Human Molecular Genetics
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Module - 02
Lecture - 06

Let us test your understanding of Pedigree and Genetics
And
Complications in Mendelian Pedigree patterns

Welcome back to the week II lecture. This is the second lecture in the week II, where we will be discussing about the pedigree. We already have had introduction to pedigree, as to how you would construct a pedigree by talking to people , understood all the symbols that we use; we also understood the power of pedigree analysis, as to whether it would tell you whether it is a dominant phenotype, recessive phenotype, resulting from a gene that is located in the autosome, X chromosomes, Y chromosomes and so on. So, now we are going to look at some problems.

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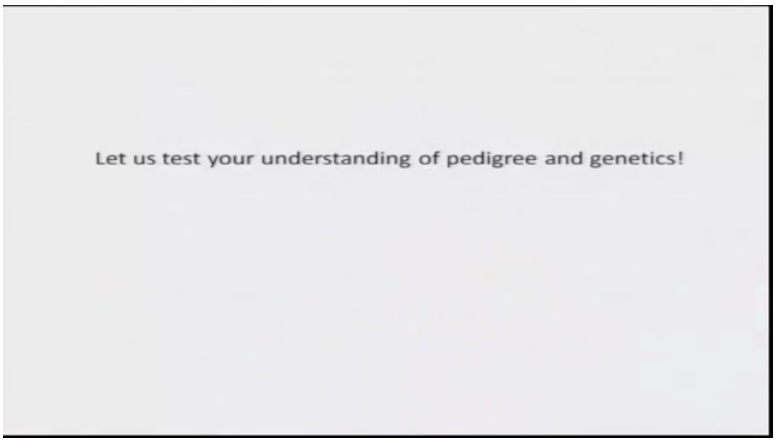

Let's test your understanding as to how good you are in understanding the pedigree and whether you will be able to talk about some prediction with regard to the genetics, and then we will move into what is called as exceptions. It is not that all phenotype that you will look at are falling into one of the four or five rules that is autosomal, dominant, recessive and so on. There could be some exceptions and how that might contribute to the complexity in the pedigree. So, first let's look into some examples of the pedigree.

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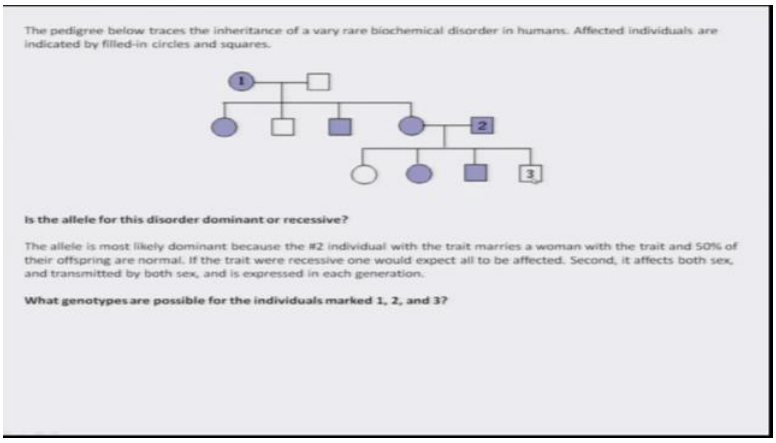

This is one example. So, the pedigree given here traces the inheritance of a very rare biochemical disorder in humans. Affected individuals are indicated by the circle, what you have seen. So, every individual that is shown here, the filled one, are having a particular disorder. So, the question is, is the allele for this disorder, dominant or recessive? The phenotype resulting from dominant condition or is it recessive condition that is the question that we ask. That's very easy, because we have discussed already that if a phenotype affect both male and female and transmitted by both male and female and if one of the parents was also affected, it is likely that it is a autosomal dominant disorder.

So, the allele is most likely dominant, because if you look into, for example here, then you would find one of the parents affected and likewise anywhere that you go on and so on and this is obviously an autosomal dominant disorder. Now; the question here is what is the genotype for the three individuals – individual 1, 2 and 3? Can you use this pedigree and the phenotype that is denoted to arrive at what would be the genotype of that individual? The answer is, "yes, we can". So, how do you do this?

