Human Molecular Genetics
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Module - 01
Lecture - 02
Fundamentals of Central Dogma – Part II
(DNA, RNA and proteins; mutations)

Welcome back to this human molecular genetics course. In this particular lecture we are going to understand and discuss Central Dogma and see what are the exceptions to central dogma?

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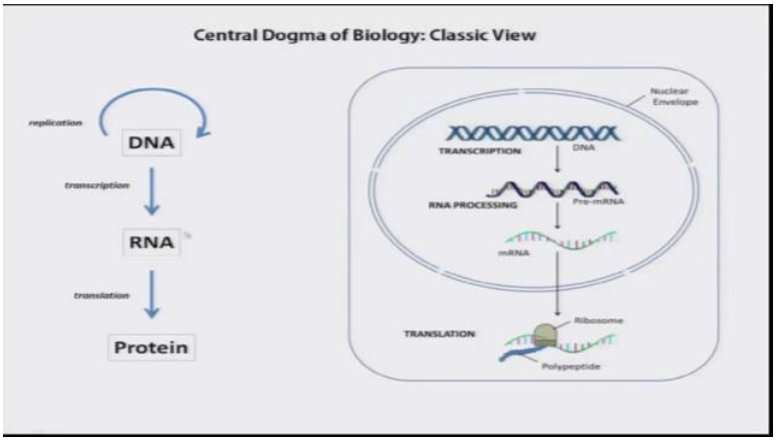

So, what we discussed in the previous class is that DNA is copied into RNA and the RNA gives signal for making the protein and proteins do the function. So, what we are going to see is that is it universal? So, everywhere is this the law that DNA to RNA to proteins? So, that is something that we are going to look at.

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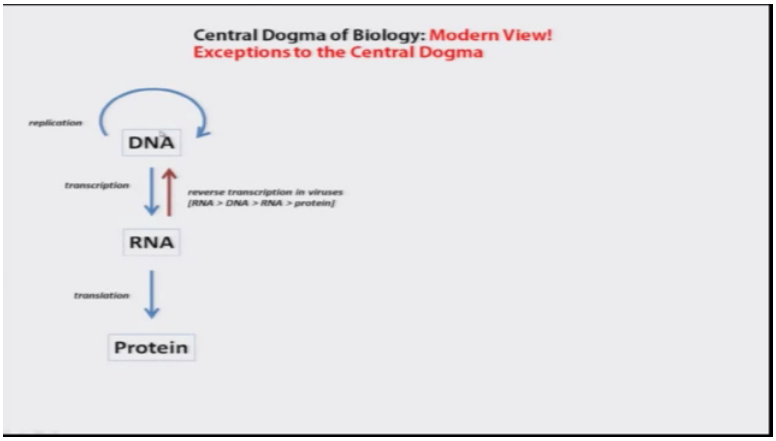

So what is the modern view? Are there any exceptions to central dogma? That is the first question that we are going to look at. So, what we know now is that the DNA to RNA copying is not unidirectional; it can happen the other way too. For example, the RNA can be copied into a DNA; that we learnt from viruses. There are viruses, which has got the RNA genome, which uses a specific type of protein, which helps them to convert the RNA into DNA and in some viruses, the DNA again is converted to RNA to make protein. So, in this way what we are trying to say is that it is not always that the DNA is copied to RNA; there are exceptions wherein you have RNA being copied into DNA; that is one.

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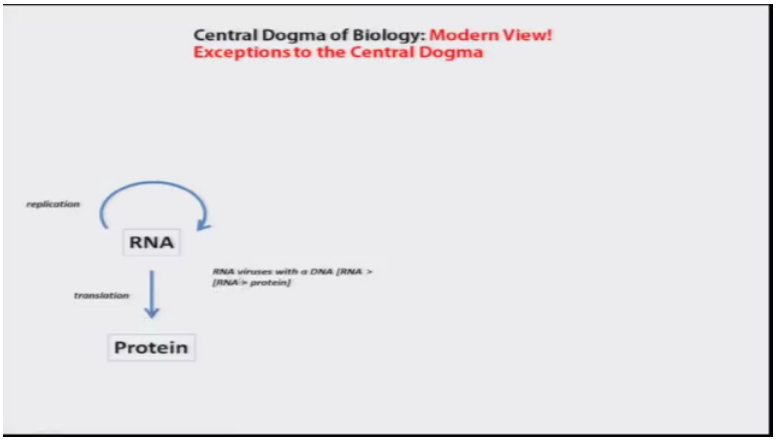

