Human Molecular Genetics
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Module – 02
Lecture – 09
Practice Session – 1
Problems related to pedigree analysis

So, hello everyone, I am Anupama and welcome to the problem-solving class of human molecular genetics course. Today we will be solving some problems related to pedigree, but before we delve further in the topic, I hope you must have seen first and second lecture of week II. I hope explanation while solving the problem will help you build your concepts and make it more clear. Now, not wasting much of your time, let's do the first problem.

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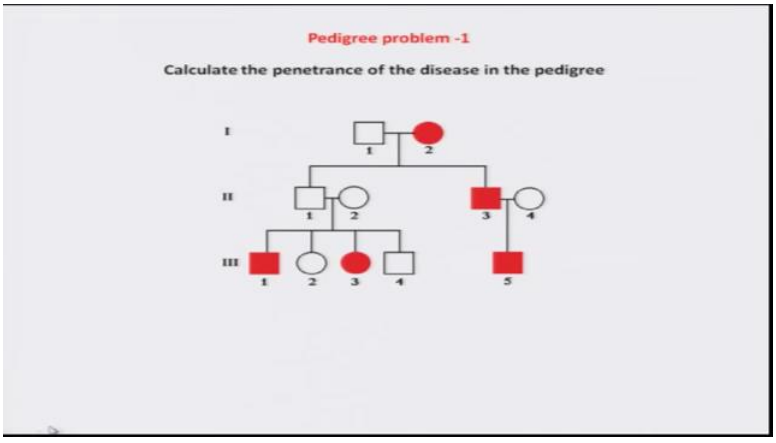

So, the first problem for today is to calculate the penetrance of the disease in the pedigree. Now the, to understand this problem, we need to know what is penetrance. So, it so happens that in many diseases, even though the individuals have the genotype related to the disease, phenotypically he or she is normal. That is you have the disease causing gene, but you don't have the decease. This is called incomplete penetrance. Having learnt that, in this pedigree we need to find out individuals with the disease that are phenotypically showing it and the ones who have the genotype for it.

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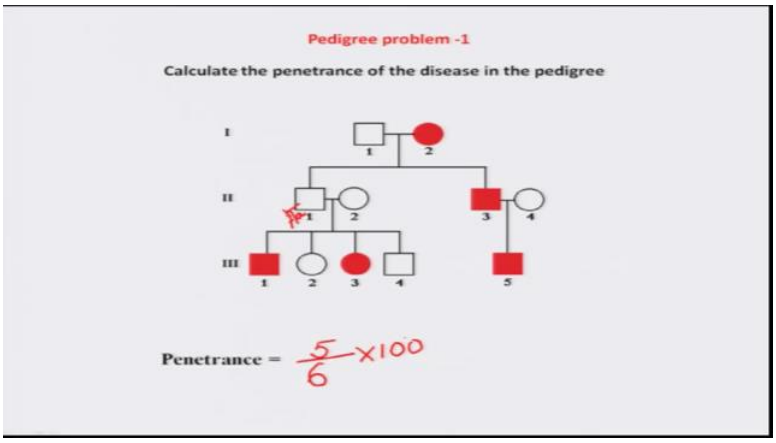

Now, let's see which all individuals have the disease. Now, that's the easy thing. We can just count the number of individuals whose boxes are filled; in this case, the red ones. So, there are five individuals which have the phenotype for the disease. Now, we have to look into the genotype. So, if you see this pedigree, in the third generation 1 and 3, they have the disease, however neither of the parents have the disease. So, it seems that individual II 1, that is this individual, should be carrying the genotype for the disease. However he is not manifesting the disease phenotypically. So he, the genotype for this person should be A and a, as his parents 1 and 2, out of the two, 2 has the disease. So, this brings us that there are 6 individuals who has the genotype, but out of 6, only 5 are showing the disease. If you divide 5 by 6 and multiply it by 100, then this is the penetrance for the disease. So, this is how we calculate penetrance of any particular disease.

Now let's look into the second problem.

