, having a defective allele, how it would be transmitted in the family.

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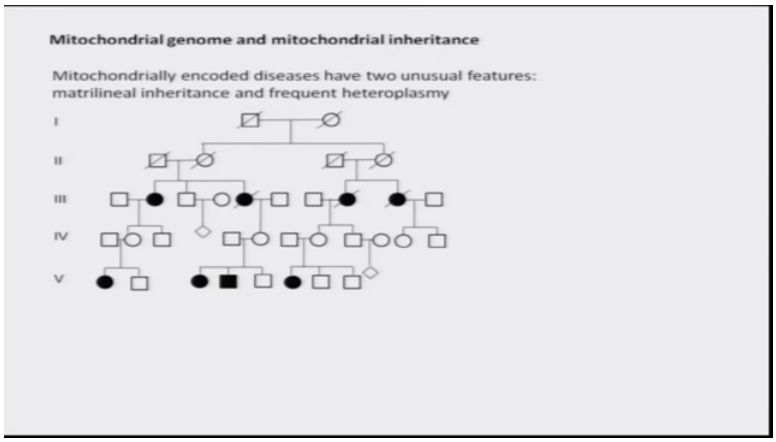

So, this is for all the genes that are present on your genome, the 23 pairs of the chromosome, autosome and X chromosome. But, we also have DNA in one of the organelle that is mitochondria and it is, mitochondria is very, very important for your function of the cells, because it provides energy and mitochondria has its own DNA and the DNA if it is defective,

you could have conditions; there are conditions that affects, there are muscular dystrophies, there are neurological disorders resulting from defect in mitochondrial DNA. Moreover, mitochondrial DNA is also transmitted. You receive mitochondrial DNA from your parents. So, if that DNA is defective, how would it be transmitted? That's one particular question you are trying to address here, because the phenotype is very, very unique; the segregation is rather very, very unique. So, that's what you are seeing here. So, there is a family that is drawn, pedigree and we are looking at a mitochondrial disorder and you see that a large number of them are females, affected.

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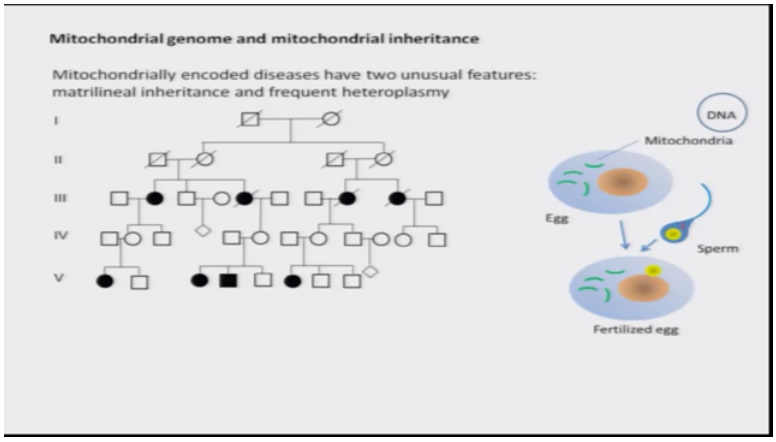

Let's look into the unique thing about mitochondrial DNA, because the mitochondrial DNA that you receive, you receive it invariably from, whether you are male, whether you are son, you are daughter; you receive the mitochondrial DNA from your mother. The reason being, you have a cell, which is the egg, which is yet to be fertilized and it carries the mitochondria, which carries the mitochondrial DNA, which is circular and it has got certain genes, which are transcribed, makes proteins, which are required for mitochondrial function. Now, what is interesting is that when the egg and sperm fuse to form what is called as the fertilized egg or zygote, the interesting aspect is that the mitochondria of the sperm are not transmitted to the embryo, the fertilized egg. So, it is only the mitochondrial, mitochondria of the mother that is retained in the egg. Only the nucleus that carries the DNA is allowed to fuse with the egg. Therefore, if you are a male you don't contribute your mitochondrial DNA to the next generation. It is invariably the mother who contributes. So, any defect that if you have developed in your mitochondrial DNA that is not going to the next generation. You may receive a defective DNA from your mother, but you will

not contribute that or segregate that to the next generation. Therefore, the inheritance pattern of this particular phenotype resulting from mitochondrial DNA defect is going to be very, very different.