You also have other exceptions. There are viruses which do not have DNA at all; their genome itself is RNA. So, what do they do for them to make copies of their genome, which is of course RNA? They make copies of the RNA and these RNA's are either copied or directly used for making protein depending on the virus that you look at. So, therefore here what you

see is the information is processed directly from RNA to protein. They do not have DNA at all.

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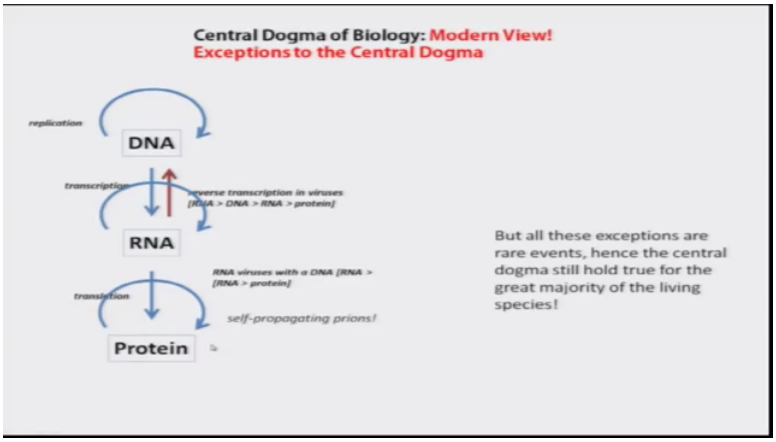

There are also other exceptions. For example, there are, know, forms which you call as prions, wherein you have the protein being copied or meaning, it is not identical but the functions of the protein being copied which is normally to form aggregates, and this is known in certain infectious disorder that could affect the brain, leading to neurodegeneration. But, still there is a debate whether these can be called as a living organism. Therefore, we do not know whether that really falls into the central dogma. But, what is known is that the protein can itself propagate, by using one or the other way of making other proteins, behave the same way; that is something earlier thought to be not possible. So, these are self-propagating species Proteins of course, they cannot live outside a living system, but still that explains that there are other forms of inheritance, meaning from one to the other the information can go through protein as well. So, these are obviously exceptions; these are rare examples. However, whatever we know of the DNA to RNA to proteins, this is still true for a great majority of the living species, therefore they obey the law; we can call it as law.

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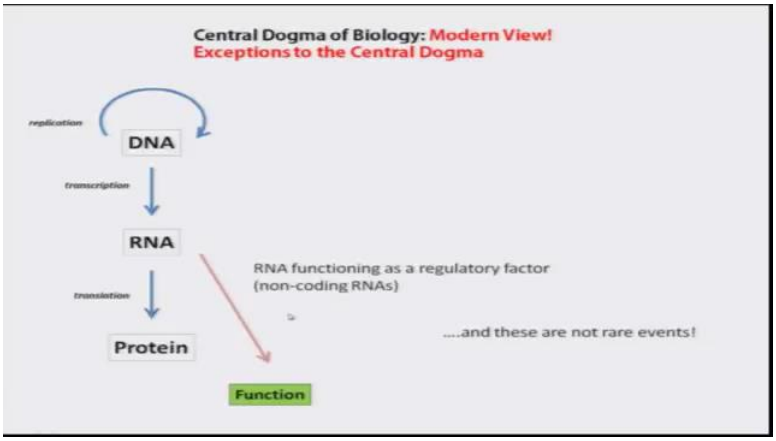

But what we know now is that there are group of RNAs which function directly as a bio-molecule, wherein, the information that they have to function as a biomolecule is not via protein, but directly as RNA and this is now emerging as one of the major players in the cellular physiology and such RNAs are called as non-coding RNAs and they are of different sizes. Some are called as micro RNA, being very small to very long, non-coding RNAs, have diverse functions. Some of them function for example as modulating the chromatin, the chromosome whether it is ready for transcription, making a transcript or not or even silencing a particular gene and many other functions. For example, of the two X chromosomes present in a human female, one is inactive and this inactivity of that particular chromosome is brought about by one of the long non-coding RNA which changes the way the chromosome behaves and makes it available for transcriptional process. Therefore, now we know that a large number of such RNAs exist in our cell, which regulates many of the physiological process. So, this is obviously one of the exceptions of the original concept of Central Dogma, that all this information has to go from DNA, RNA and then to protein. So, now you know that there are RNA that also functions directly, without being processed or copied as RNA and these are not rare events; you have in almost every cell that we talk about.