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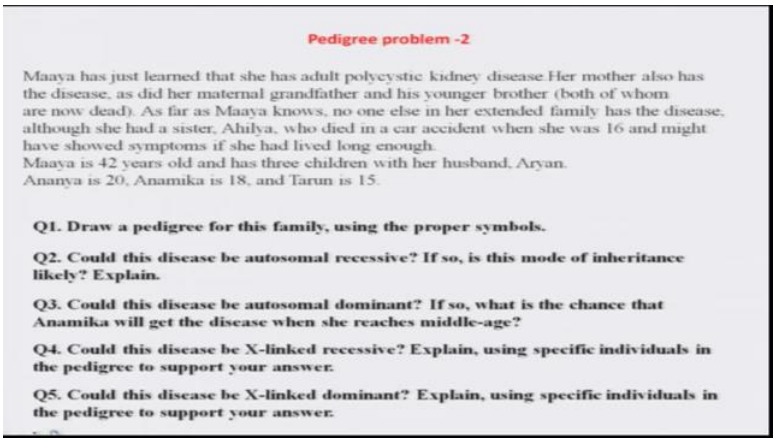

The second problem is bit big and I will go through it. Maya has just learned that she has adult polycystic kidney disease. Her mother also has the disease, as did her maternal grandfather and his younger brother, both of whom are now dead. As far as Maya knows, no one else in her extended family has the disease, although she had a sister, Ahilya, who died in car accident when she was 16 and might have showed symptoms, if she had lived long enough. Maya is 42 years old and has three children with her husband Aryan. Ananya is 20, Anamika is 18 and Tarun is 15. So, this is the question which is being shown in front of you. Now, there are few problems related to this pedigree. So, we will go one by one to all the problems.

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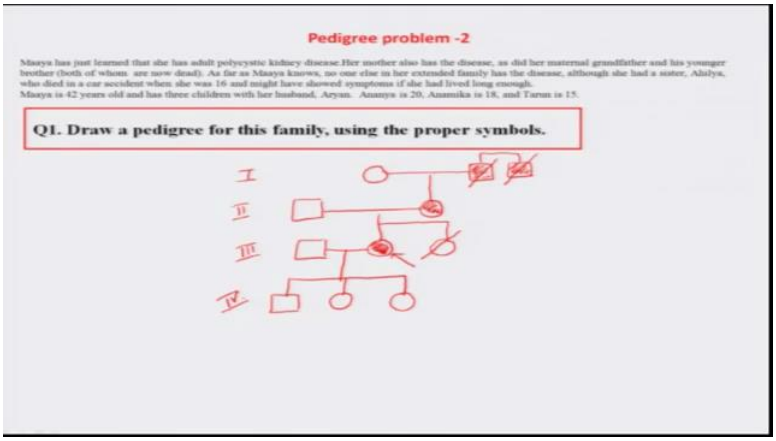

Now, our first problem is ‘draw a pedigree for this family using the proper symbols’. So, let's draw it here. We got the information about this family through Maya. So, Maya is a proband and she' is female. So, let's draw a circle for her and as she was diagnosed for the polycystic kidney disease, so we will fill this circle. Now, let's draw Maya’s parents. As we know from the problem that her mother also has the disease, so let's draw her parents. The circle denotes her mother and she had the disease and this square denotes her father, as did her maternal grandfather and his younger brother both of whom are now dead; Maya’s mother and now her parents that is Maya’s grand parents. So, this symbol that is square denotes his grandfather, grandmother and now her grandfather’s younger brother also had the disease, so we will fill the circle and both are dead.

Now, let’s come to Maya again. As far as Maya knows, no one else in her extended family has the disease, although she had a sister Ahilya, who died in a car accident when she was 16.

So, Maya's sister Ahilya, she died, when she, in a car accident, so we will just cross and now let's look into Maya again. Maya is 42 and she is married. So, this Maya's husband Aryan and she has three children that is Ananya, Anamika and Tarun. They are young, so we don't know that whether they would have the disease or not. So, this is the pedigree, which we have drawn from Maya. Maya is the proband, so we will make a arrow and let's now denote the generation. This is first-generation, second-generation, third-generation and fourth generation. So, this is how we draw pedigree.