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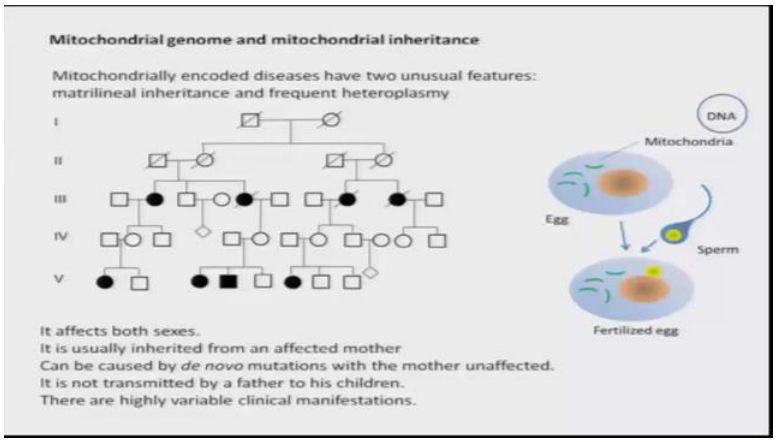

So, how do you really analyze that? It affects both sexes, because you know mother contributes to both male and female and the egg is anyway, is given by mother and whether it would develop into a male or female depends on the sperm, but sperm doesn't contribute to the mitochondrial DNA. It is usually inherited from an affected mother; mother is carrier or she is showing the symptoms for a particular disorder. Can be caused by de novo mutations, meaning the mutation could have come in the egg itself. For example, the egg somehow had a mitochondria, which had some defect and therefore that embryo developed. This is called the de novo, meaning a new mutation coming in germ cells.

It is not transmitted by a father. As I told you, father doesn't contribute to the mitochondria that are there in the embryo. These are highly variable clinical manifestations, reason being, you could have difference in terms of the number of mitochondria that is having the defective DNA. If majority of the mitochondria has got defective DNA, you are going to show a phenotype, which could be severe. Only if it is 10% of the DNA or 10% of the mitochondria carries the bad DNA, your symptoms could be milder. So you would have variations in the manifestations. That is what is called as heteroplasmy. That is the term that is shown on the top, and it is called the

matrilineal inheritance, meaning it is always transmitted by mother and frequent heteroplasmy, meaning it is a variation.

It is not that every mitochondria in a cell is defective and it varies. When the cell divides, how the mitochondria is distributed to the two daughter cells that determines whether the cell would function normally or not. It so happened that one of the two daughter cells inherited most of the bad mitochondria, having bad DNA, that cell may not function as good as the other cell which is lucky enough to get most of the good mitochondria. So, how severe the phenotype depends on how, what is the burden of that cell in terms of how much of the bad mitochondria, how much of the bad DNA that it inherited. So, that's why you show or you see a variation. So, these two, that the Y chromosome which is transmitted by male to son, likewise the mitochondrial DNA transmitted by mother to next generation which only runs through one of the two sex is really, really very interesting. That helps people to understand how we evolved.

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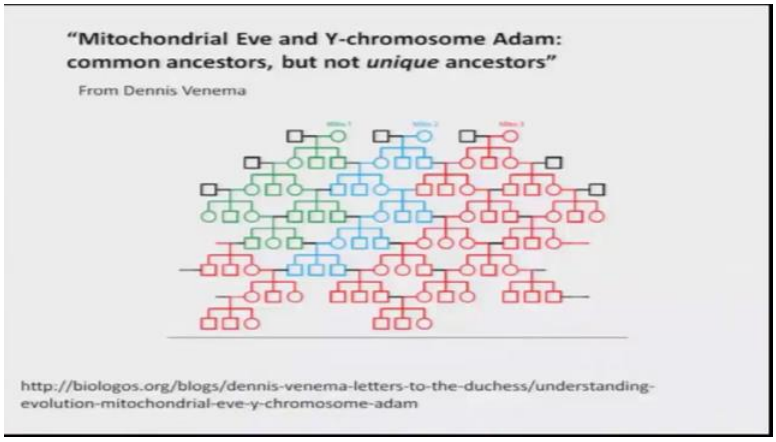

