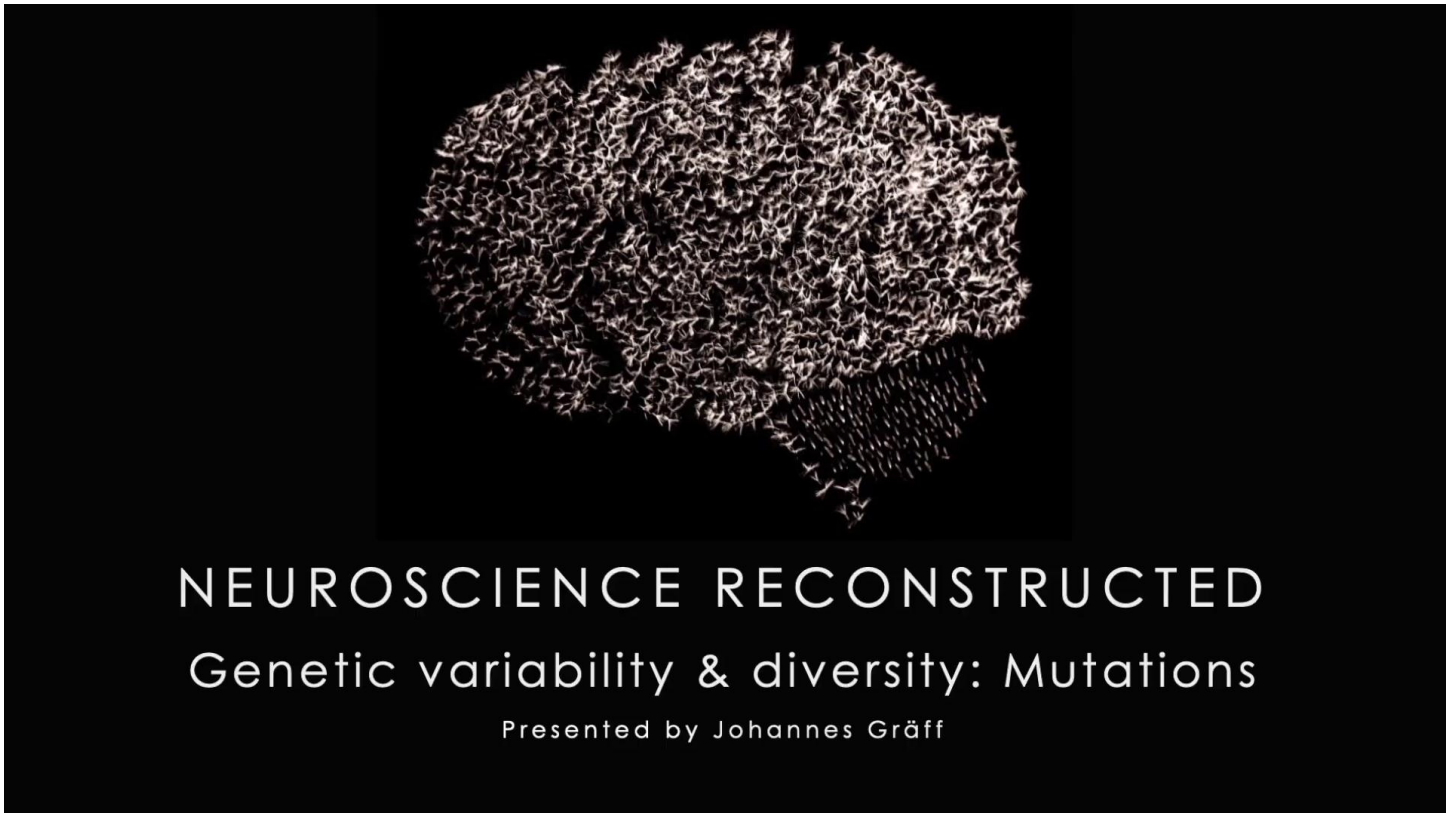

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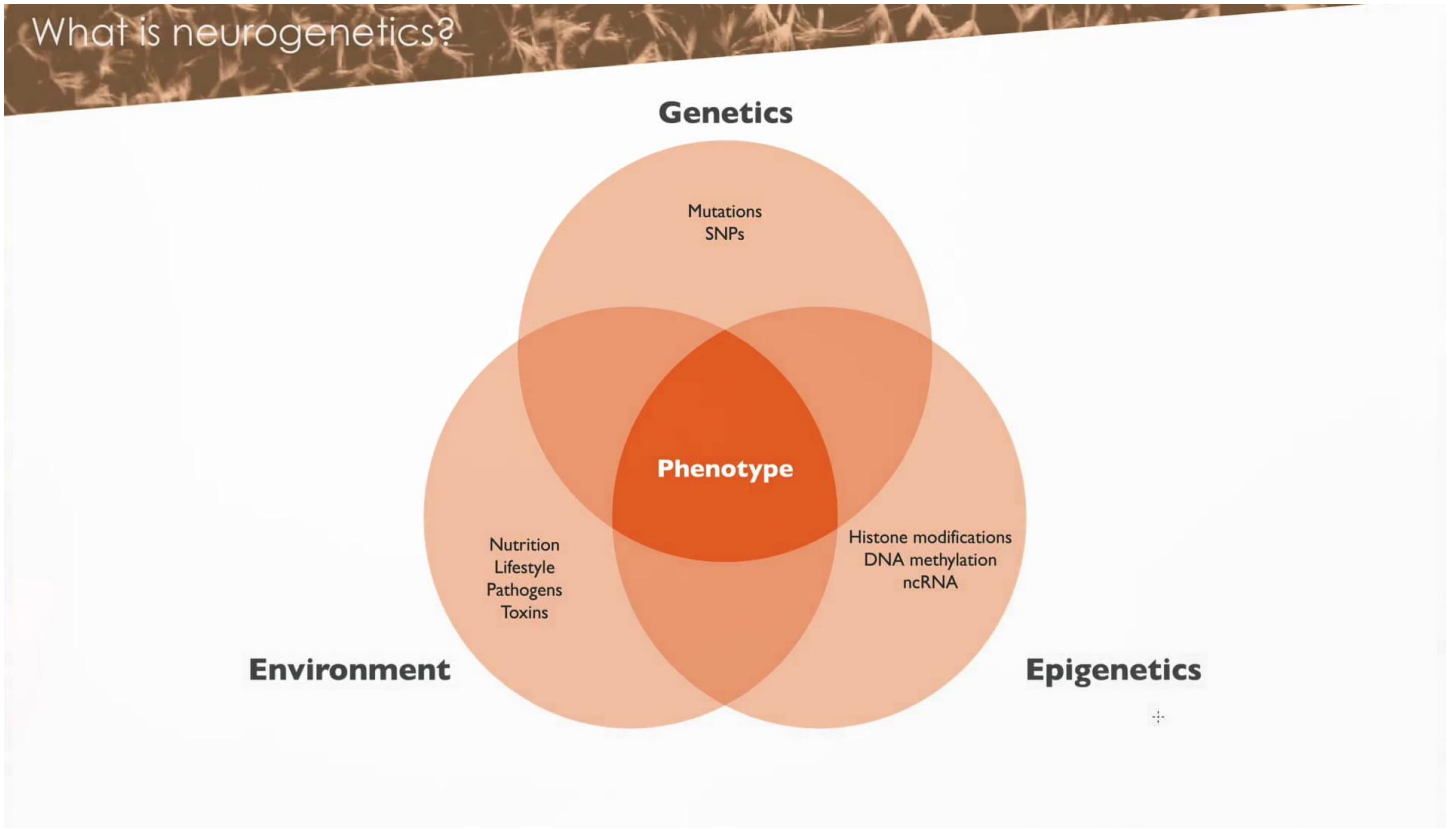


When we talk about genetics, then we talk about gene regulatory networks, mutations, single nucleotide polymorphisms, that together with epigenetic modifications, bring the phenotype into being. We're going to spend the next few minutes looking deeper... Delving deeper into the mutations and the single nucleotide polymorphisms.