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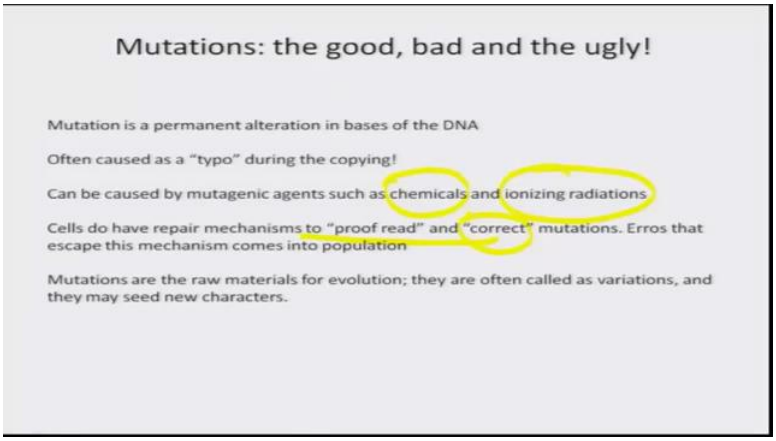

Now, with this recap of Central Dogma we are moving into a new concept that is mutations. So what are mutations? Are they good, bad, ugly, doesn't help you? So, this is the concept that we are going to discuss today, in this particular lecture. So to define mutations, mutation is a permanent alteration in bases of the DNA. When I say permanent, that every copy, every daughter cell that is being produced would have the same change in it, in the DNA; so, therefore it is permanent and it can run through families. Therefore, these are permanent alterations. How do mutations come in? Often they are caused as something like typo during copying. When you type in a computer or your cell phone, you may not spell a particular word properly. This happens because it is an error and similarly, when the DNA is being copied in your cell, sometimes there is an error the way it's being copied and this is very, very common and such errors are normally fixed by our system. Like for example you have, MS-word you have a spell check which looks into words that are not spelt properly. Similarly, in our body, cells have process which look through whether it is copied properly or not and that is why most of the errors are removed in your DNA, fortunately.

In addition to being error, there are many agents which could be chemical or physical, ionizing radiations, which can cause change in your DNA. That is what is shown here. For example, you could have chemicals and radiations which can get into your body, get into the cell and make changes and the changes could be very, very deleterious to the survival of the cell, therefore the organisms. As I told you, you have mechanisms in place in your cell, which proof read, pretty much looks at whether the copying process is accurate or not and try to correct the mutations. So, you are able to fix the mutations, remove the changes; therefore your daughter cell is identical to the mother cell. So very rarely, the errors are not fixed and if it does happen, then the error comes into the population that may, for example when the germ

cells, the one that forms sperm or egg if they have a mutation and it so happened that if these germ cells had a chance to fertilize and form an embryo, then you are going to see that change in the DNA of that particular individual and whether the individual would be normal or abnormal depends on where the change is. It could be a change no way connected to the function of any gene, then the change does not affect the individual. But if the change is there in the gene, for example that gives you a particular character, then you may develop a particular disease or for example, you may have the sixth digit like what we spoke about, so that is how know an error which escapes the proof reading process comes into populations. It is not always that the changes you see in the DNA are bad. In fact, the changes that you see are the raw material for evolution. You all look different, we behave differently. We evolve because of the changes that are there, taking place in your genome. So, these are raw materials and often the changes that you see in the genome and from one individual to the other and the populations are called as variations, meaning they are different from each other, because there is difference in your DNA and these differences can give new characters.

