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W5L27_Gene Mutations and Genetic Disorders (Guest Lecture) Dr. Antara Das, Azim Premji University

Hello all. Welcome back to the I Think Biology Lecture series on genetics. My name is Antara Das. I am a faculty at the Azim Premji University. Today I will be discussing gene mutations, their causes, and how they lead to genetic disorders.

The main aim of this lecture is to give an overview of gene mutations and we will be comparing point mutations and large chromosomal abnormalities. We will distinguish between silent mutations, missense, and nonsense mutations. We will identify a few commonly known genetic disorders and look at their causes. So, what is a mutation? A mutation is a heritable change in the DNA sequence of an organism.

Such an organism with an altered DNA sequence is also called a mutant. The mutant may have an easily detectable morphological change in the phenotype compared to their wild-type counterparts. For example, the coat color in animals, black versus albino or flower, and petal colors in plants could be an example of a phenotype. What causes mutation? Sometimes mutations can be spontaneous. It could result in a change in DNA sequence during DNA replication transcription or other processes.

The mutations could also be induced by chemical relations such as ethyl methyl sulfate, and ethyl bromide which is an intercalating agent or it could be induced by radiation such as exposure to UV rays, X-rays, or gamma rays. All cells in our body possess DNA repair enzymes that try to minimize the number of mutations. However, sometimes the patients can escape these checkpoints and when these mutations occur, what are the effects? So, the Center Dogma of genetic information dictates that DNA codes for genes, and these are transcribed into an mRNA. mRNA is then translated into proteins. A gene will often encode information to form a protein and these proteins are biomolecules that perform a variety of functions in the cell.

When there is a change or a mutation in the DNA sequence, it can result in a misfolded protein, a truncated protein, or a completely non-functional protein. This protein change can also result in

a different phenotype and that can be easily seen or sometimes the phenotype also could be hidden. Here is an example. Each line represents a chromosome and we have two homologous chromosomes, one from each of our parents. Each homologous chromosome is made up of double-stranded DNA and here we can see a wild-type sequence and there is no change in the DNA sequence.

If there is a mutation, in this case, the mutation is shown in red point in homolog 2, the AT sequence has changed to CG. Now this change from A to T in homolog 1 to C to G in homolog 2 is an example of a point mutation and sometimes these mutations are simply referred to as A to C mutation. An individual who carries a mutant allele in only one of its homologous chromosomes but carries a wild-type allele in the other homologous chromosome is referred to as a heterozygous individual. Since there is only one base pair in the DNA sequence that is affected by this mutation, this is an example of a point mutation. However, gene mutations could be broadly classified into two types.

First are the point mutations which involve a mutation in one or a few adjacent base pairs. But there could be large-scale changes in the gene and it could involve several genes in a chromosome, it could be a complete duplication of a chromosome or complete loss of a chromosome. We are going to first look at different kinds of point mutations and among point mutations, we could divide them into base substitution mutations or indels. We're going to first look at base substitution mutations. Base substitution mutation is nothing but when a base is released by another base.

Now we know that there are four nucleotide bases in DNA and if a purine is released by a purine or a pyrimidine is replaced by another pyrimidine then those mutations are called transition mutations. So here in the diagram, we can see that an A to G conversion or G to A conversion will classify as transition and similarly, C to T and or T to C will be classified as transition mutations. However, if a purine is released by a pyrimidine or vice versa then those mutations are called transversions. So for example, if it's an A to C mutation or a C to A mutation those mutations are referred to as transversions. Now going back to our previous exam here we can see that only one base pair was erected it is a base substitution mutation and the change from the wild type is from A to C hence it's a transversion mutation.

Now based on the chemical nature of the base substitutions, we could further divide them into synonymous or silent mutations, non-synonymous or recess mutations, or non-sense mutations. This classification applies to genes that code for proteins and we will see why. Silent mutations are those that do not affect the protein sequence. Here what you can see is a DNA sequence and hence you can see T instead of U's these will then they will be converted to mRNA the thymine residues are going to be replaced by an acid. Nonetheless when we look at the base pairs they form a triplet and each of them will be coding for an amino acid.

If you look at the second amino acid over here this is valine and it is coded by GTA. Now when this A is replaced by a T the amino acid valine remains the same. This is an example of a silent mutation. So here the A in valine is replaced by T. It's a transversion mutation but the amino acid sequence of the protein remains the same. Hence the effect of the mutation on the protein and the phenotype sometimes can remain undetected because there was no change to the protein sequence and hence very no change in the phenotype.

Missense mutation on the other hand results in an amino acid substitution which means that one amino acid is replaced by another amino acid. Now over here if you look at the third amino acid which is protein it's coded by CCC and in the mutated sequence it's changed to threonine which is coded by ACC. Now when such a substitution reaction mutation happens such an amino acid protein is changed to something else such as threonine here these mutations are known as missense mutations. Here in the triplet, we see that the C is mutated to an A residue so this again is an example of a transversion mutation. The amino acid sequence from the wild type has been altered and hence it is likely to change the structure and or function of the protein and hence it would have an effect on the phenotype.

Nonsense mutations substitute an amino acid residue with a stop codon. So in this example, the last residue is tyrosine coded by TAC; it is mutated to TAG which will code for a stop codon. Now we can see that the C is changed to G over here so this is again an example of a transversion mutation. The mutated sequence now has a stop codon. If the stop codon is in the middle of the protein sequence, truncated protein will be produced.