Notes

Summary

0m 05s

Genetic variability & diversity

Genetic variability

Presence of genetic characteristics (genotype) that vary

Genetic diversity

Proportion of polymorphic loci across the genome

Importance

Biodiversity, adaptability and evolution

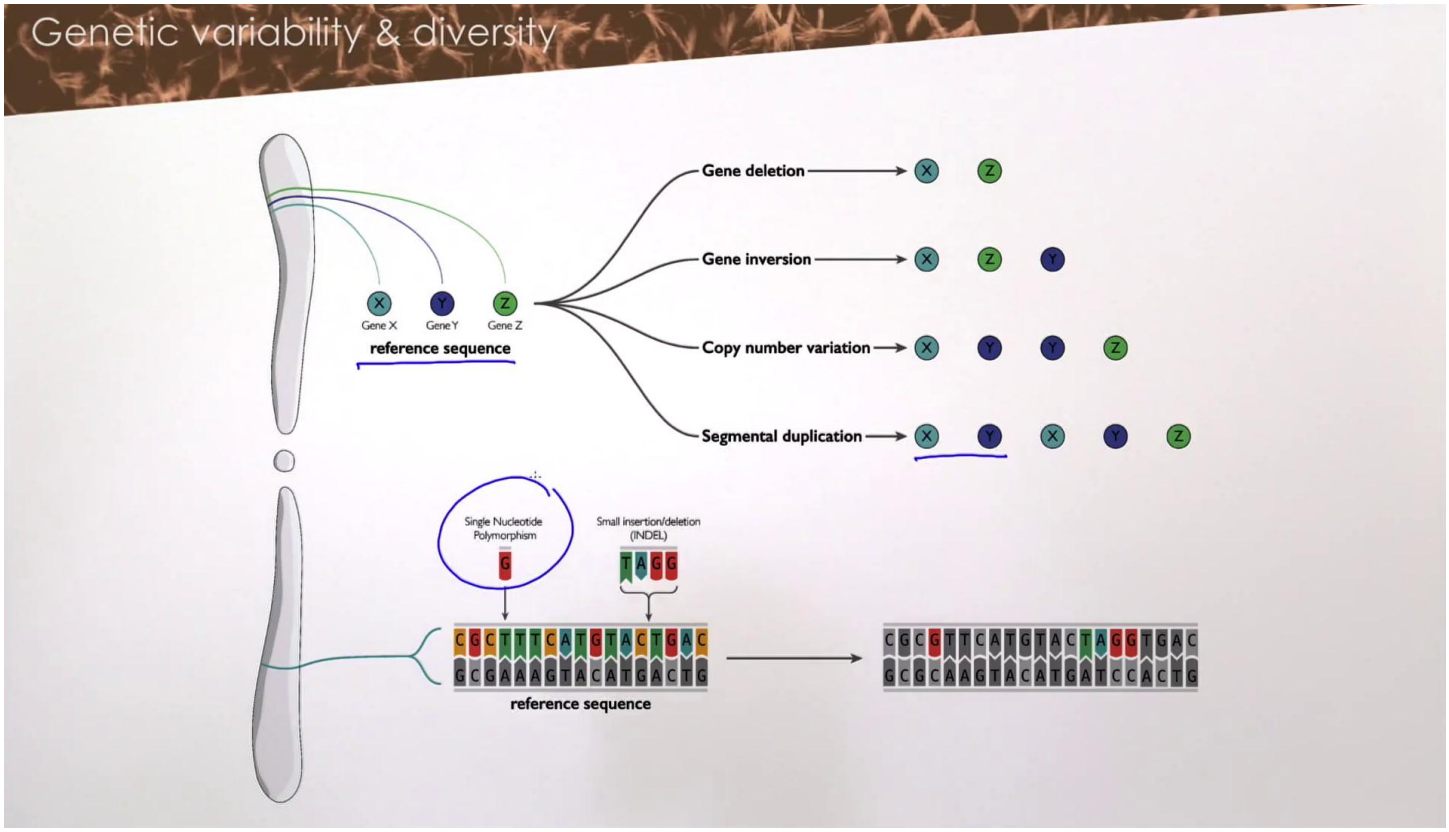
Epidemiology, genetic risk factors and personalized medicine

What do we mean when we talk about genetic variability and diversity? By definition, genetic variability, is the presence of genetic characteristics such as different genotypes that vary. Genetic diversity is the proportion of polymorphic loci across a given genome. The importance of genetic variability and diversity, becomes obvious if we think about biodiversity, adaptability and evolution. Because evolution could not happen, without the presence of genetic diversity. Furthermore, the importance of genetic variability and diversity is also given on a translational level, going into medicine, because only with genetic diversity and variability can we fully understand the epidemiological consequences of a given disease. Can we understand the genetic risk factors that predispose a carrier to develop a certain disease, and can we then move into what is called personalised medicine treatment approaches.

Notes

Summary

0m 29s

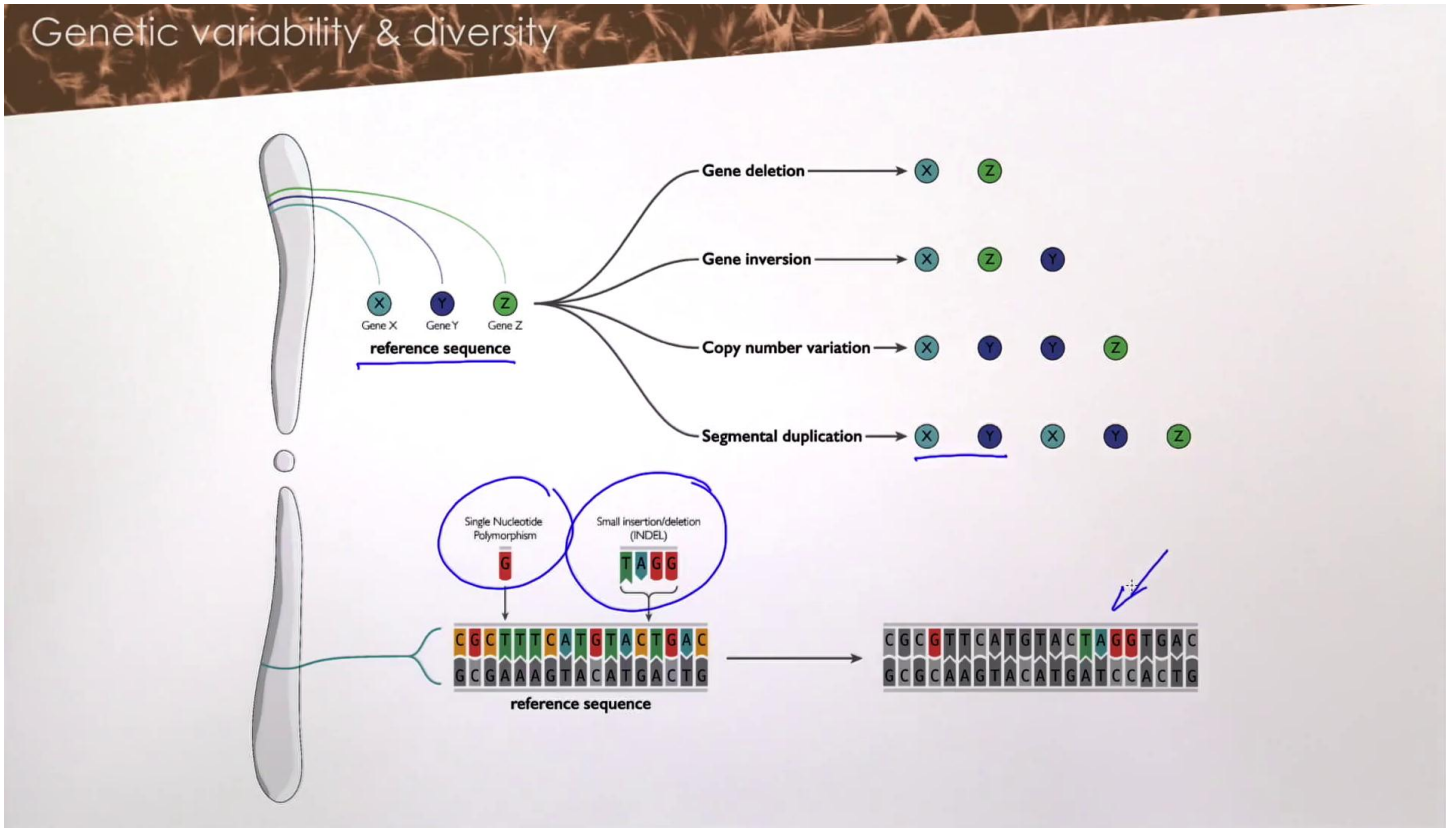


If we look now at genetic variability, between different genes, let's assume then that we have a given reference sequence that is composed of gene X gene Y and gene Y, and gene Z. Through a process of gene deletion, what can happen is that we simply get rid of gene Y in the middle so that the ultimate sequence is only going to be composed of gene X and gene Z. What we can also have, that leads to genetic variability, is a so called gene inversion. Gene inversion makes that in this case, gene Z and gene Y have switched their positions so that the ultimate sequence of our three reference genes is X ZY and no longer XYZ. Furthermore, we can have a phenomenon called copy number variation in which gene Y has been duplicated. So the ultimate sequence will be XYYZ. Or we can even segmentally duplicate a given sequence. In this case, we have duplicated the sequence X and Y, so we have two times X, Y which makes that the ultimate sequence is going to be composed of XYXYZ. Now, inside a given reference sequence, we can have have the occurrence of so called single nucleotide polymorphism, which is nothing else than the substitution of a given base in our reference sequence.