The characters could be beneficial or not beneficial depending on the conditions you live in. For example, there is a mutation or change in the DNA that gives me a better vision, then this may become beneficial to me in condition where there is not enough light. However in a, in a place whether it is well lit, it is not going to make a big difference. So, whether a given change gives me a phenotype is selected or not selected, beneficial or not beneficial, also depends on the condition that you are looking at. Let us see about the different mutations and when they become beneficial, when they may not be beneficial. So, what are mutations?

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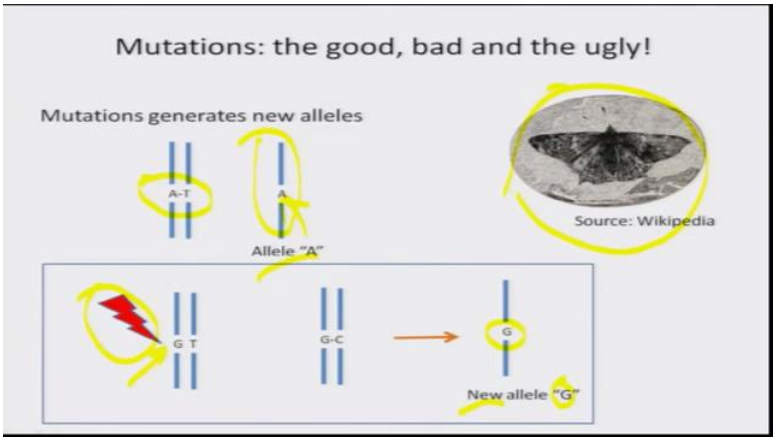

As I told you, these are changes in your DNA. So as we discussed, the DNA is made up of bases like what you see here., what is shown here in the two lines are the double strand DNA. We are looking at a particular region of the chromosome where you have the complementarity, between A and T. So, what you see normally is, if it is part of a gene, you take the coding strand and you call it as, this region it has got allele`A', because that represent this particular base. So, there could be a change. For example, you have some agent. It could be mutational event happening because of some chemical or physical agent or it is an error. When it is being copied there was a copying error, as a result instead of A you have G in that place and therefore in the coding region, you would have G instead of A. So this `G'allele, you call it as new allele because it is not present in the original parental allele, right? So, now from A to G you have a new allele that comes into population. Now, whether this would give you a new phenotype, new character depends on whether it changes the way the gene functions.

One of the classic examples shown here is a kind of insect, whose wing colour is dictated by, likewise, certain genes. So, these are pigments that are deposited. As a result, the insect would look more darker or lighter depending on how much pigment is deposited in the wing. For example, you have buildings that are around which are having darker, colour, then this insect which has got for example, dark wing color might escape from its predator. So, that gives an advantage. But however, if the building or the surroundings where these insects live have more white colour or lighter colour background, then these insects would be caught by the predators. So, as such these changes in the gene may not affect the survival of the insects or animals or humans if there is no change in the environment. So, it depends on the change,

whether it gives you a new property or not. So, it is not that always a given change would make you unfit. So, that is one aspect.

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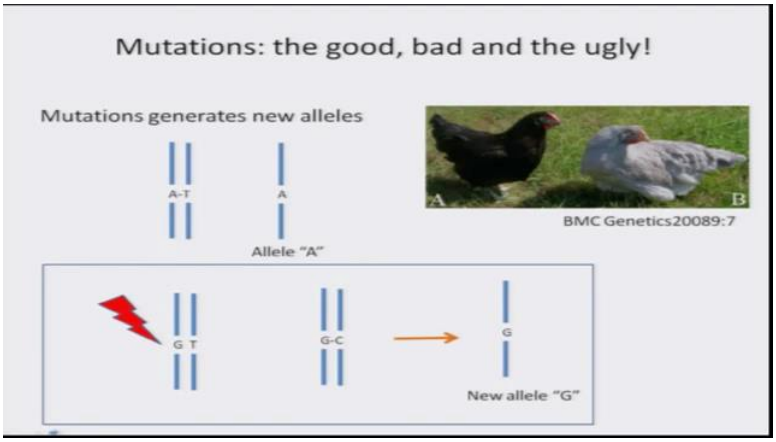

You can likewise look into the other example, wherein the feather colour in birds; these are the pigments that you see which more or less depends on the variations that you have in the gene that control the pigmentation process. But these are examples and likewise you can have other examples. So, that is what we talk about, the two terms.

