The big picture

? Guiding question(s)

- How do gene mutations occur?
- What are the consequences of gene mutation?

Keep the guiding questions in mind as you learn the science in this subtopic. You will be ready to answer them at the end of this subtopic. The guiding questions require you to pull together your knowledge and skills from different sections, to see the bigger picture and to build your conceptual understanding.

Gene mutations are structural changes or alterations in the DNA sequence of an organism and play a captivating and often surprising role in shaping human health, as exemplified by sickle cell anaemia (**Figure 1**). This genetic disorder is caused by a specific mutation in the haemoglobin beta gene (HBB). HBB is responsible for production of haemoglobin, the oxygen-carrying protein in red blood cells. A single alteration in the genetic sequence leads to the production of abnormal haemoglobin.

Overview (/study/ap 422- cid- 755105/o

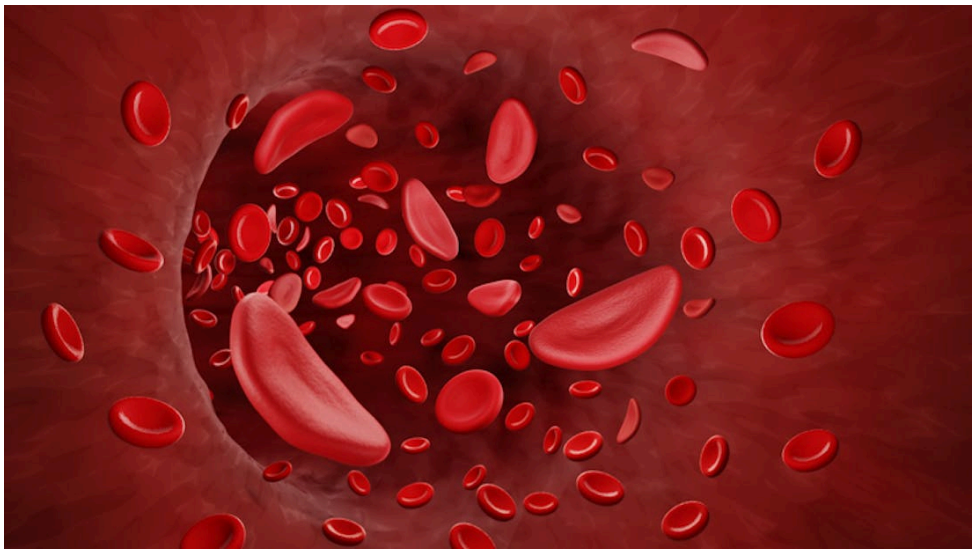


Figure 1. Sickle cell anaemia is a disease that causes red blood cells to have a crescent or sickle-like shape.

Credit: ARTUR PLAWGO / SCIENCE PHOTO LIBRARY, Getty Images

The consequences of this mutation are profound. Abnormal haemoglobin molecules can polymerise under low-oxygen conditions causing the red blood cells to adopt a sickle shape. These deformed cells are less flexible and prone to clumping, obstructing blood vessels and impeding the normal flow of oxygen. This cascade of events gives rise to the various health complications associated with sickle cell anaemia.

Interestingly, the same mutation that causes sickle cell anaemia also provides a unique advantage: protection against malaria. In regions where malaria is prevalent, individuals with the sickle cell trait, carrying at least one copy of the mutated HBB gene, are less susceptible to the disease. The altered shape of their red blood cells hinders the ability of the malaria parasite to infect and reproduce within them, reducing the severity of malaria symptoms and providing a survival advantage.

These intriguing phenomena raise several compelling questions about gene mutations:

- How can a single mutation in a gene have such divergent effects on human health?
- What precisely occurs at the molecular level to deform red blood cells into a sickle shape?
- How can our knowledge of gene mutations be used to develop more effective treatments for sickle cell anaemia?

Student view

Overview (/study/ap 422- cid- 755105/o

In this subtopic, you will learn about different types of mutations as well as consequences and causes of mutation. Additionally, in section D1.3.1–3 (/study/app/bio/sid-422-cid-755105/book/gene-mutations-id-43806/), you will discover fascinating techniques utilised in research and disease treatment, including the cutting-edge field of gene editing. By the end of this subtopic, you will have gained a deeper understanding of the intricate mechanisms of gene mutations and their potential implications for developing more effective treatments for conditions like sickle cell anaemia.