Notes

Summary

1m 33s

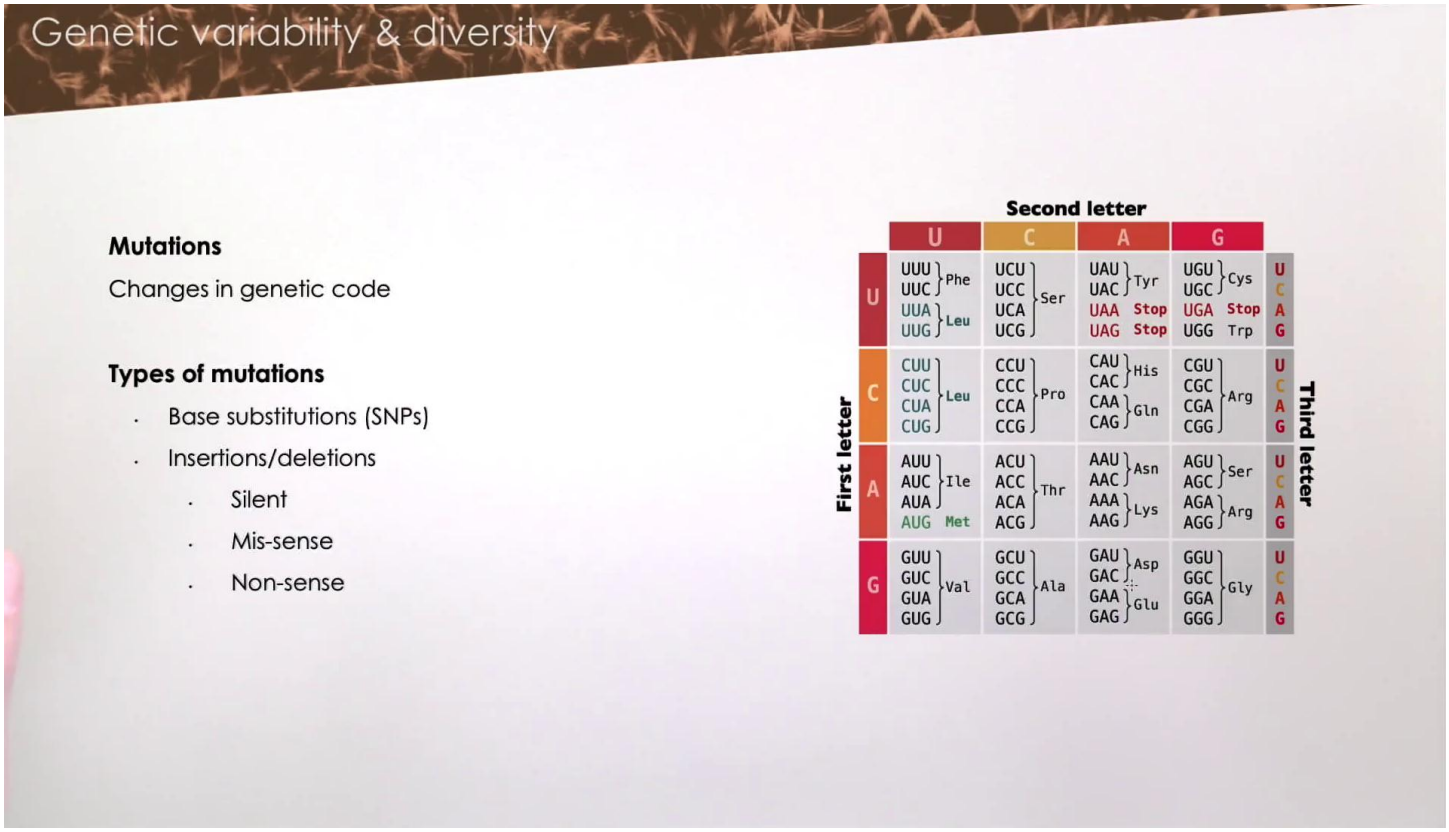


In our case, this would be thymine, which has been replaced with guanosine, which obviously changes the reference sequence. At the same time, we can also have something that is called an indel, which can either be an insertion or a deletion of the reference sequence. In this case, what we are going to insert is four but different basis, TAGG, so that the outcoming sequence has been modified accordingly to be coding now for a different reference sequence.

Notes

Summary

3m 10s

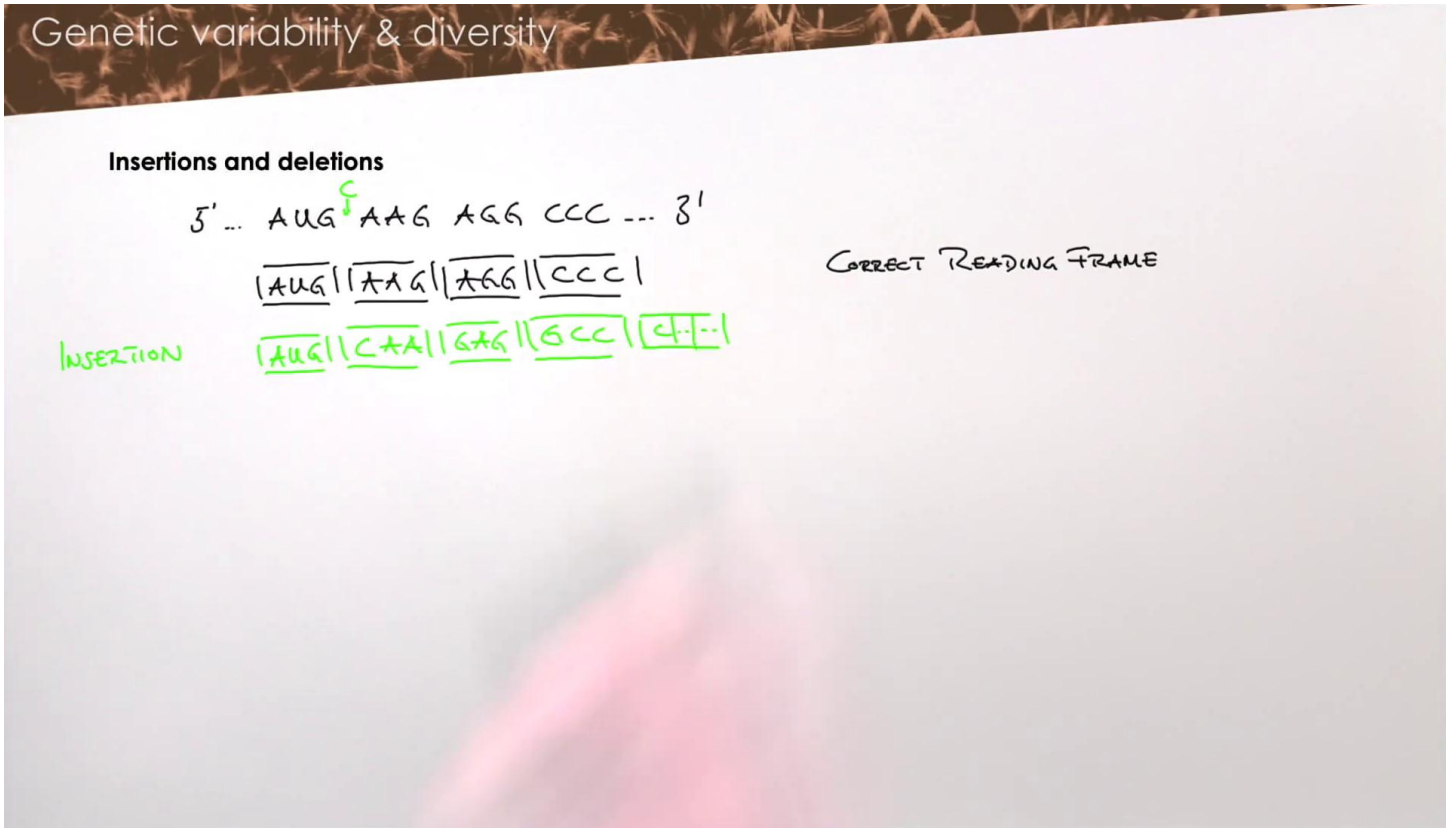


What these changes then lead to are so called mutations. Mutations by definition are nothing else than changes in the genetic code as we have seen last time, which is defined by three letter codons. The types of mutations that we can have are base substitutions, which is equivalent to single nucleotide polymorphism as seen on the slide before, and what we can also have is these so called indels, which are insertions and deletions.