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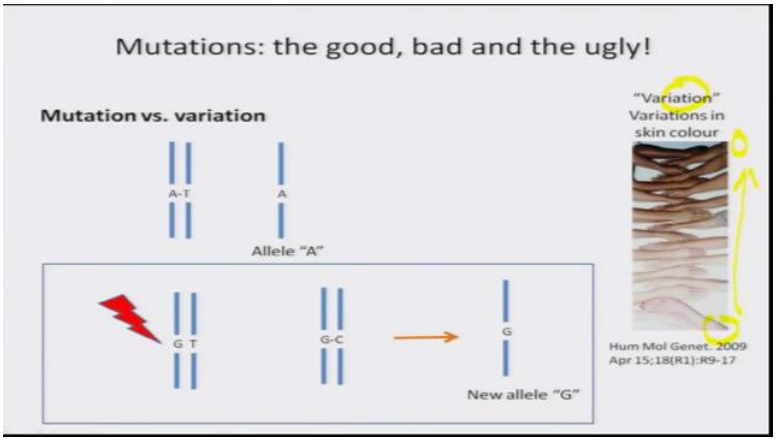

One is called as mutation, the other term what you call as variations. What is the difference between these two? For example, what is given here is variations in the skin colour. So, you have individual that have very, very fair skin to very dark skin. So, there is a gradient that you can see. This again, the change in the, skin colour is brought about by change in the pigmentation process which is a physiological process regulated by multiple enzymes and

proteins. Also depending on the kind of variation that you have, the amount of pigmentation varies, depending on your genotype. But, all of them are normal. I may be having a fair skin or darker colour skin, but I am normal otherwise; I am absolutely fine. So, these are brought about by variations in the gene, but do not affect my survival. I am as good as any other person, but that is not always the case.

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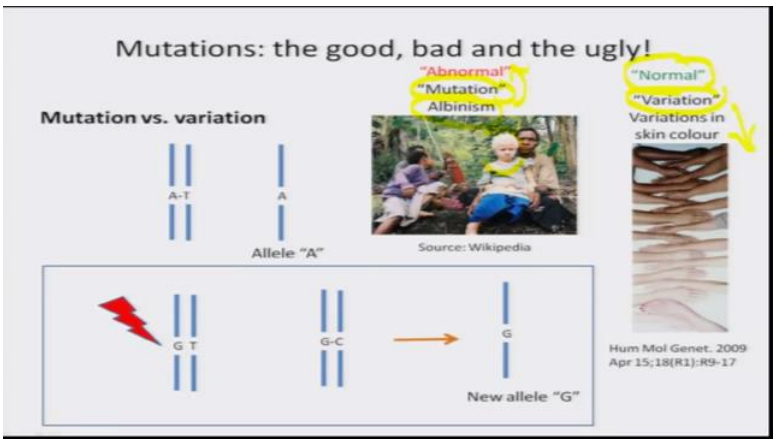

For example, here you have an individual who is affected by a condition called Albinism, wherein there is complete lack of pigmentation as you can see here these are from New Guinea Islands and you can see the population, mother and others, they have darker colour skin, but this individual is completely white, because there is no pigmentation and this might affect the survival of the individual. Here, the vision is affected; there are many other congenital problems, because of these changes. Again this happens because of change in the DNA. Whether the variations that you see which gives a different skin colour which we call as normal, because it doesn't affect their survival, the same kind of variations are also there in the DNA which makes this condition called Albinism, but this individual is abnormal, because it affects their survival. So, if a variation affects the survival or fitness of that individual, then you call that variation as mutation. If a variation is present in normal individual and it doesn't affect the fitness of that individual, you normally call it as variation? This is the definition for variation versus mutation.