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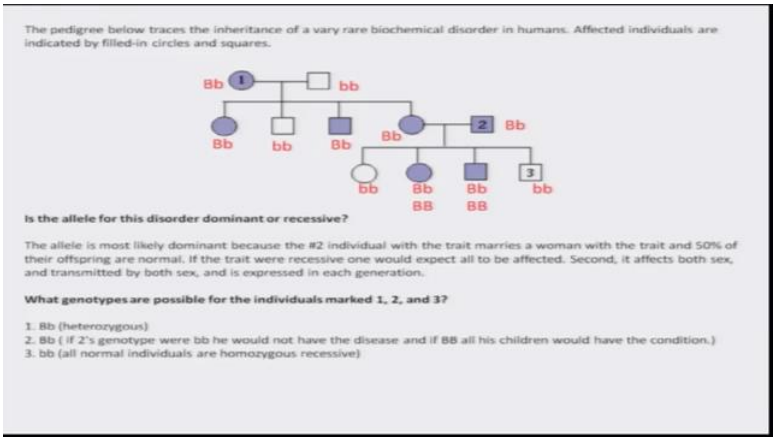

You pretty much plot the genotype. So, let's start from number 1. This individual must be having the defective allele, resulting in the phenotype. Now, for her to show the phenotype, even one copy of the bad allele is good enough. But she also would show the same symptoms, if she is homozygous for the dominant allele. So, how do we know whether she is homozygous for the dominant allele or heterozygous for the dominant allele? The answer is you can look into the next generation. In the next generation, of the four children, one of them is normal and this individual, he could be normal only if he had received a normal allele from her mother, because father would contribute one allele, mother has to contribute the other allele, because it is autosomal and obviously, this allele should have come from mother, therefore she should be heterozygous for the dominant allele. That helps us to arrive at this individual also must be heterozygous for the dominant allele.

Let's look into the next generation. Here, this individual is showing the disorder, but what we do not know is genotype. He could be homozygous for the dominant allele or heterozygous for the dominant allele. Now, how do you know whether he is homozygous or heterozygous for the dominant allele? Just the way we have done here, we can look into this generation and you find two individuals are asymptomatic, not showing the disorder. That means that they should have inherited one normal allele from each of the parent; she obviously contributed one allele and he must have contributed the other allele, therefore he also should be heterozygous.

That brings us to these two individuals and these two individuals really will not be able to tell whether they are homozygous for the dominant allele or heterozygous for the dominant allele, because both are possible. Because this capital B can come from here or from here or both

can come from both parents, so therefore there is a 50% probability for each one of the individual that they are homozygous for the dominant allele or heterozygous for the dominant allele. So, with that we will be able to tell the genotype of number 1, number 2 and number 3, without any confusion, as to what would be the genotype like shown here. So, this is how you will be able to arrive at a conclusion as to what would be the mode of inheritance, whether an individual is likely to be a carrier or homozygous for a mutant allele, if the phenotype that you see is a dominant character.

Now, let's go and look into another problem.

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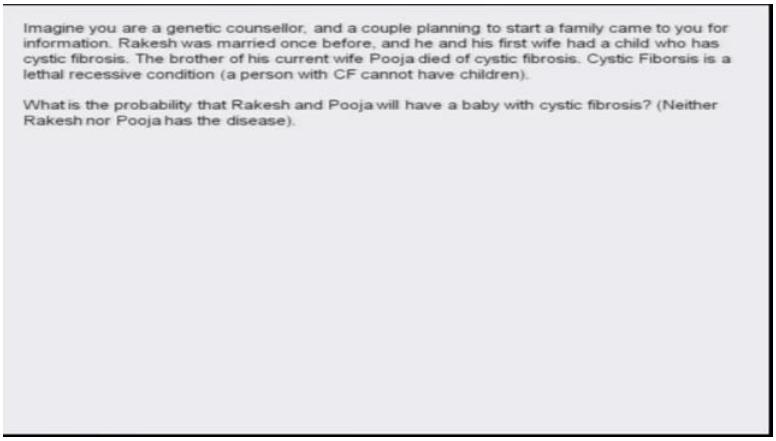

So this time, assume that you finished the course and you have become a genetic counselor and there is a family comes to you for an advice with regard to the risk of their future children having a particular genetic disease. So, the condition is given below, you can read it on the screen; that a couple, husband and wife, planning to start a family came to you for information. This individual Rakesh was married once before and he and his first wife had a child, who has cystic fibrosis. It is disease that is really, really severe and the person don't survive long. The brother of the current wife, his second wife, Pooja, had cystic fibrosis and he passed away and this condition, cystic fibrosis is a lethal recessive genetic disorder and of course, they can't have children because they don't survive that long. So, as and when you have a homozygous condition for the recessive allele, it does not go to the next generation, normally.