Notes

Summary

3m 46s

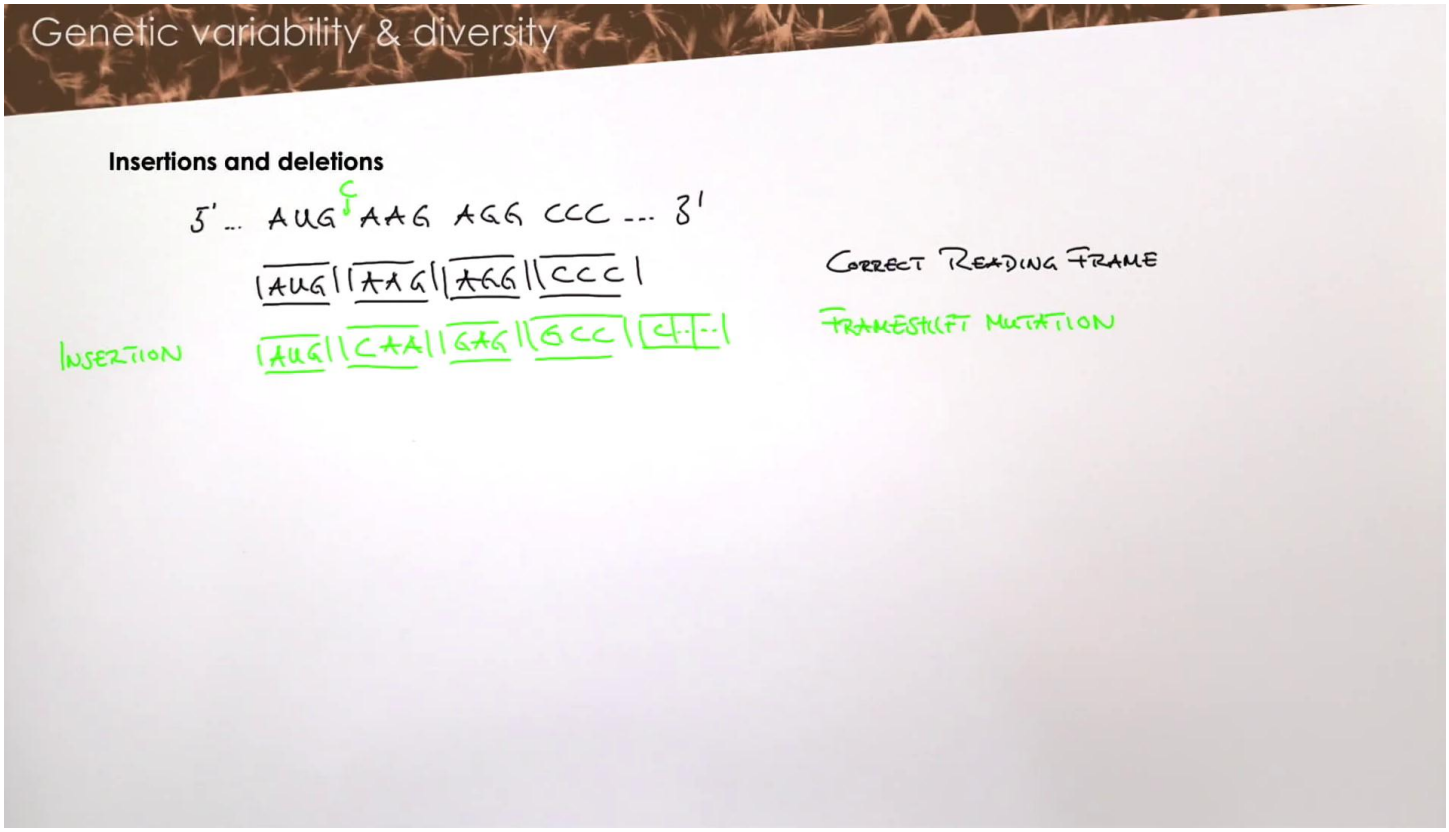


On the next slide, we're going to understand better, the consequences of such insertions and deletions which can be silent, which can be mis-sense, or which can benon-sense In order to understand insertions and deletions better, we're going to draw a reference sequence up here which has a directionality, five prime two, three prime, which we will draw on the level of the mRNA sequence. We're going to have AUG, AAG, AGG and CCC. This, as you know, is this language of nucleic acid on the mRNA level. If it is coding for a gene, is written in so called codons. This stipulates that the result in codon sequence is as follows. We have AUG, codon number one, AAG, codon number two, AGG codon number three, and CCC codon number four. This we will call is the correct reading frame. Now, let's assume that we have an insertion, and let's assume that we're going to insert a cytosine here, in which case our sequence will be changed as follows. The first codon remains untouched, AUG, but that then we have this inserted C, so it changes the content of each codon that is downstream of the insertion. Here we will have GAG, GCC, and another codon that will start with C.

Notes

Summary

4m 18s

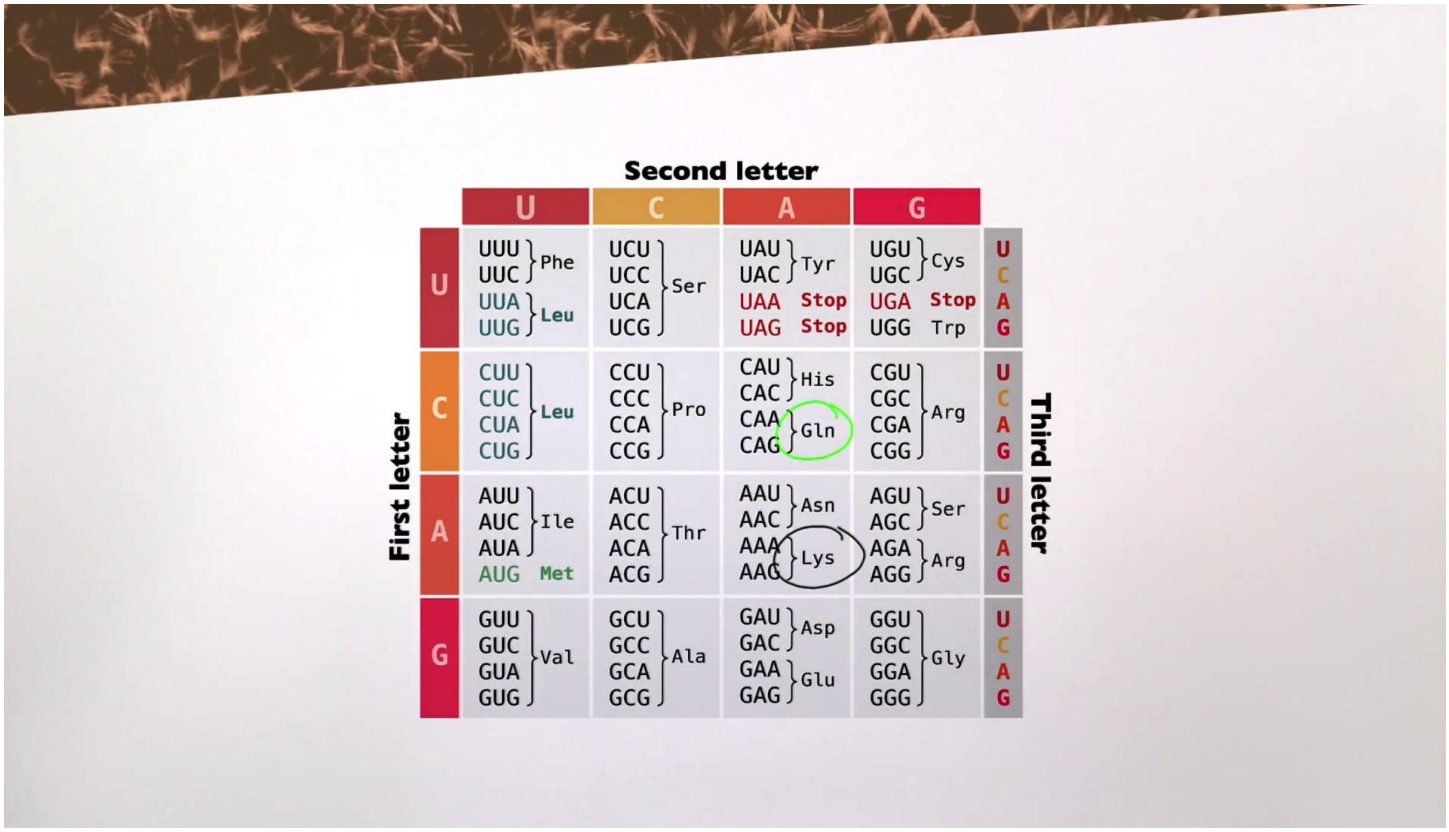


What happened here is that we have, an insertion of the cytosine, which shifted the reading frame of the codon. Hence, this is called a frame shift mutation. Now, let's go for a second to the genetic code and see the consequences of this frame shift mutation on the outcome on the protein level.