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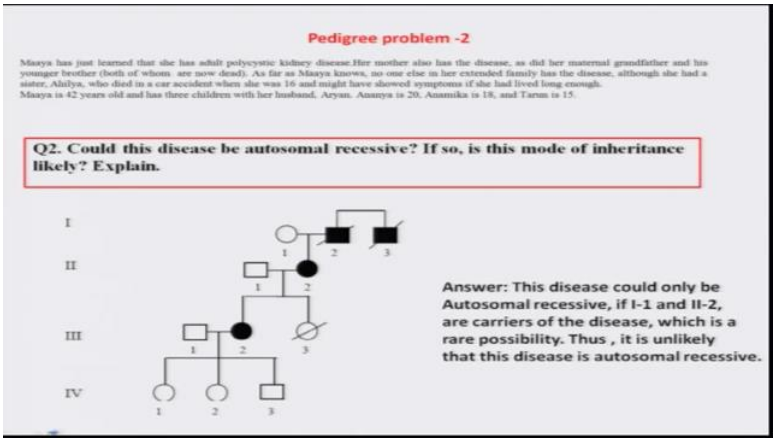

Second question and I have shown the pedigree for the reference to answer the questions which would be coming ahead. So, the second question is 'could this disease be autosomal recessive'? If so, is this mode of inheritance likely? Explain. So, like looking into the pedigree, if you see, almost all the generations have the disease. So, it doesn't seem that this is a autosomal recessive disorder, it seems that it is autosomal dominant. But, let's look into what are the possibilities through which we can explain that this mode of inheritance can also be a autosomal recessive one. So, if it is a autosomal recessive disorder, then if you see II-2, that is this one, this person, so to have a disease in second 2 and if it is autosomal recessive disorder, then 1 should also be a carrier and similarly if III-2 has the disease, then 1, II-1, should also be the carrier for the disease. But it is very unlikely that both of the persons, that is I-2 and II-2 are marrying to a carrier. So, it doesn't seem that this is an autosomal recessive and hence it is an unlikely possibility, which I have written that this disease could only be autosomal recessive, if I-1 and II-2 are carriers of the disease which is a rare possibility. Thus it is unlikely that this disease is autosomal recessive.

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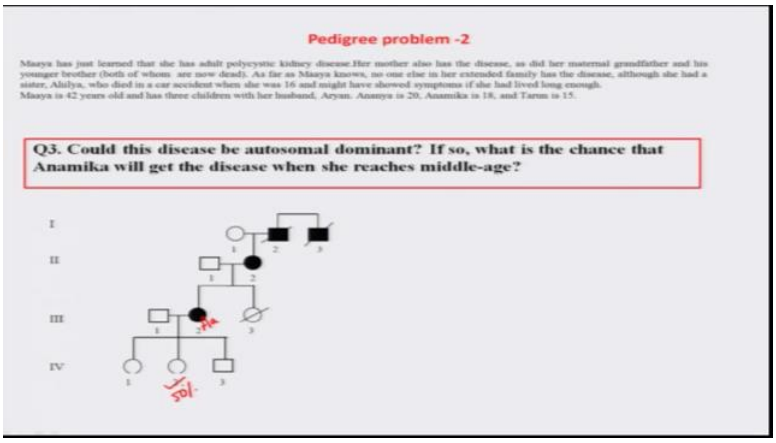

Now, let's look into the third question. Third question is could this disease be autosomal dominant? If so, what is the chance that Anamika will get the disease when she reaches middle age? Now, suppose second daughter of Maya is Anamika, that is IV-2, coming to the first question, it seems likely, very likely that this is a autosomal dominant, because if you must have gone through lecture first of week I, where we have explained what is, how does the pattern of autosomal dominant is, that in all the generation it shows and it affects male and female equally. So, it seems that very likely that this is an autosomal dominant.

Now, what is the chance that Anamika will get the disease when she reaches middle age? Now, Anamika's mother Maya, at age of 42 she has developed the disease. So, she must be having, her genotype must be if we denote capital A and Small a for the, for her genotype, then it is likely that Anamika would have 50% chance, as one of the gameteswill be coming from Maya. So, it seems that 50% chance is for Anamika to develop the disease.