So, the advice they wanted to ask was what is the probability that Rakesh and his second wife, Pooja will have a baby with cystic fibrosis, because there is a family history. So, the only information that you have is that, these two, Rakesh and Pooja, they don't have the disease. They are asymptomatic. They could be carriers, but that is what the, what the risk is. If they are carriers, they are likely to have children in the next generation which could be affected. So, how do you really use this information, whatever they narrated to build a pedigree and predict the genotype and predict again whether their children would have cystic fibrosis. Let's do the practice, ok? So let's draw the pedigree. So, who is this? You are going to talk about the individual Rakesh,

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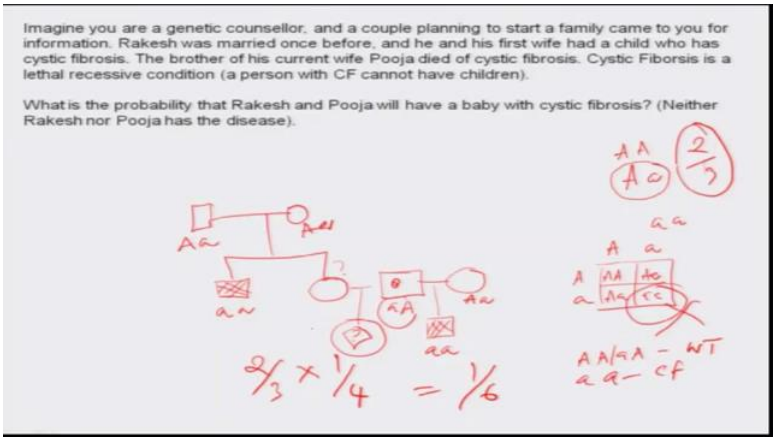

Here is Rakesh, right? So, he is asymptomatic, he is normal and his first wife, she was normal and their son had cystic fibrosis. Now, he is married again and this is Pooja. Now, they are planning for children and we don't know whether eventually they have a child, whether he or she would have cystic fibrosis. So, what is the other information you have? So, what we know is Pooja's brother passed away because of cystic fibrosis. So, this is the information you have. But nobody else is affected. Obviously, her parents, you have interviewed and they are normal; let's assume that way. Now, how would you draw the genotype? Let's look in here. So here, this individual is affected and let us say cystic fibrosis is resulting from a recessive condition; that is what the information already given.

Let us say 'a' is causing cystic fibrosis. If you are autosomal dominant you will have cystic fibrosis. If it is capital or you are heterozygous, then you are wild type; let's have this information. Now, can we put the genotype? Yes, we can and this guy, Rakesh is normal. Therefore you would expect him to be heterozygous for the mutant allele, because he is

normal, but his son had the disease. So, he must have contributed one of the bad alleles; likewise, his first wife. Now, what about Pooja, his second wife? So, let us look into that probability that her brother had cystic fibrosis. That means his genotype should be homozygous for the mutant allele that is small a small a.

If his genotype is this, then her parents who are normal should be heterozygous. Otherwise, you would not have gotten the disease. The question is what would be her genotype? She is normal, wild type. Therefore she cannot be a genotype which is homozygous for the mutant allele. She has to be either heterozygous or homozygous for the wild type. So, how do you know which is possible, which one of these two is possible, because now we have to talk about the probability of this particular kid having cystic fibrosis. So, what you normally do is, in genetics you put the punnett square because these are the parents; so you say, two types of gametes, two types of gametes and then you have these possibilities.

What we are saying is this is not possible because she is normal. So, the probability that she would be heterozygous depends on one of the three conditions. That is, in this combination this is a probability of her having the heterozygous condition which results in the, what is called as cystic fibrosis. If this is the case and we know the phenotype that is we are talking about a condition and certainly he is having the carrier. He is a carrier because his first son had cystic fibrosis, because of the homozygosity and obviously, the probability is you can easily calculate this way, which is equal to one sixth, is the probability that this particular kid would have or develop cystic fibrosis. This is the kind of calculation you can tell and predict and then say whether in the new generation somebody would have the disease or not. So, this is how the pedigree also would help you to arrive at certain conclusions.

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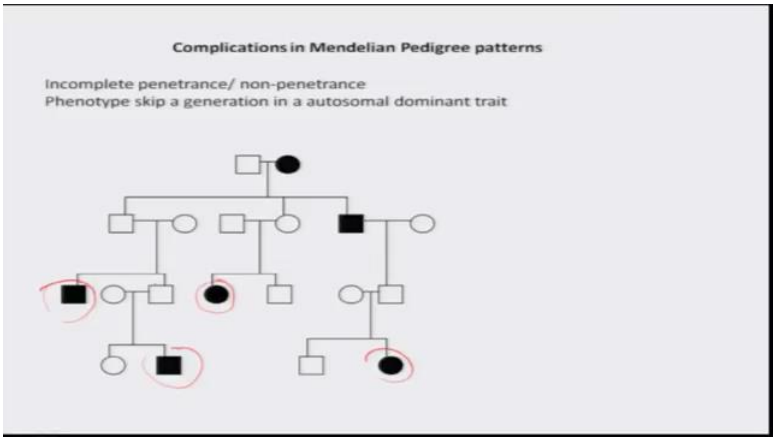

Let us look into the complications. Pedigree analysis is not always simple. There are many conditions that really do not follow the typical Mendelian segregation in terms of phenotype. There could be problems. One problem that often you face in case of dominant disorder is penetrance, meaning that you have what is called as incomplete penetrance, like what is shown here. You call it as incomplete penetrance or non-penetrance, meaning you may have the genotype, but you may not show the phenotype. At times, you may have the defective allele, but you are not showing the symptoms, you are normal. It happens because of a complex genetic interaction; let's not get into that.