Notes

Summary

6m 23s

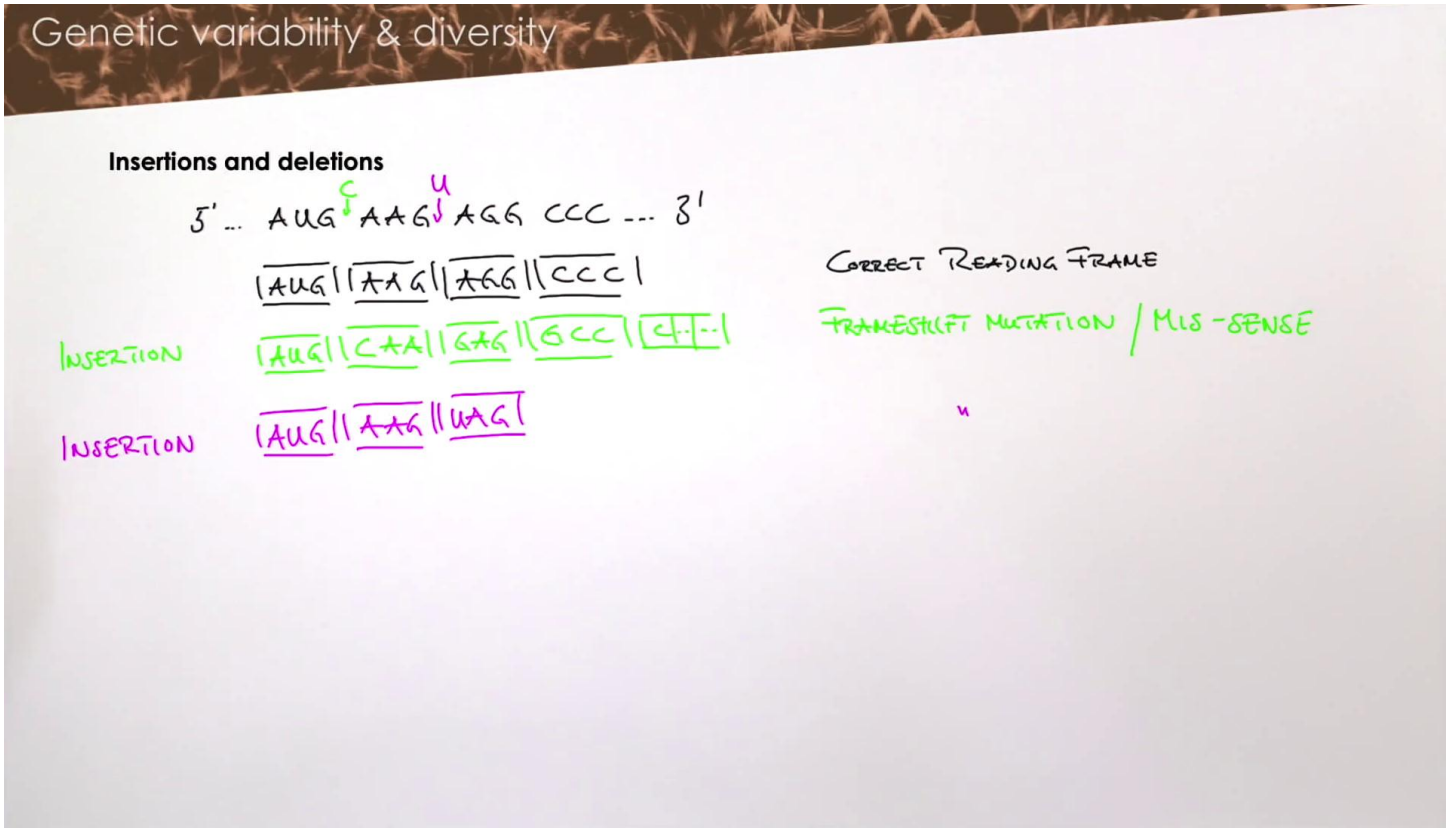


Let's look, for instance, at the second codon. In the correct reading frame, we had the letters A, A, G, meaning that this codon codes for the amino acid lysine. Now, let's look at the second codon after the frame shift mutation, which is now composed of a C, an A, and another A. In which case this codon now codes for the amino acid glutamine. Now, in this case, if the frame shift mutation happened, yet the codons are still functional, they have just changed their meaning between lysine and glutamine, we refer to as this mutation being a so called mis-sense mutation.

Notes

Summary

6m 50s

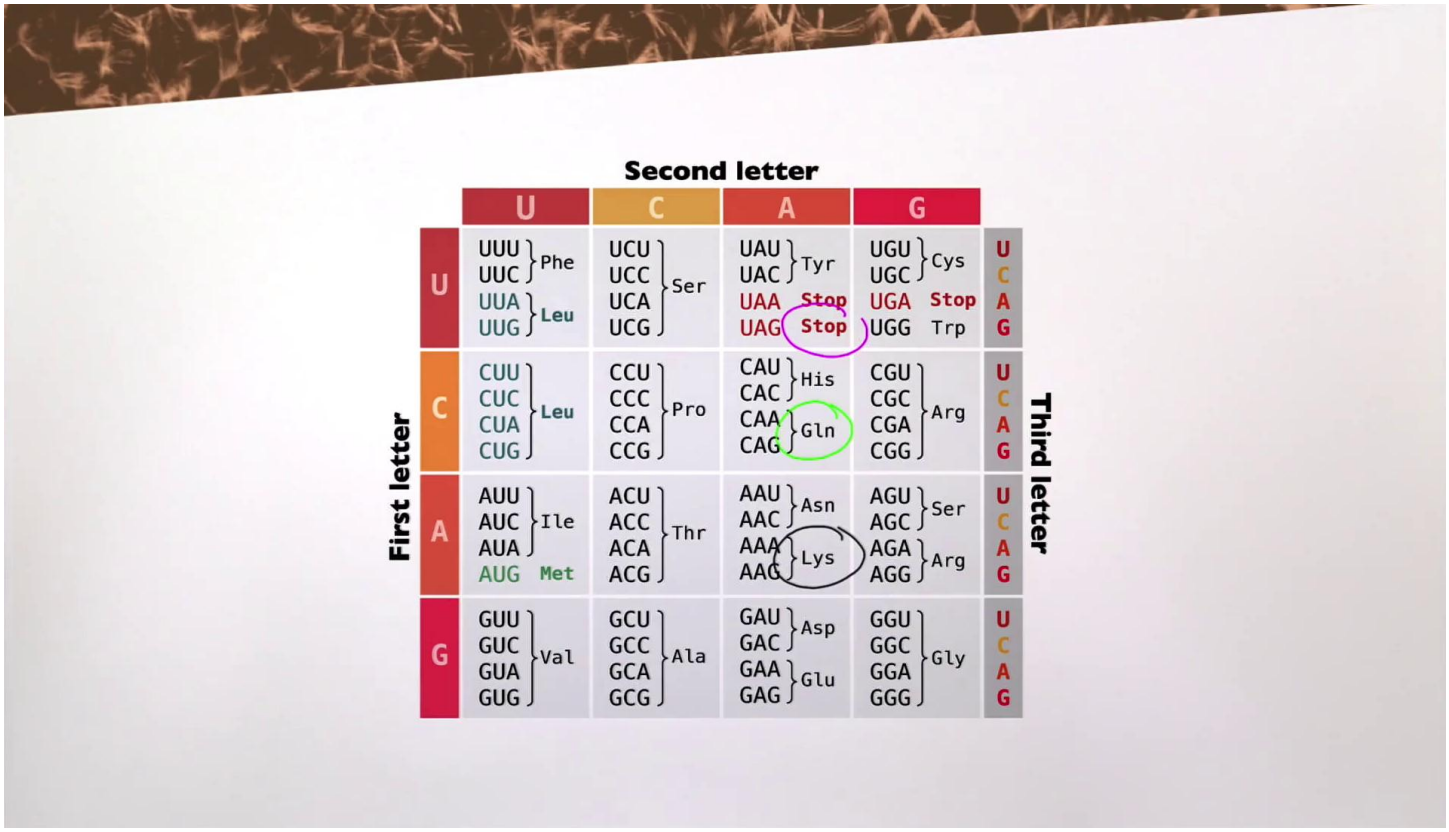


Now, let's look at yet another insertion. In which case, we're going to take our correct reading frame again but insert a uracil here. What happens to the first codons, the first two codons, is that they are not going to be changed. But if we now insert this uracil here, our third codon is going to be UAG. Now what happens with this mutation, which is also a frame shift mutation, is the following.