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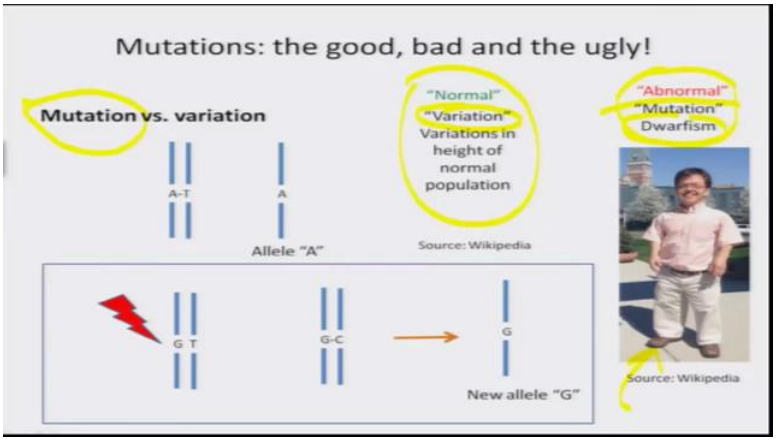

So, we will look into some more examples. For example, you have a condition called, height. If you look into your class size or your colleagues of the same age group, not all of them are of the same height. This is one of the classic examples of normal distribution. If you score the number of individual that are very tall versus very, very short and in between ranges you will find a perfect bell shaped curve which is called as normal distribution and this again is, like many of the conditions is, regulated by your genes as to how tall and so on. So, this is brought about by variations in your genes that give you different height and this is normal, because it is not that a person who is tall is abnormal or the person who is not that tall is abnormal; all of us are normal.

But there are conditions, wherein mutations affect the growth and individuals are stunted, like the one person you see here in this photograph, may be 3 feet as the height of that individual; that you call as a dwarfism, because he is abnormal, meaning in the normal population you don't see individuals that are this short. So, they are associated with certain other conditions and therefore this is abnormal, and you don't find in the normal population. Therefore we know for sure and such conditions sometimes happen because of mutations which affects even at times the fitness of the individual.

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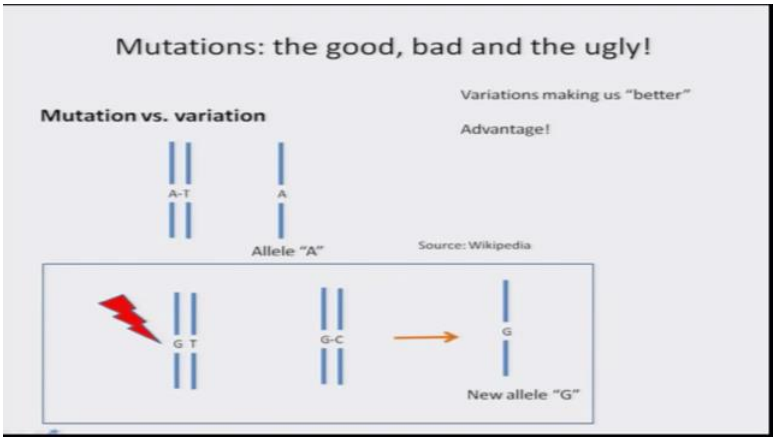

The question is that, as we discussed there are mutations that reduces your fitness, but can there by such change which increases your fitness? In fact, evolution always produces such, changes and these are selected and with time that becomes what you call it as normal. In other words, can variation make us better, give me some advantage? The answer is, yes it does.

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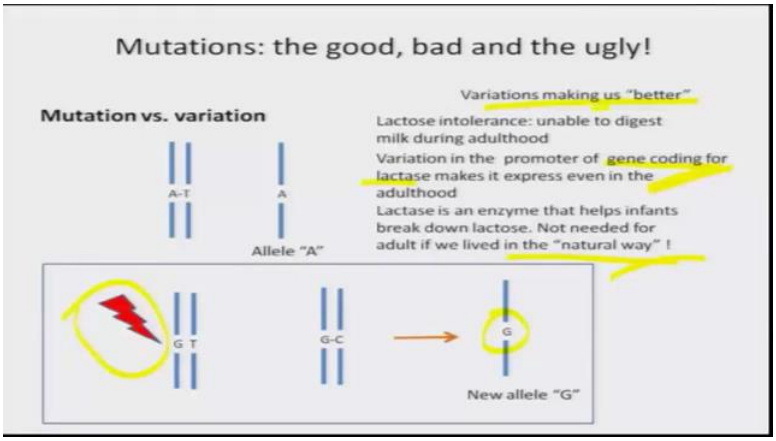