So, let's look into this family. What is this family? In this family what is that you see an autosomal trait or, autosomal dominant trait or recessive trait? You can easily see that that almost every generation you have affected and the affected is either male or female transmitted by both male and female. That means it is autosomal dominant. But, what is interesting here is that you do have individuals like, like here who are affected, but you don't see their parents being affected. But here, again you have an affected, but this generation you don't see anybody affected. Likewise you see an affected, but this generation it is not affected. You see an affected, this generation is not affected. So, this is what we call as penetrance. It is not fully penetrant; just having a genotype doesn't ensure that you would have the phenotype. So, that is what called as penetrance.

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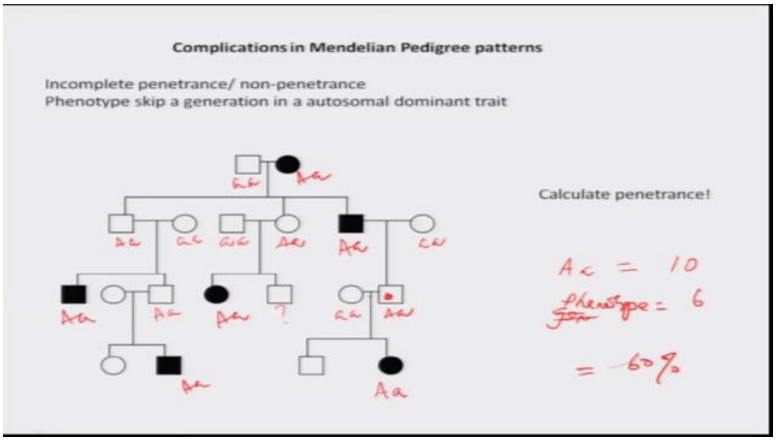

Now, how do you really calculate the penetrance, because it is very important for you to calculate penetrance? What is the probability that if I have the genotype for this particular phenotype I would develop the phenotype as well? So this is an important question that you want to tell. So, this you can calculate for a particular phenotype. Let's calculate here, how do you calculate penetrance? You can do that. So, assuming it is a dominant disorder and it is autosomal dominant, I would easily say that the capital A causes this disease, therefore this individual is this and here, here, here, here, here.

Let us see the segregation. They must have received one of the 'a', the mutant allele from the generation and this is 'married in', meaning she is not related to this family, DNA wise; she is married in to this individual. So, assuming that she would be alright, you would expect her genotype to be having the normal allele, wild type homozygous. This 'a' should have come from this individual, but he is a carrier. You can denote like this and he is asymptomatic. This 'a' had come from here and therefore she should have been homozygous for the wild type and he is normal, therefore homozygous for the wild type and she is having the dominant allele, should have come from one of the parents. He is married in, therefore his genotype could be this and she could be heterozygous. We don't know, we can't say; it could be penetrance.

Likewise, here if you see, this guy should have been heterozygous; assuming married in she is wild type. Likewise, he is having the phenotype. Therefore, you will assume his father contributed this bad allele, he is heterozygous. This is how you plot it. Now, let us look at the minimum number of individuals that are heterozygous for the mutant allele. We can calculate that - 1, 2, 3, 4, 5, 6, 7, 8, 9, 10; minimum is ten., How many of them have, show the

phenotype? 1, 2, 3, 4, 5, 6; so, the penetrance is 60%. So, this is how you arrive at the calculation. So, if you could get a very similar number for the same disease in a number of families, you can with confidence say the penetrance level. So, that also help you to predict kind of what would be the probability a given kid could have the disease and so on. So, this is how you calculate. This is one of the complications in Mendelian; you would find individuals that don't show symptom, but yet they are having a genotype.