Notes

Summary

7m 45s

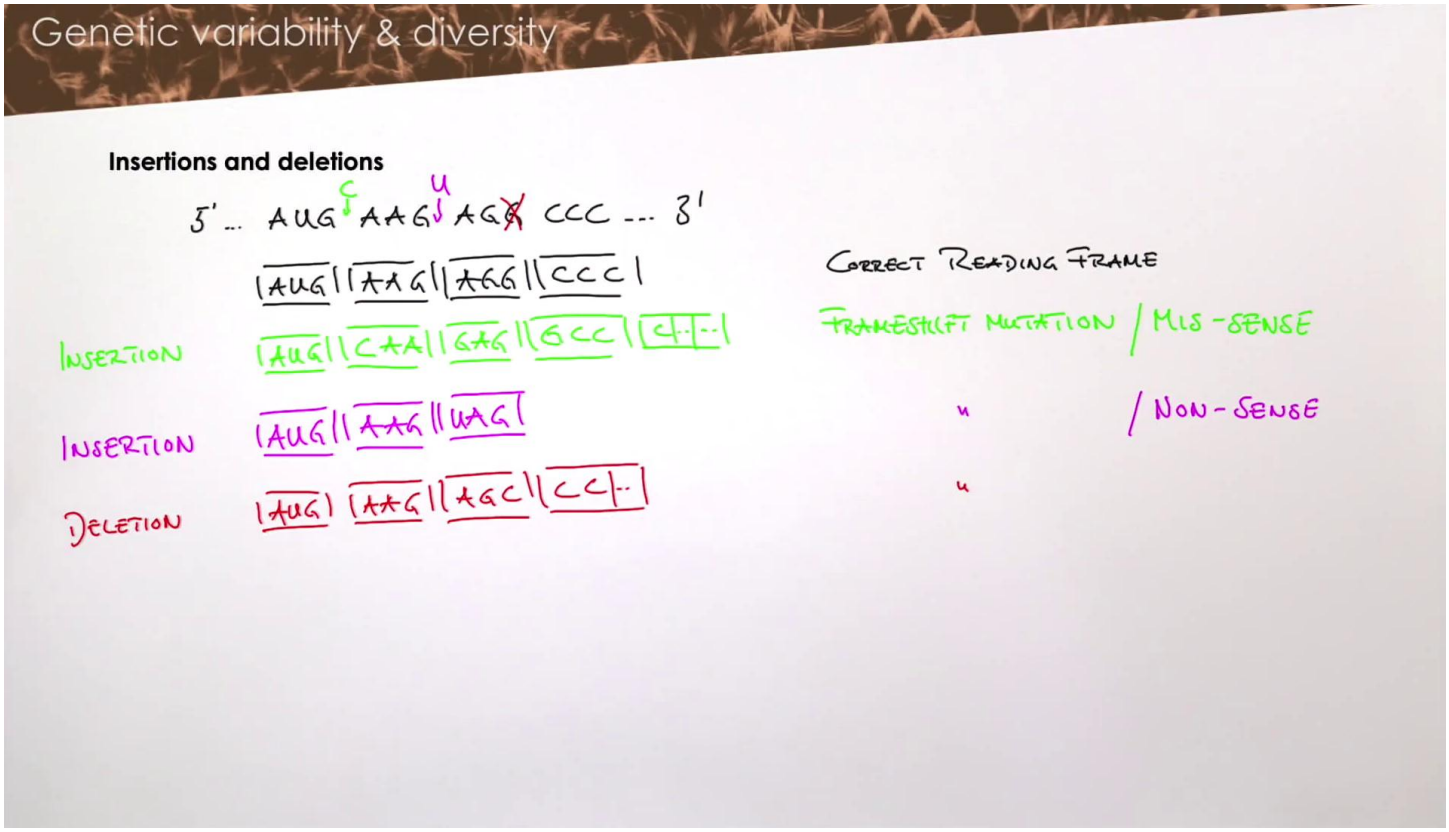


If we now look at the genetic code, we will immediately appreciate that UAG now codes for stop, which means that no longer do we have an amino acid produced here which signals the cell to stop translation.

Notes

Summary

8m 21s

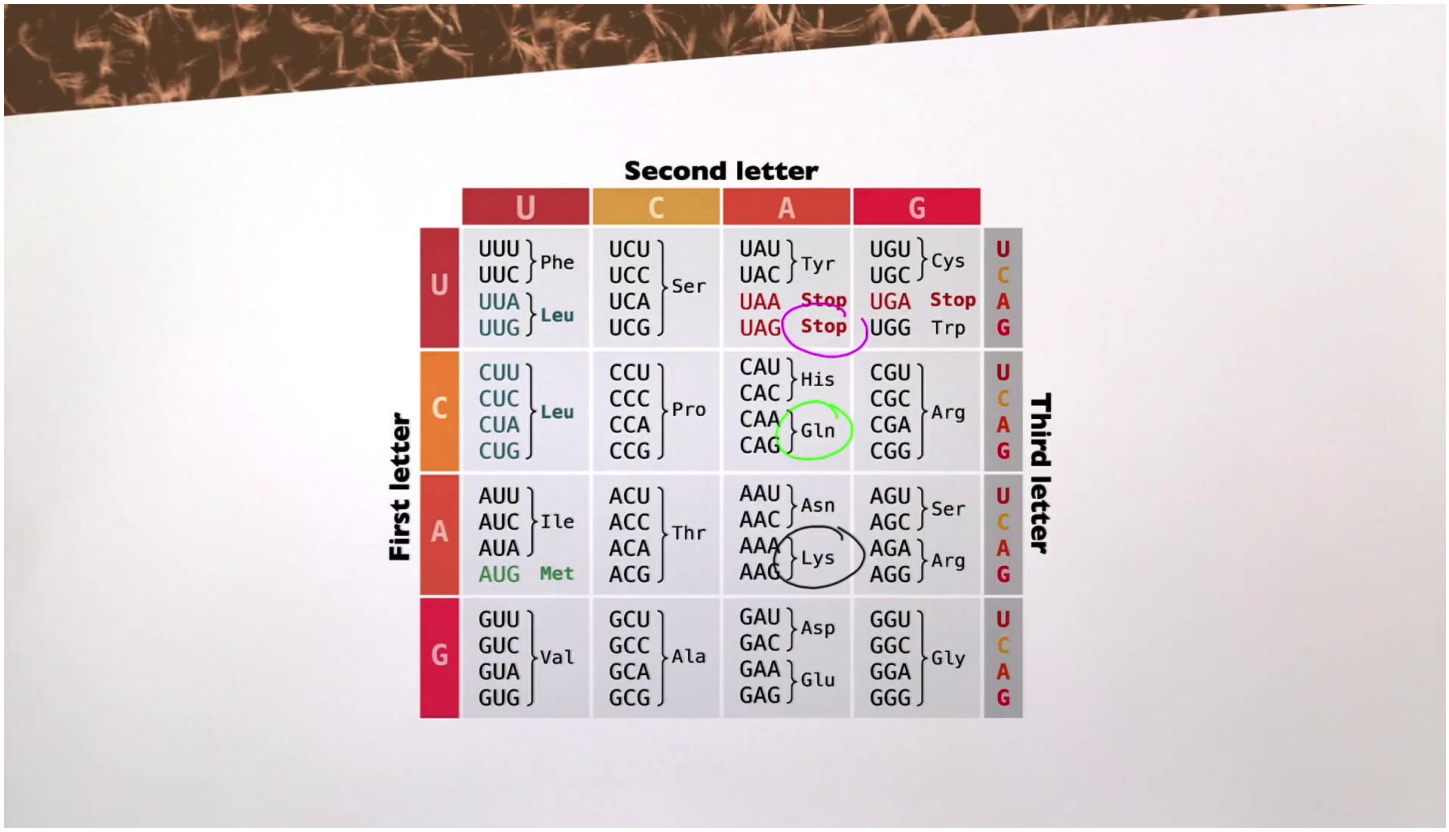


Hence, in this case, we refer to this frame shift mutation as non-sense Let's now look at deletions. Let's assume that we are going to delete our G, the third position in the third codon here. The resulting triplet sequence, is going to be AUG, AAG, and then we're going to have this deletion here, AGC. The first letter of the fourth codon is going to become the third letter, of the third codon. In this case, this is also called a frame shift mutation. Now, let's see if it is a mis- sense or a non-sense mutation. If we now compare the correct reading frame, the third codon of the correct reading frame, which was AGG, to the new codon in the deletion scenario.