So, this is you know, this is something which I really recommend all of you to go to this particular blog, written by Dennis Venema. She has written a beautiful blog on how Y chromosomes and X chromosomes really the DNA sequence there we can use to analyze and understand how we evolved. So, we can really talk about what could be the mitochondrial sequence or the genome sequence, where, from where we evolved; we talk about we all evolved from Africa. So, this is the, is it, is it a myth or is it a reality? Is it possible? Can we scientifically

prove this and people have used this to, DNA material to strengthen the hypothesis that all of us have evolved from a common ancestor somewhere in Africa.

So, why is it so easy to test this hypothesis using Y and Y chromosome and mitochondria is because of this fact. For example you have, different mitochondria, meaning they have difference in the DNA sequence, right and three individuals and they keep marrying and you have a large population. By looking at the sequence difference, you will be able to really trace who could have been the original mother who seeded the mitochondria. So, it is easy for us to see because always the mother contributes the mitochondria to the next generation.

Likewise, we can use the Y chromosome or sequence therein and which could be for example, individual 1, individual 2, individual 3; there are variations in the Y chromosome gene sequence and this sequence, we can really trace it and we will be able to understand the ancestry; who are the original fathers and then how the population has mixed and this is possible only if you have traced the mitochondria and Y chromosome, because you know the, the segregation is either from father or from mother. However if you are trying to trace for example, an autosomal gene it is very difficult, because you cannot trace now, as all sort of mixture takes place, it will be very difficult to understand whether it has come from one of the two parents or both of them and so on. So, it is extremely difficult.

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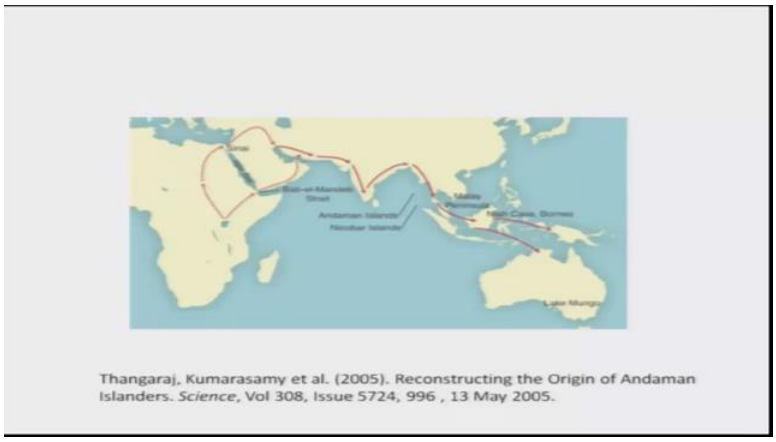

So, most of the studies, where people tried to understand the population dynamics or migration of population, evolution, they have looked at the sequence difference in Y chromosome and mitochondria and tried to link and come up with a hypothesis and one of the studies that came from India by a group at Hyderabad, really used this mitochondria and Y chromosome sequences to support and come up with an hypothesis which suggests that our forefathers evolved around 200,000 years ago, somewhere here, Northern Africa and they probably migrated close to the sea shore. This is you know, people thought that this stripe went like this, but what we understand, probably they went through the sea route; they did not go through the land route, but they probably went through the sea route to the other parts of the world. These are now the current hypothesis.

It was all because of our understanding of the mitochondrial DNA sequence and how they are transmitted and how the Y chromosome is transmitted, what are the sequence variations. You can use this to even go beyond three generations, four generations, may be hundreds of generations back and you will be able to tell how related we are with, in relation to the other races in the world and so on. So that is the power of genetics and that is what we pretty much looked at in this particular chapter. We will see you in the next week.