Prior learning

Before you study this subtopic make sure that you understand the following:

- The structure of DNA (see subtopic A1.2 (/study/app/bio/sid-422-cid-755105/book/the-big-picture-id-43236/)).
- The steps of protein synthesis (see subtopic D1.2 (/study/app/bio/sid-422-cid-755105/book/big-picture-id-43547/)).
- Natural selection (see subtopic D4.1 (/study/app/bio/sid-422-cid-755105/book/the-big-picture-id-43238/)).

D1. Continuity and change: Molecules / D1.3 Mutations and gene editing

Gene mutations

D1.3.1: Gene mutations D1.3.2: Consequences of base substitutions D1.3.3: Consequences of insertions and deletions

Learning outcomes

By the end of this section you should be able to:

- Explain that gene mutations are structural changes to genes at the molecular level.
- Outline the consequences of base substitutions.
- Outline the consequences of insertions and deletions.

Student view

Overview (/study/ap 422-cid-755105/o

To understand the impact of mutations in DNA on both the cellular level and on the whole organism, we must first explore the question: How do gene mutations occur?

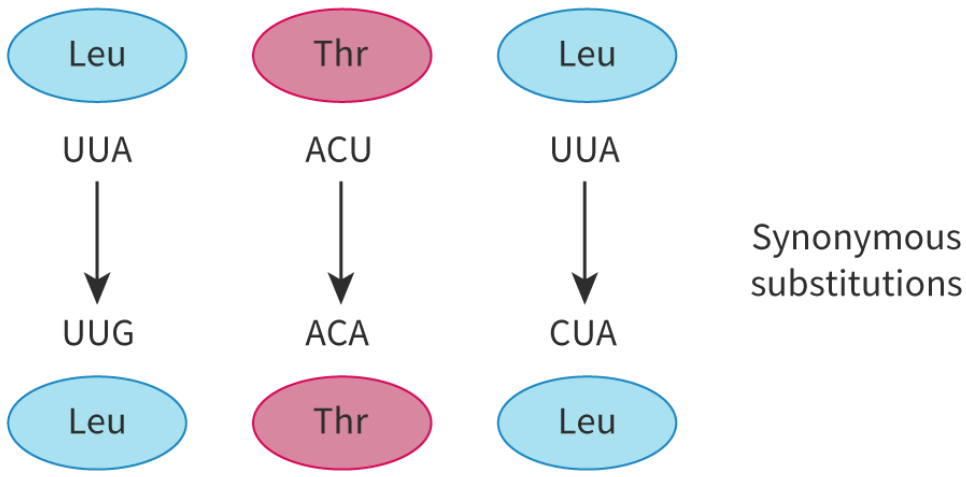
Mutations in DNA can arise from various mechanisms with substitutions, insertions and deletions as the most common. These mutations cause structural changes to the gene.

Base substitution mutations are known as single-nucleotide polymorphisms (SNPs) and are the most common type of genetic variation. SNPs occur when one nucleotide is replaced by another nucleotide in the DNA sequence.

This change in the DNA sequence may or may not have an effect on the structure of the protein depending on whether the substitution is synonymous or non-synonymous.

- Synonymous substitutions: known as neutral mutations as they do not change the amino acid sequence due to the degeneracy of the genetic code.
- Non-synonymous substitutions: change the amino acid sequence having different effects on protein function, possibly leading to protein malfunction.

These two types of mutation are compared in **Interactive 1**.



Interactive 1. Synonymous and Non-synonymous Substitutions.

Student view

The interactive provides a comparison between two types of DNA mutations, namely synonymous substitution and non-synonymous substitution. There is a slider with the help of which users can toggle and compare two images.

The first image demonstrates the concept of synonymous DNA substitutions using a codon table example. Synonymous substitutions are DNA mutations that change a nucleotide without altering the encoded amino acid. Examples in the image are for Leucine (Leu) and Threonine (Thr). Codons UUA → UUG (both code for Leu). Similarly, UUA → CUA also codes for Leucine. Codons ACU → ACA (both code for Thr). Despite nucleotide changes (UUA → UUG, ACU → ACA), the amino acids (Leu and Thr) remain identical.

It illustrates that silent mutations preserve protein sequences and demonstrate codon degeneracy (multiple codonsame amino acid).