Notes

Summary

8m 43s

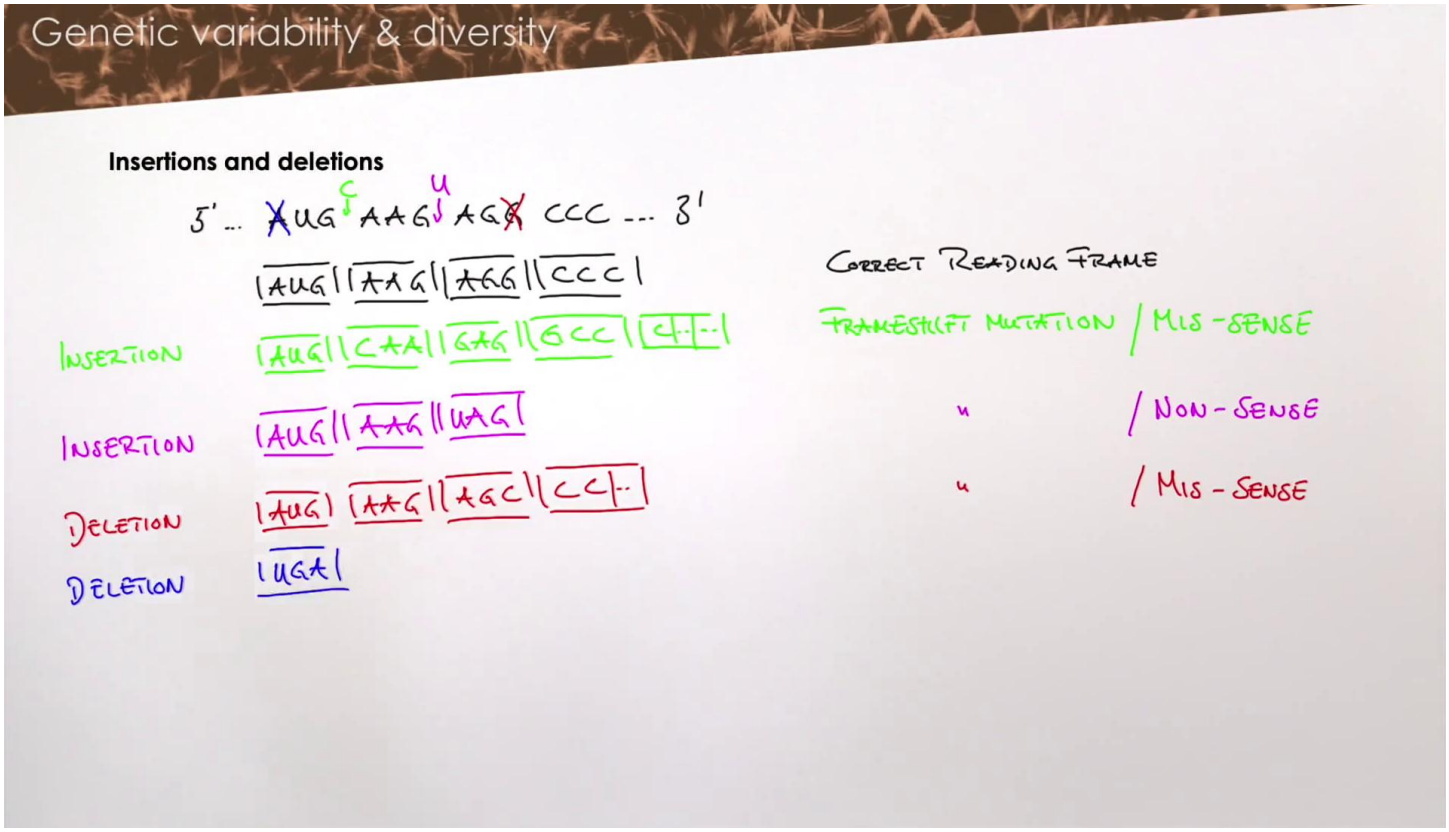


We are going to compare AGG, coding for R-gene, with AGC, which now codes for serine. Hence, we are in the presence of a reading frame that can be read fully on the amino acid level.

Notes

Summary

9m 42s

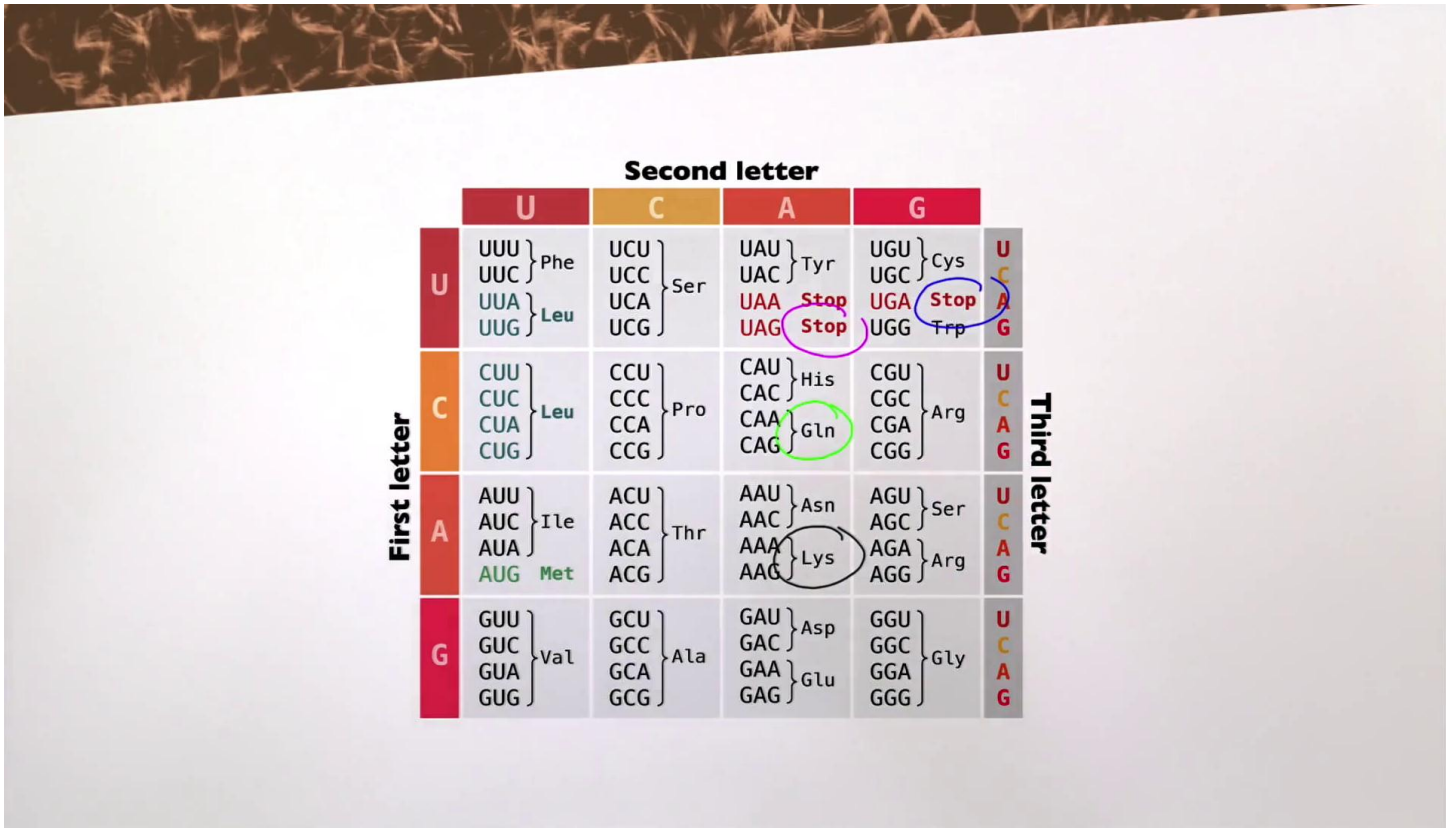


Thereby, we refer to this type of mutation brought about by a deletion as mis-sense. Finally, let's look at another deletion. We're going to retake our correct reading frame but simply delete the A here. In which case, the first codon will become UAG.

Notes

Summary

10m 05s

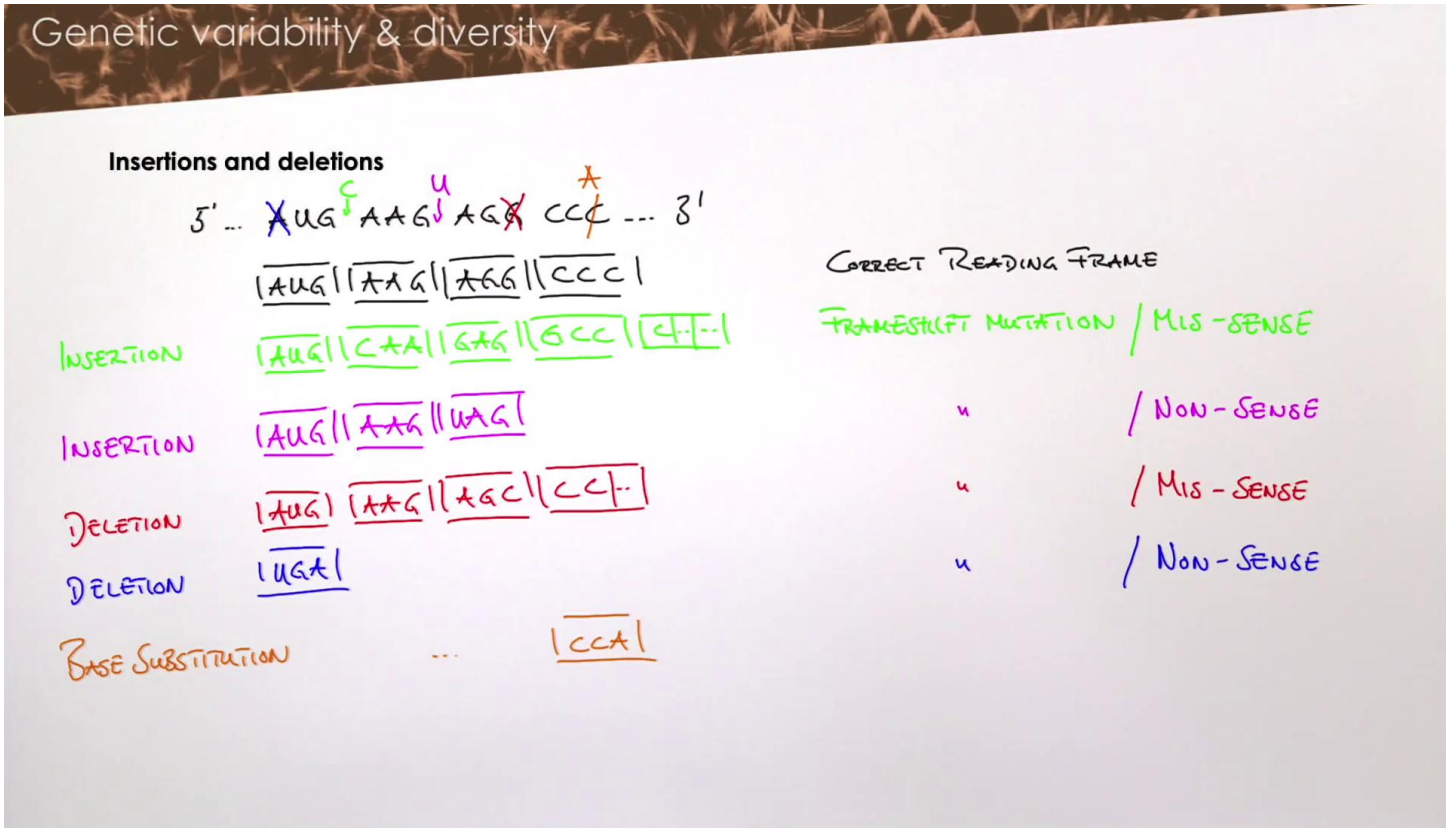


If we switch now to the genetic code, we immediately see that UGA also signals stop.