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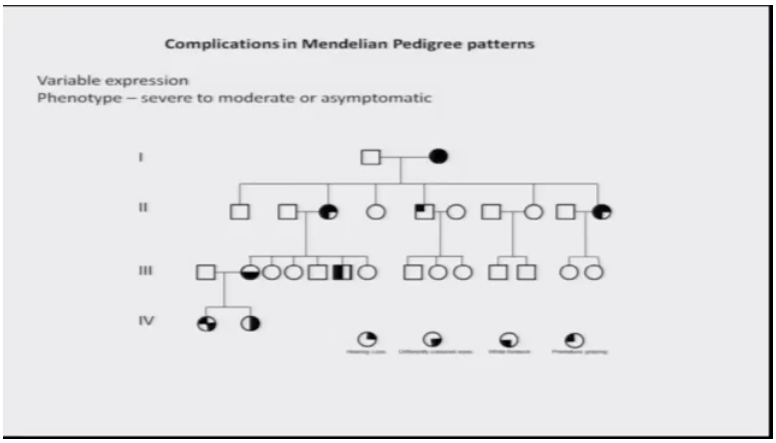

The other factor that influence your pedigree analysis is variable expression, meaning you have a disease allele, but whether or not you would express a phenotype depends on various other factors and here it is not like penetrance. Penetrance is black and white; whether you have the disease or we don't have a disease. But, often you have a condition which is in between these two. That is you have the disease or the symptoms, but it may not be that severe. It could be milder in some individuals, it could be very severe in some, it could be moderate and that also can be denoted in the pedigree, like what is shown here. For example you could use different types of filling.

For example, this is a severely affected individual, not that severe, somewhat milder and these are very mild phenotype. So, you can use different filling in, in the symbols for individual, whether circle or square to denote the spectrum of phenotype or the symptoms or severity. That would also help you to understand how the disease, in terms of its severity, runs in the family. So, it is another information that can easily be brought in which could help in understanding even the other factors that contribute to the disease. So, this is another variable.

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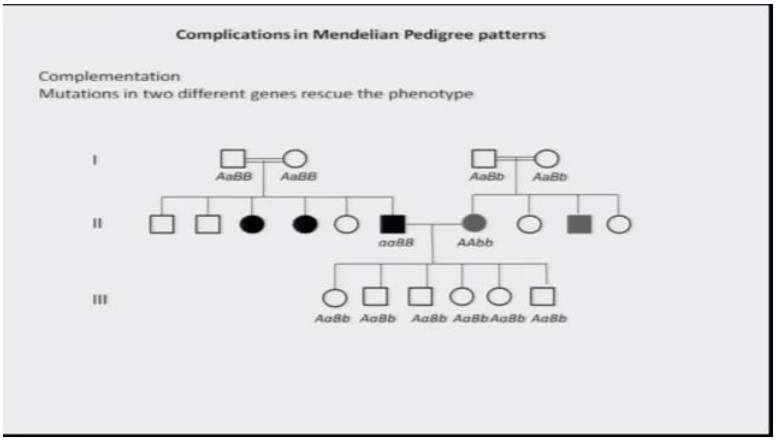

You have other conditions. For example you may have a disease that is resulting from a particular genetic defect, particular genetic mutation in a gene. But, all of a sudden the phenotype may vanish from an individual. He may have a mutation, but may not show the phenotype. This is called as complementation. More often you have heard in condition, wherein you have hearing loss because of a genetic defect. Let's see like here. We are talking about a genetic defect in two different genes and here in this family for example, it is resulting from defect in, for example this small 'a', and you have a heterozygous parents and you have defect and you look at this particular individual, who is having the defective allele in homozygous condition. Therefore, you are showing the symptoms and he is married to an individual, again having a very similar condition, but she is having a defect in altogether a different gene and that condition is also recessive and therefore, you have both copies in homozygous condition and she is showing the symptoms.

It so happened, when marriage happens between two such individuals having very similar conditions that resulted from two different gene, the next generation you would find that, that their children are normal. It happens, because one of the gene defects can mask the effect of other gene defect. This is called as complementation, meaning whatever defect that results from here that is rescued by the other gene defect. On their own they result in disorder, but when they come in combination like this, it rescues. This is unknown in certain unique cases and this, by looking into the pedigree, only looking into the pedigree, you will be able to tell, and you would not anticipate that they are having the genotype. You would assume that they are heterozygous, therefore they are not showing, but there are complications. You should

really look at such kind of cases as well. These are exceptions, but not very common; but it is a rare condition. But, certainly there are conditions like this.