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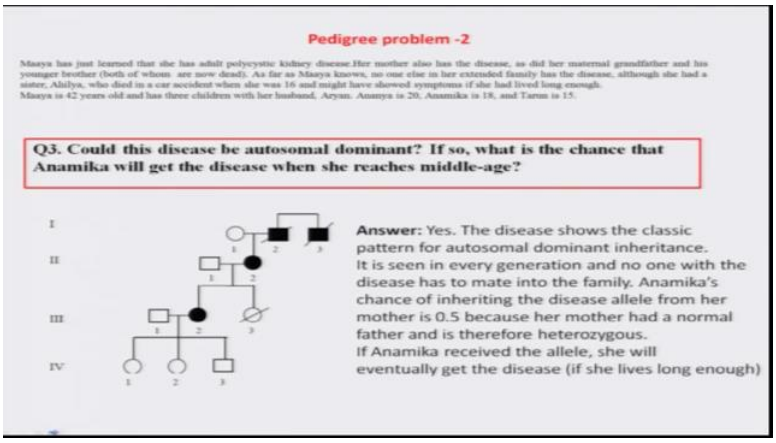

Now that's what I have written here, which you can very well read that this disease shows the classic pattern of autosomal dominant inheritance as it is seen in all and Anamika has .5% that is 50% chance to develop the disease.

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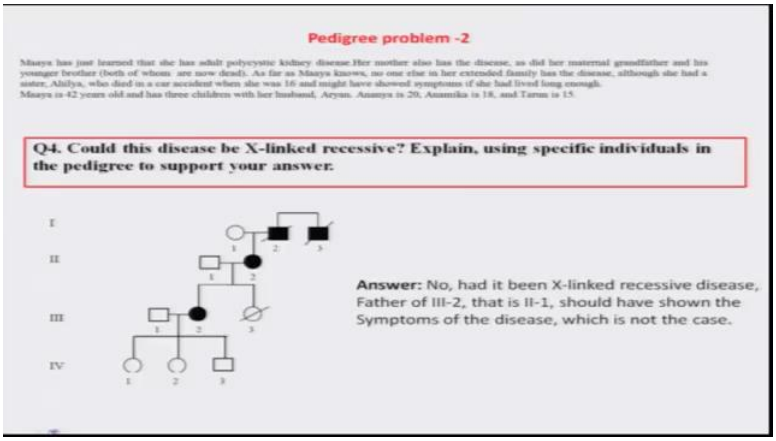

Now, let's look into question number 4. Could this disease be X-linked recessive? Explain using specific individuals in the pedigree to support your answer. So, what are the rules? Like, if it is X-linked disorder, how the pedigree should be? Now, if you see, it is coming from I-2 that is male to female well taken and may be I-1 is carrier. But, had it been a autosomal recessive, then II-1 should also be showing the disease, because this II-1 is male and for X-linked recessive, it shows in the male. So, it doesn't seem likely that this, this could be a X-linked recessive. So, that's what I have written that 'no, had it been X-linked recessive disease, father of III-2, that is Maya, that is II-1, should have shown the symptoms of the disease, which is not the case.

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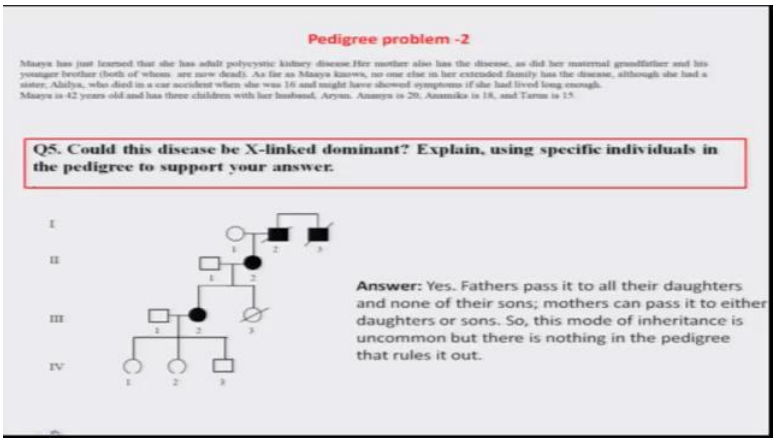

Now, let's look into the fifth question. Could this disease be X-linked dominant? Explain using the specific individuals in the pedigree to support your answer. Again, if it X-linked, then it passes from male to female and from female to both the genders, like to her sons and daughters. So, that's what is being seen. So, it can be, but this mode of inheritance is uncommon. But, there is nothing in the pedigree that rules it out. So, that was with this pedigree. That was pedigree problem – 2. We solved five questions and we ruled out why this pedigree is not X-linked recessive or autosomal recessive and X-linked dominant and most likely this is autosomal dominant disease. Now, this was a problem which was related to a particular pedigree.