Truncated proteins most likely go for a non-functional protein or they are degraded hence it will lead to a very pronounced phenotype. Now we said that the point mutations could also have indels. Indels are mutations in which either a base pair is added or a base pair is deleted. So indels can again have one of the few base pairs that are either added to the DNA sequence or they are removed from the DNA sequence and because of this indels lead to what we call spring shift mutations because they affect the reading frame of the amino acid sequences. As a result of indels the amino acid sequence is altered and this can either result in a truncated protein or it could lead to a non-functional protein; it depends on the nature of the indels.

An example of an indel is seen here. So we have a wild-type sequence that goes for four amino acids, serine, valine, proline, and tyrosine. If two base pairs U and E are deleted then the reading frame changes from serine, alanine, leucine, and leucine. So we can see that deletion of two base pairs changes the reading frame and now we have a completely different sequence of amino acids hence the polyurethane chain would also undergo changes depending on the amino acid sequence and this can lead to a change in the phenotype. So how do these gene mutations lead to genetic disorders?

A genetic disorder is a disease that is caused by a change in the DNA sequence. Genetic disorders can be caused by a mutation in one gene or multiple genes or a combination of genes and environmental factors. They can also be observed in large-scale changes to the chromosome structure such as changes in the number or structure of the entire chromosomes. Sickle cell anemia is a form of an inherited blood disorder. Sickle cell anemia affects the red blood cells turning them into sticky, sickled, or curve-shaped RBCs instead of the normal RBCs. As a result, these RBCs with curved or sickle shapes are unable to perform the functions of normal RBCs.

The disease is caused by a missense mutation in the beta hemoglobin gene. So in the normal gene, we have GAG which goes for a Glutamic acid. In sickle cell mutation, it changes to GUG which now codes for Valine and this nonsense mutation results in the phenotype of the red blood cells changing from a round normal shape to the sickle shape.

Genetic epilepsy. Epilepsy is a neurological disorder. It is characterized by uncontrolled body seizures. Genetic epilepsy can have many different forms and they follow an inheritance pattern that means that it can be passed on from parents to offspring. A missense mutation in the voltage-gated sodium ion channel called SCN1A causes seizures in humans. In a particular case of such a genetic epilepsy, the normal individual in the SCN gene has the following code CTCAAATGG which codes for leucine, lysine, and Tryptophan. For an epileptic individual instead of having lysine, it codes for threonine by changing the base pair from AAA to ACA. This codes for threonine and now the sequence of the amino acids has changed This one amino acid change can lead to a seizure disorder.

Huntington's disease. This is an autosomal dominant disorder. The mutation is in a gene called Huntington which when mutated leads to the Huntington protein getting aggregated in neurons and thus slowly killing the neurons. This disease has a mid to late-onset in humans and the mutation arises when there are excess repeats of a particular codon called CAG and more than 36 repeats of CAG would lead to a mutated Huntington protein aggregate whereas normal individuals have less than 25 repeats of the CAG in the Huntington gene.

So only if this Huntington gene has excess repeats of this particular codon CAG it will form these protein aggregates and lead to cell death. So what do you mean by autosomal dominant disorder? Here is an example. So if a parent has Huntington's disease and the other parent is normal and doesn't have Huntington's disease then they have a 50% chance of having a child with Huntington's disease. So the capital H which represents the dominant mutant form of the gene will cause this Huntington protein to aggregate and will be inherited by 50% of the proteins hence any child of such parents will have the likelihood to have Huntington's disease with the 50% chance. So one copy of the new gene is enough to cause the disease.

Genetic disorders can come in many forms. There are many or more genetic disorders that are known to humans. Some are autosomal like Huntington's disease, achondroplasia which is a

form of dwarfism. The others could be x-linked such as hemophilia, Duchene muscular dystrophy, etc. Others could be caused by polygenic disorders which means there is more than one gene involved and these include disorders like hypertension, diabetes, congenital heart defects, and others.

Now lastly I also want to discuss chromosomal aberrations which are changes that affect several genes in a chromosome and could involve either the addition or deletion of an entire chromosome completely. So it could be a deletion event so a part of a few of the genes on a particular chromosome could be deleted. It will result in a chromosome that's shorter in length. The opposite could happen. It could have a duplication event where one or several genes in a chromosome are doubled and hence it will result in a slightly longer chromosome.

They could also have something called a translocation event where the genes on one homologous chromosome are exchanged with another chromosome and the position of the genes are changed. Now what are some of the examples of chromosomal aberrations? Very commonly Down syndrome. It is because of a gain of an extra chromosome specifically the twenty-first chromosome and over here we can see that in the karyotype we can see that there are three copies of the twenty-first chromosome which means that this individual has an extra copy of the twenty-first chromosome. Down syndrome leads to distinct facial features, and intellectual disability and causes developmental delays. Early intervention approaches can help people to manage Down syndrome.

We could also have a chromosomal loss and Turner's syndrome is an example of that. It's a congenital condition that affects women. These individuals have only one X chromosome so they have 44 plus one X chromosome so they are missing one chromosome Turner syndrome leads to short height and leads to another kind of developmental defects. And with that, I would like to summarize today's lecture with the following points. We saw that gene mutations could arise because of spontaneous events or they could be induced by environmental factors. Base substitution mutations can lead to silent, missense sense, or nonsense mutations. Indels can lead to frameshift mutations. Gene mutations can lead to loss of function and cause genetic disorders. Large-scale chromosomal aberrations can result in changes and lead to genetic disorders as well. With that, I would like to thank everybody for joining us today. See you in the next series. Thank you.