Notes

Summary

10m 33s

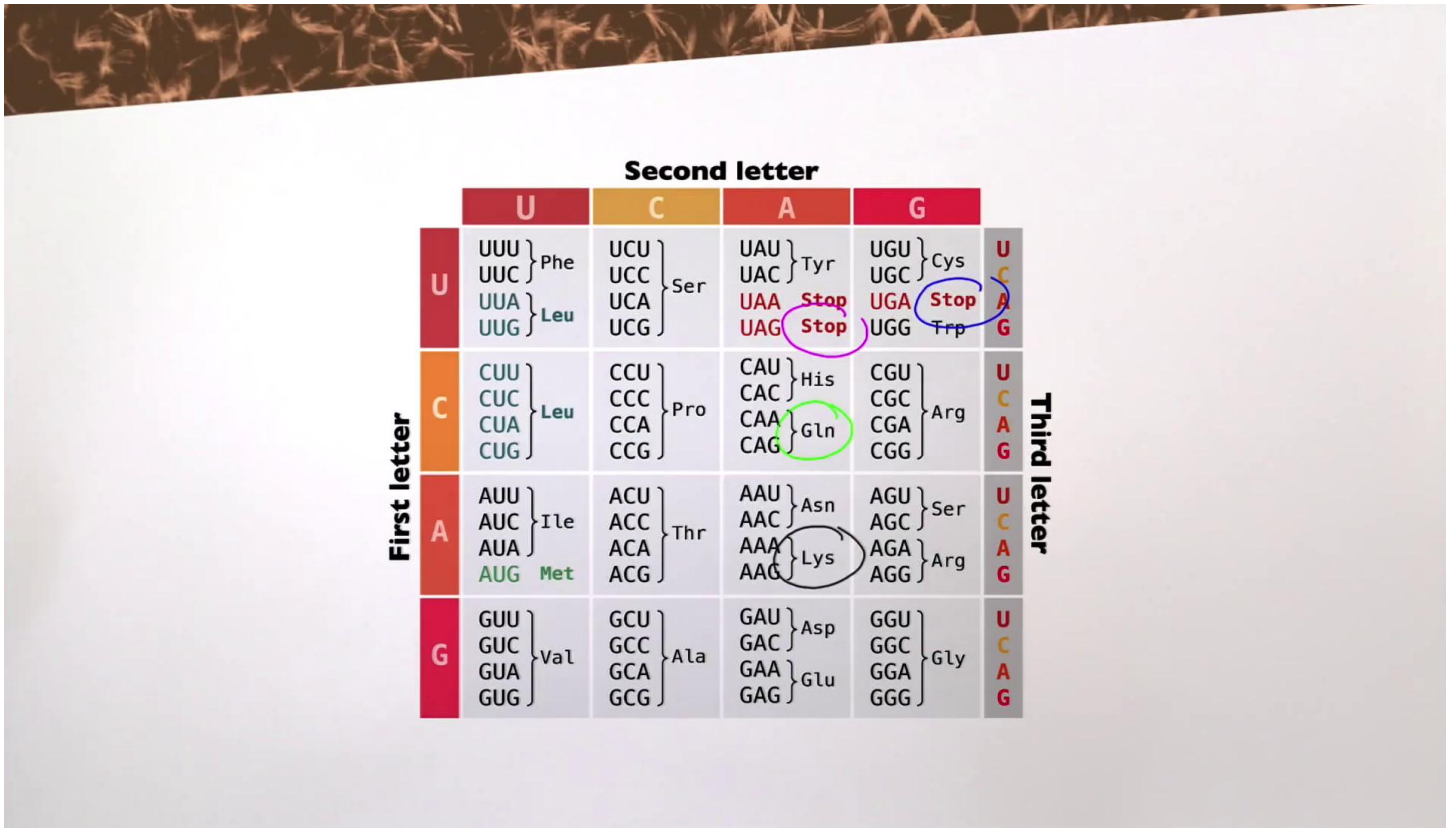


Hence in this case, we are in the presence of a frame shift mutation that does not make any sense because of the insertion of the stop codon. In this case, we are in a situation that does not make any sense, on the amino acid level. Hence, we are in a situation of a frame shift mutation that is called non-sense Finally, let's assume that we're simply going to substitute, this C with an A here, adenine. In which case, this is called a base substitution where the first codon, the second and the third codon, are not going to be touched and the fourth codon is going to be CCA.

Notes

Summary

10m 41s

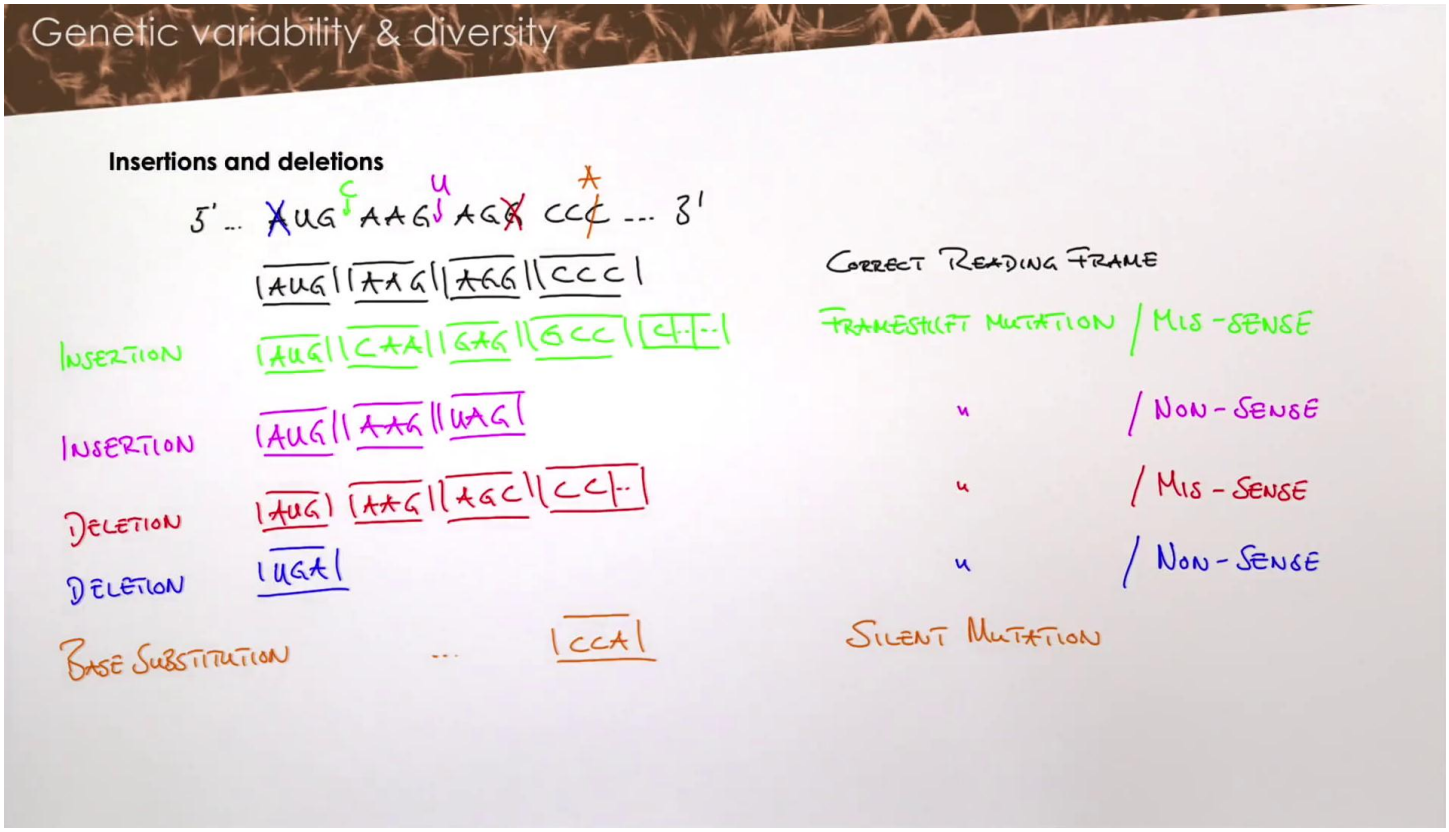


Now, if we again check the genetic code, we're going to compare now what used to be the fourth codon in the initial correct reading frame, which was CCC coding for Prolin, with CCA, which again codes for Prolin.

Notes

Summary

11m 36s



In this case, therefore, we are in the situation of a silent mutation.

Notes

Summary

11m 54s