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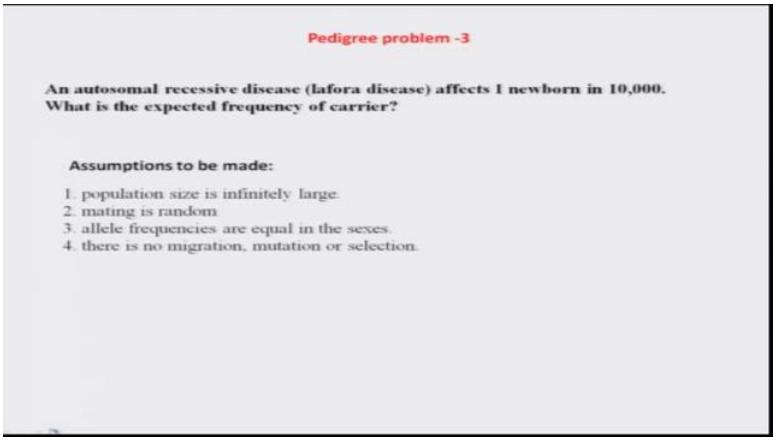

Now, there are problems to a population too. Now, let's look into such problems, that is our pedigree problem – 3 for today. So, let me read the question for you. An autosomal recessive disease, suppose lafora disease, affects one new born in 10,000, so what is the expected frequency of a carrier in a population? Till now, the problems which we were dealing was with the particular pedigree. But now, we have come to a population. So, before we solve this problems, there are few assumptions, which are required to be made, like in mathematics we do assumptions, so in genetics also, to solve a problem related to a population, we need to make some assumptions. So, what are the assumptions?

The assumptions which need to be made are that population size is infinitely large that is it is quite a large population. Mating is random, that is it is not specific that one, only a particular community be the one marrying each other. That will change the frequency of the alleles. Allele frequency are equal in the sexes that is there are no sex biasness that this particular

allele will only be in male or this particular allele will only be in female. So, not such biasness should be there. There is no migration, mutation or selection. That is in the population, the population is neither migrating nor there are mutation nor there are selections. So, why are we making these assumptions? Because we are, we need to calculate a frequency for a allele. So, we are defining the boundaries for the populations.

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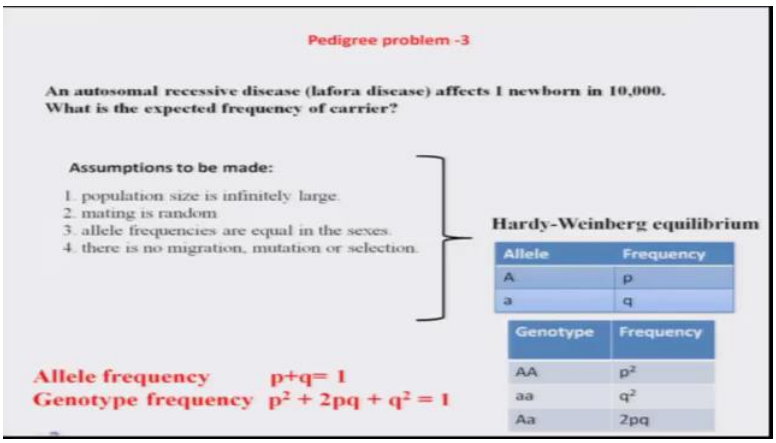

So, these assumptions, taking, if you take these assumptions, this was proposed by Hardy-Weinberg and this is the equilibrium. So, it was proposed that if there is a allele "A" and its frequency is "P", similarly there is another allele "a" and its frequency is "q", now, if you calculate the genotype frequency in the same population, the population with these assumptions, then a homozygous "AA" will p^2, a homozygous small "aa" that is q^2, excuse quiet and the carriers that is capital A and a would be 2pq. Having understood this, so there are two equations which we have, like for allele frequency p+q = 1 and for genotype frequency it is be $p^2+2pq+q^2=1$. So this, these two equations will help you solve problems related to population genetics considering the above four assumptions.