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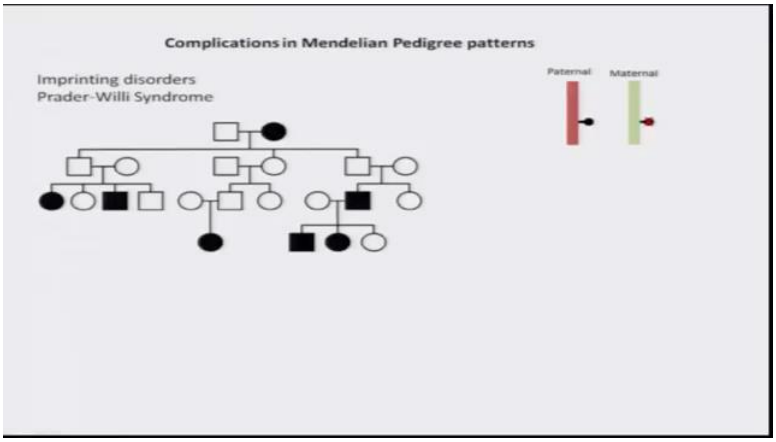

The other complication in Mendelian pedigree pattern is imprinting, imprinting disorder is what you call; caused by a defect in genes that are normally expressed from one of the two alleles that we receive from parents. These are autosomal obviously, therefore when you look into the gene copies one of the copy received from father, the other one has come from mother and we know, for certain genes only the allele that you received from father or mother would express. So, that is something that is shown here. So, as you can see here that you have a gene that is present in both maternal and paternal chromosomes and what is shown here is that, for example if you look into this lollipop, assuming this is a gene, this gene is expressed only when it is located on the paternal paternal copy. So, only that particular gene is expressed; the one that is located on the maternal chromosome is silenced. In some other gene it is the reverse that is opposite.

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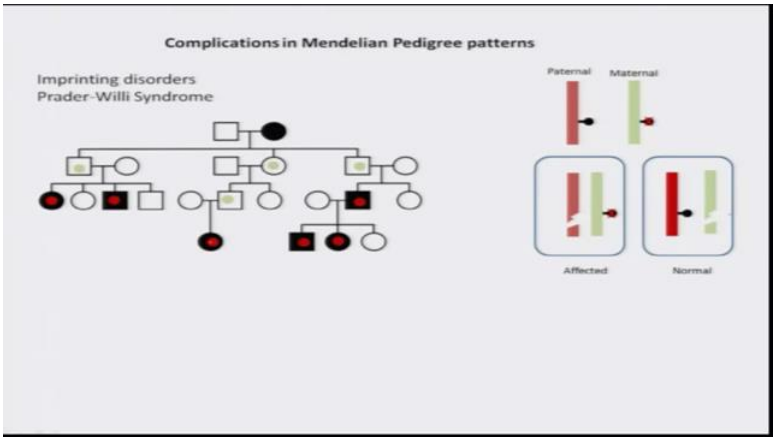

So, what would happen in this case is that, for such gene, for example a gene that is normally expressed on the paternal allele, if the mutation for the same gene is present on the chromosome which gets silenced for this particular gene, now this, if an individual having this kind of a genotype where the mutation is present on the maternal copy, then he would still be normal, because anyway this copy is supposed to be silenced. On the other hand if the mutant allele happened to be the paternal allele, now that, although the other copy is wild type, this cannot rescue this, defect, because this gets silenced. Therefore, this individual would have the disease. So, what you see here is a pedigree, wherein the colours that the dots either within the circle or the square which represent the carriers, now what we are trying to show here is that how the same defective allele, when passed through either mother or father results in having a given disorder or not.

So, you can look here, for example this individual is a carrier and he also shows the phenotype. So, he has the defective gene, but this he inherited from his father, therefore you show it as red colour, like what you can see here. This paternal allele is red colour. So, he received it from father, therefore it is red and that should be expressing since that is you know having defect you end up showing Prader - Willi syndrome; likewise his daughter and his son. However his father is normal, though he is carrying the defective allele, because this particular defective allele has come from his mother. Therefore, this is maternal and the maternal copy anyway should be silenced. Since he has got father who has donated the normal allele, he is alright.

Likewise you can see here, from mother, this is again, it is silenced; therefore, it is not affecting her daughter and again she is able to contribute this mutant allele to the next

generation that is to his son. Again the son is not affected, because this is maternal allele and it is silenced anyway. But however, when it goes to the next generation, you see the disease coming up, because this is a paternal allele that should be expressed here, because this, this goes from a male. Likewise you see that how a defect, depending on whether it is paternal or maternal which lineage it is passing through would end up developing into a disease, depending on the parent of origin effect. So, that's an example of imprinting disorder and such complications really when you look into the pedigree, it would be very difficult to understand the segregation pattern, unless and until you know that they are representing imprinting disorder.