One of the examples is lactose intolerance. You may be surprised why I am calling it as advantage; let me explain. Lactose intolerance is the condition wherein when you drink milk you are unable to digest the milk. So, you have problem and it happens because of a change in a DNA, in a gene that codes for an enzyme which helps in digesting the lactose. This enzyme is called as lactase, an enzyme which helps in digesting the milk. Now, why do you say there is a variation in the promoter? The promoter as you recall, is a region on to which a transcription factor comes and binds, makes RNA and the RNA is translated into the protein.

Now, what happens if you have a change in the promoter? Now, the change is such that, the gene is expressed even when you are an adult. To begin with it was not expressed. Why? Because, you are dependent on the milk when you are young; when you become adult you are able to, take other forms of food and survive, you are able to digest. Therefore milk is not your primary food, whereas that is not the case for infants. Therefore you need enzymes to digest milk when you are young, but with time you do not need to be dependent on the milk. Therefore, your gene which helps in the digestion of milk protein is no longer required. So, what happened was there was some change, again what you call as mutation that is denoted here, which produce certain novel allele which made this particular gene which codes for the lactase to express even in the adult. Now because of the change, now you can drink milk now and you are able to digest, so that is something beneficial.

It has given you, to begin with that is not normal phenotype, but a phenotype wherein you are able to digest milk even when you are not dependent on the milk for, as a, the primary source of food. So, that is something good, we can drink milk, digest and be happy. So, that is what is written here, milk was not needed by the adult. If we lived in the natural way, then we may not be feeding on milk. Therefore, even if the gene is not expressed it doesn't matter. But, these kinds of mutations helped us, we can now digest milk. So, that is one example as to how variatons can also make us or give some phenotype that makes us better.

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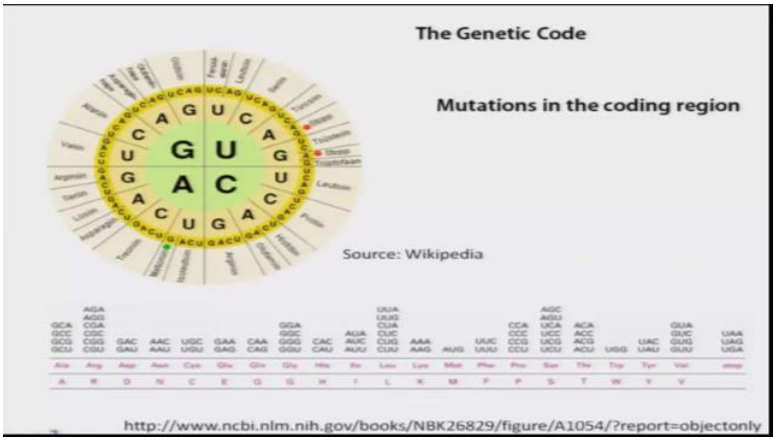

Let us going back to be genetic code, so what we discussed was there are mutations. The mutations we spoke about were there are changes in the DNA and the DNA, the new variant that came in is called as allele. So, the new allele is normally very, very rare in the population. But, if the allele has got some advantage to offer to that particular species, then

that over populate, because they are more successful; you know individual carrying that allele is more successful as compared to the others and therefore the allele spreads in the population. They are successful, they marry more and their descendants will carry that allele. Therefore they are more successful and so on, then it becomes the normal or the so called the wild type, like for example the lactose intolerance what you call now has become a minority and, and in fact that was wild type to begin with.

So, how does the mutation really affect the gene function? Majority of the mutations or the mutational events are random, meaning when the changes happen, the changes are random. It happens anywhere; it is just like you are blind folded. I am given a gun, I Just shoot. I don't see anybody, I shoot; but this room is full of people, then, more often than not I am going to hit one or the other. But, if it is only one individual in this room, if I tried three different bullets, then whether or not I will be able to hit that person the probability goes down, something like that. So, your DNA has got, the bases and the genes are not spread out or present in every segment of the DNA. They are, spread out throughout the chromosome. So, if the mutational process is random, then normally the probability of a change in the DNA affecting a gene goes down. So, more often when the change happens in the so called coding region, the region of the DNA that gives you the codes, then the probability of that particular change affecting the protein function goes up. So, that is what we are going to discuss. We are going to discuss how mutations in the coding region affect or what are the different types of mutations that may affect the coding region.