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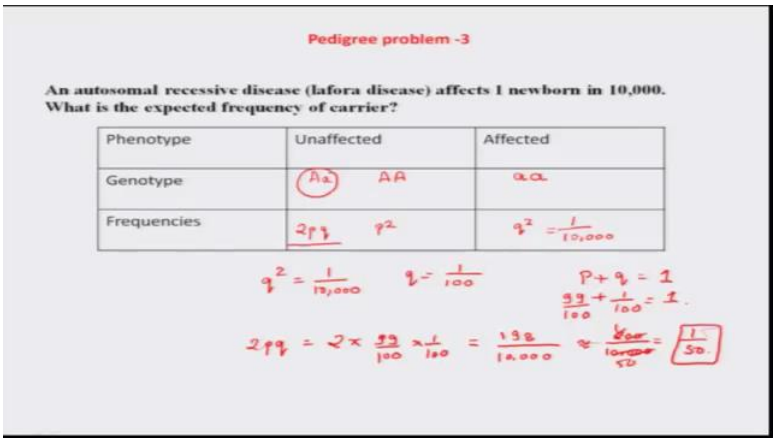

Now, let's look into the problem which was before us. So, this is an autosomal recessive disease, lafora. Now, let's look into what would be the genotype for unaffected and affected. So, genotype for the unaffected would be capital “A” and small “a” and capital “A” and capital “A” (AA). Since it is a recessive disease, so it would be only manifested into individuals who carry small “a” and small “a” (aa). So, and the frequencies if we write, this would be p^2, this would be q^2, and this would be pq. Now, we know from the problem that recessive disease, the q^2, is 1 by 10,000 and we have to figure it out what is the frequency for the carriers that is capital “A” and small “a”; that is we have to calculate 2pq. To calculate 2pq, we need to what is p here. So, if q^2 is 1 by 10,000, so q would be, very simple, 1 in 100. Now, as you remember, p+q = 1. So, if q is 1 by 100, then p would be 99 by 100, to make it 1. Now, we need to calculate 2pq. So, 2 into 99 by 100 into 1 by100(((2*99)/100)*(1/100)). Now, if you multiply, this would come around 198 on 10,000, approximately we can say 200 by 10,000, which would be 1 by 50. So, we know that the expected frequency of the carriers would be 1 by 50. That is every individual, every one individual in 50 would be carrier for this disease.

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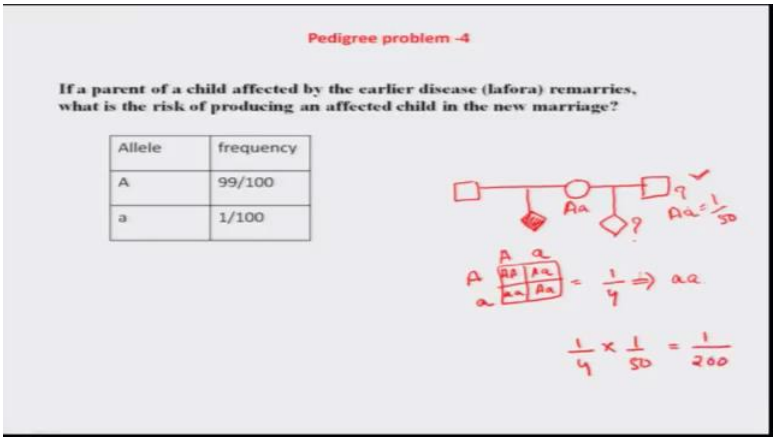

Now, let's look another problem which is related to the same. Now, if a parent of a child affected by the earlier disease, that is lafora, remarries, what is the risk of producing an affected child in the new marriage? Let's make a simple pedigree here. So, we have an affected child, we don't know the gender, so I'll just make like this and this is affected and these two are his or her parents. Now, one of the parents decides to remarry. Suppose, mother remarries and now they have, they are willing to have another child, gender we don't know. But, what is the frequency or what is the chance for producing an affected child? Now, since she had a child which was affected, so she must be a carrier for this disease. Let's write "Aa". Now, we need to know what is the frequency of, or what is the chance of this person to be carrier for the disease?