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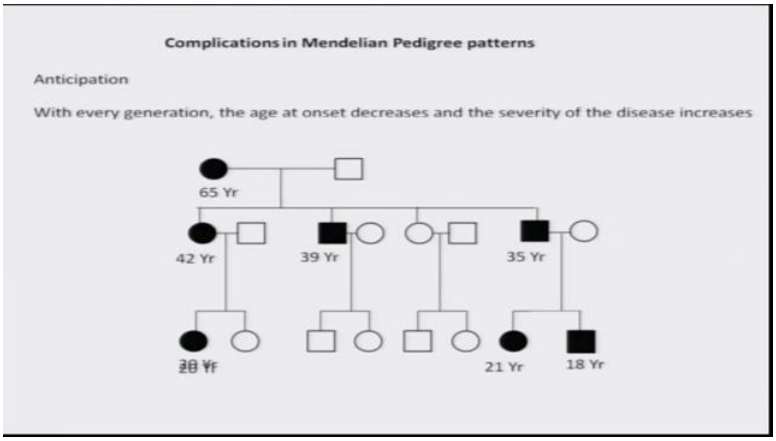

The other example is called as anticipation. So, if you recall, we have discussed one condition called as variable expression, wherein in every generation it may become severe or less severe or moderate or more severe and so on. But, there is one condition in which, in every successive generation, the disease become more severe and severe. Not only that, the age at which you develop the disorder is, the age at onset become, it decreases. For example, in the current generation it could be the age at onset is 12, in the previous generation it could be 20, the generation before it could be 40 and that is what denoted here. If you can see here, now you have condition, three generation family and you can see here this individual carried a defective allele and it is a dominant disorder; every generation both male and female affected and you can see that she developed a disorder at 65, in this generation it is around 40, in next generation it has become around 20. So, this is called as 'anticipation'. So, you can expect in the next generation the disease to become more severe and earlier onset and this happens because of one particular group of mutation called 'dynamic mutation', which we will be

describing later, but this is something very, very unique and exception to a typical Mendelian pattern.

Now, we are going to look into some issues with regard to how the mutation happened, when does it happened and where did it happened. You may have a disease all of a sudden in a family, need not be inherited; the previous generation may not have had any symptoms and this happens, because of what is called as de-novo mutation, meaning, something happening for the first time in a family. So, in germ cells there was a defect and as a result, you have a genetic mutation and from next generation onwards you see the symptoms and such kind of mutation can happen anywhere. It is a random event. It can happen in the germ cells, it can happen in non-germ cells, for example somatic tissue.

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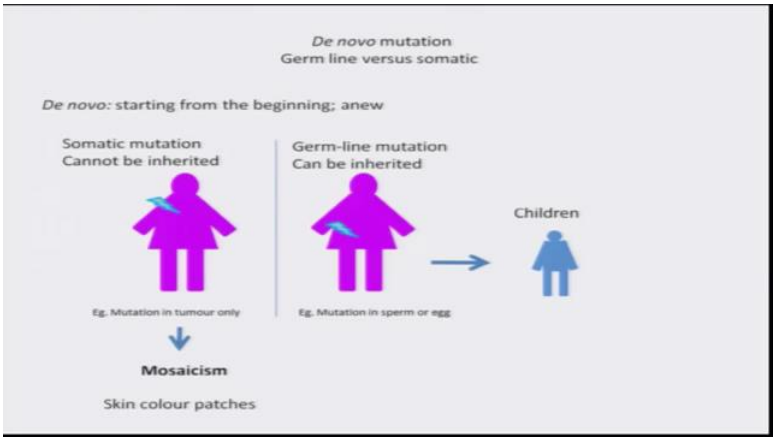

So, depending on where it had happened, it affects whether it will be inherited or non-inherited. For example if you have what is called as somatic mutation, mutations happening somewhere in your body other than your germ cells, it may result in certain condition for example, many tumors or cancers result from somatic mutation. But, they are not transmitted. Such kinds of defects are not there in the germ cells, so it does not go. But, if there are defects that happen in one of the germ cells of an individual and if it so happens that that germ cell led to the formation of an embryo and children, then you would see that, in next generation onwards you have the phenotype. So, these are called as germ - line mutation that can be transmitted.

But, it may so happen that the somatic mutation may occur, that is you have a mutation in your other than germ cell and then you have group of cells in your tissue, some of them are having one particular mutation, other one is wild type, this is called as mosaicism. So, that can result in some individuals having patches of different colors of skin that is one example of mosaicism. So, how does that happen? So, there are two different possibilities for this kind of complexity.