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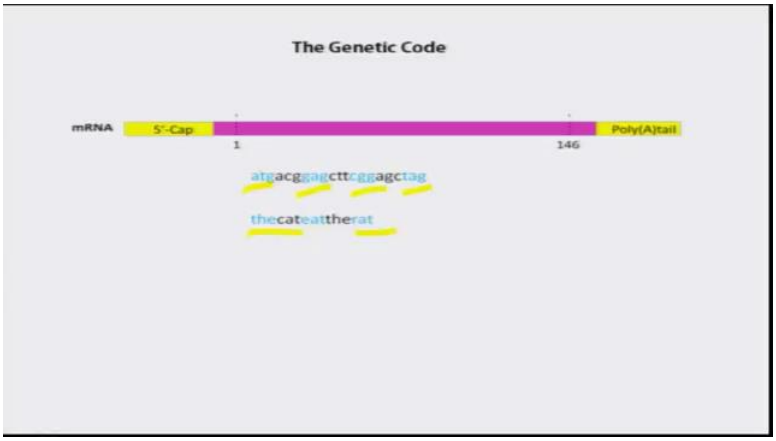

Let us come back and look into how the mutations can affect the coding region. So, this is something that we already discussed. That is you have a genetic code given in your DNA that is being copied by the RNA and we said that the genetic code is a triplet; as we discussed that, for example each one giving a particular signal for a particular amino acid as shown here. So, when it is grouped like this, I am able to read it as `the cat eat the rat'. So, what happens in the mutational process?

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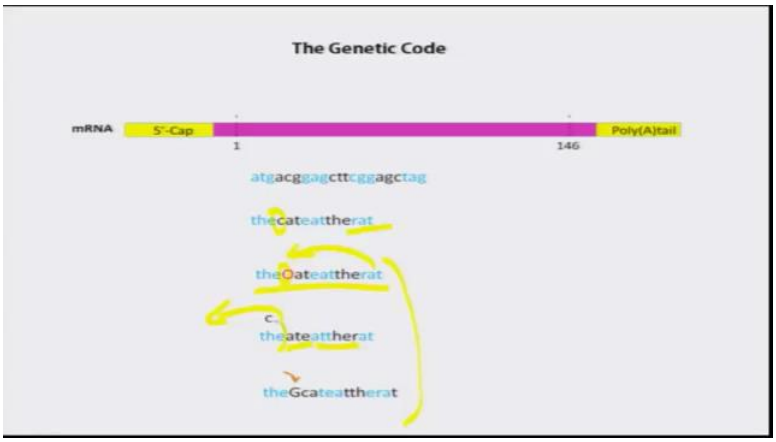

There are various ways of mutations. For example, we are going to discuss only this part that is the one example using the three letter alphabetic sentence that we can read in English. So, let us say that, 'C', this particular base, let's call it as a base, now that gets replaced by a different base let's say 'O'. Then this change affects the meaning of the sentence. What we said was the predator cat is able to eat its prey, which is rat. Now, because of one base change the meaning is affected. As a result, what you have is that the predator for the rat could be

oat, a meal that is eating for example the rat, which is meaningless; it cannot happen. Therefore, you have changes that may change the meaning.

You have another example wherein one of the base is removed. As a result, the triplet now starts again, the loss of which now you are unable to read it; the C is gone, now I am unable to construct the three letter sentence once again or I add a new base here that pretty much shifts. Therefore, again I cannot read. So, these are the different kinds of mutations. So, what we have discussed is how changes in your DNA can be grouped either as a mutation or as a variation when the change affects the way the protein functions or the gene functions and therefore the cellular process is compromised you call it as mutation. But, if the change does not really affect the survival of the cell and survival of the individual, then you call it as variation. That pretty much summarizes how a change in the DNA can affect an individual or alter an individual's ability to cope up with a new challenge. So, with that we end this particular lecture and in the next lecture we will see how the variations affect the proteins function.