Now, as we calculated earlier, the chance for this person to be carrier that was capital "A" and small "a", if you remember it was 1 by 50 and if both are carriers, so let's draw one small punnett square, now you see that is, this is 1 by fourth chance for the child to be small a small a. So, to calculate what is the risk would be, 1 by 4 into 1 by 50 (1/4*1/50), because this person to be the carrier is, like if this person is carrier, this is 1 by 50^{th} chance and if he is carrier, and she is carrier, then this is 1 by fourth chance for the person, for the child to be affected by the disease. So, this brings us to 1 by 200. This would be the risk of producing an affected child in the new marriage.

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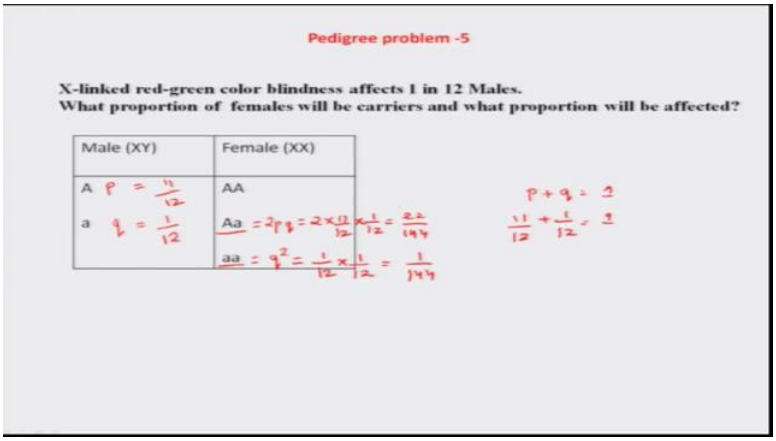

Now, let's look into problem - 5. Now, what we learned with Hardy-Weinberg equilibrium, there we assumed that every gene has two allele "A" and "a". But, there are some cases like, if we consider male, for X they are hetero, and for on this or like other, on the other hand, females they have two X chromosomes. So, when it comes to male, the equations will change. There will only be one allele, either capital "A" or small "a". However in the females, the genes which are present on X, they will follow the similar one, that is you $q^2+2pq+q^2 = 1$. Now, now let's look into the problem. This is X-linked red-green colour blindness, affects 1 in 12 males. What proportion of females will be carriers and what proportion will be affected? So, what we need to calculate here that what proportion of females would be carrier, that is capital "A" small "a" (Aa) and what proportion would be affected that is small "a" small "a" (aa).

Now, as I told, for male, so there is only one X chromosomes, so either there will be capital A or small a and from the problem we know that 1 in 12 males that is the frequency of "a" and if I say that is q it is 1 by 12. Now, if I have to calculate p, going back again, p+q = 1. So, if q is 1 by 12 (1/12), then p would be 11 by 12 (11/12) to make it 1. So, the frequency of p would be 11 by 1 (11/1). Now, I need to calculate carriers and if you remember, the carriers would be 2pq. So, this would be 2 into 11 by 12 into 1 by 12 (2*(11/12)*(1/12)), which would, 2 into 11(2*11) would be 22 and 12 into 12 (12*12) would be 144. So, the carriers, the female population would be 22 by 144 (22/144) that is out of 144 females, there would be 22 females which be, which would be carrying the, this disease. Now, we need to know what is the affected portion of the population? That is "aa" that would be q^2. So, q^2 would be

1 by 12 into 1 by 12 ((1/12)*(1/12)). So, this gives you the frequency for 1 in 144 females would be affected by the, by this disease.

So that's all and I hope, going through this class would help you solve some problems and you might, I might come up with some more problems and help you in solving them. Thank you.