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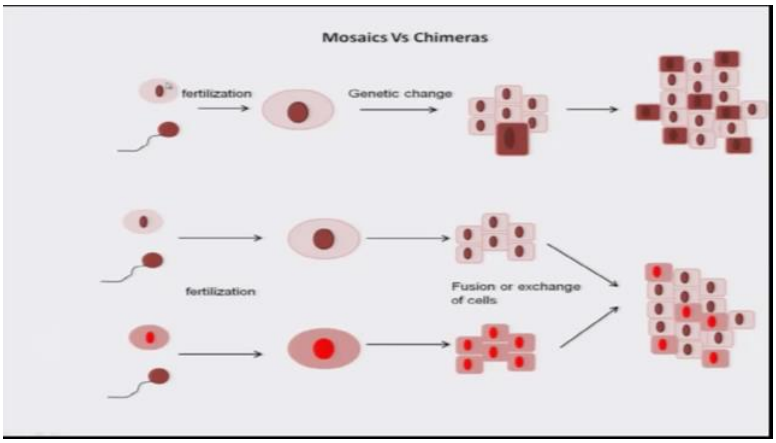

One is, for example as shown here, you have sperm and egg fertilizing and resulting in a zygote. As the zygote multiply and form an embryo, there could be one particular cell, acquires some mutation and as the cells divide and all the cells that are derived from this particular lineage would carry the mutation. So, you would have an individual who is having two different genotypes. Some group of cells are, for example, heterozygous for a mutation, the other groups are wild type for that. Or, there could be conditions, wherein during development you have had two independent embryos, resulting from the fusion of two independent sets of sperm and ovum and it may so happens that when they are developing together, they may fuse together to form what is called as the ‘chimera’. They have mixture of two different, sort of individual so to say, but eventually they develop as a single individual.

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So, when that happens, you could have variation within a body. For example, the difference in the eye color that you see and there are many such examples people have shown, wherein individuals are for example, or chimera for X, 46XX and XY. There are some cells that are XY, some cells that are XX and so on, there are conditions. Also, there are individuals who are known to have blood cells for two different blood groups and so on. There are many such conditions, which results. These are rare, but certainly they do exist. Likewise, there are germ cells which represent two different origins, and that germs, the next generation the child may not show 50% similarity, it will be much less than that, depending on which germ cell led to the formation of the kid and so on. So, this is a complexity which is very, very unique and we, we do see them.

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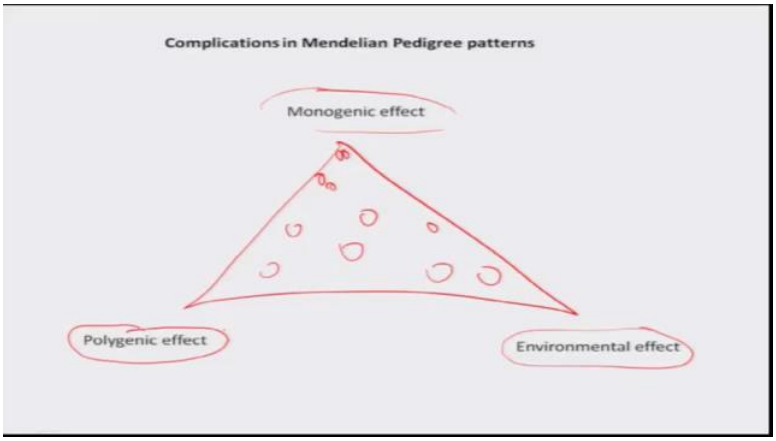

So, that is what we pretty much looked at in Mendelian patterns that is whatever we discussed so far are for monogenic disorders, meaning you have phenotype resulting from defect in mostly one gene. But, you also have conditions that are resulting from polygenic,

meaning multiple genes interacting together and forming a particular phenotype or the phenotype could be modified by the nature, which is called as nutshell. That is also, you call it as epigenetics now. For example, obesity or diabetes could be of genetic origin. But, it also depends on your life style that would, the risk of you having diabetes or obesity goes up depending on your food intake and many other lifestyles.

So, all the phenotype that you talk about today, as of now, could be result of one of the three: that is your genotype or phenotype could be because of defect in one gene or could be multiple genes or could be environmental. What we understand now is that we can pretty much put a triangle something like this, connecting these three elements - single gene defects or multiple gene defects or environmental effect and any phenotype that you look at, can be placed somewhere in the triangle. If you talk about hand clasping, that your left thumb over the right, that is probably monogenic, because we can trace it in the family; Haemophilia that we discussed, it is monogenic. But you have disorder, dominant disorder that is incomplete penetrant, meaning 60% penetrance. So, you may have a genotype, but the probability that you would develop the disease is 60%. That is somewhere here. So, there is some other gene that contribute, which rescues from that or complementation, for example, that again, it could be somewhere here, two genes rescuing each other.

Diabetes, obesity can be genetic, environmental effect. So, you can pretty much place any phenotype that you are looking at somewhere in the triangle. So, that's the concept and we will try to understand how we really dissect the genetics and genetic contribution to the phenotype. We will go on to discuss in the remaining lectures. So, that's pretty much completes the second lecture, for second week.