The second image demonstrates Non-synonymous substitution (missense and nonsense mutations) where an altered amino acid sequence may affect protein function. Examples in the image are for Leucine, Tryptophan and Glycine. Codon UUA codes for Leu but altered codon UUC codes for Phenylalanine. This is a missense mutation, as the amino acid has changed. Similarly, UGG codes for Trp but the altered codon UGA is a stop codon. This is an example of nonsense mutation, as it causes premature termination. Also, GGA codes for Glycine but altered codon AGA codes for Arginine (missense mutation).

It illustrates that missense mutations may disrupt enzyme active sites, and nonsense mutations may cause loss of function.

Making connections

Crohn's disease is an autoimmune disorder that is characterised by chronic inflammation in the digestive tract, causing symptoms such as abdominal pain, diarrhoea and fatigue.

Different SNPs have been shown to be connected to Crohn's disease. Follow this link (https://www.sciencelearn.org.nz/videos/1281-single-nucleotide-polymorphisms-a-single-change-in-the-dna-code) to learn more about research into the connection between Crohn's disease and SNPs.

Overview (/study/ap 422-cid-755105/o

Insertions occur when one or more nucleotides are added to the DNA sequence. Deletions, on the other hand, occur when one or more nucleotides are removed from the DNA sequence. You can see the effect that substitutions, insertions and deletions have on a DNA sequence in **Figure 1.**

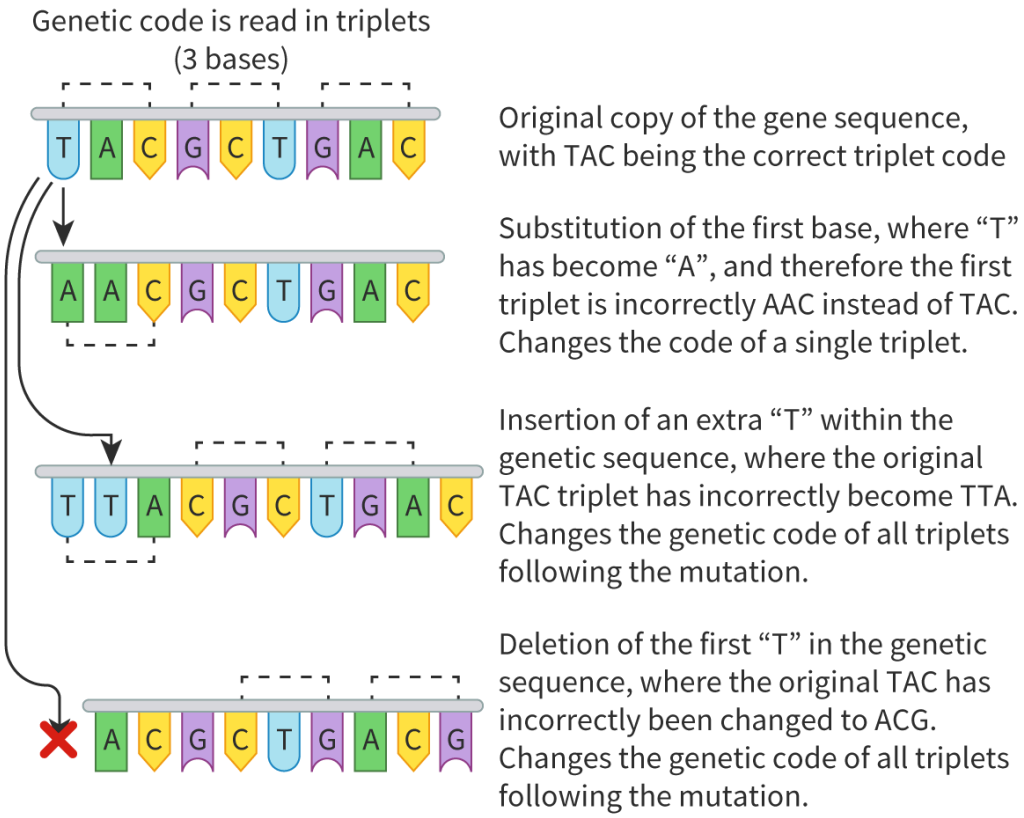


Figure 1. The consequences of a substitution, insertion and deletion on a sequence of DNA.

More information for figure 1

The image is a diagram that illustrates the effects of mutations, specifically substitution, insertion, and deletion, on a DNA sequence. It consists of three parts:

1. **Substitution:** The top part shows the original DNA sequence in triplets labeled as TACGCTGAC. Below it, an arrow points to another sequence labeled AACGCTGAC, where the first triplet has been altered due to a substitution mutation: the 'T' in the first position is replaced by 'A'. This change affects only the first triplet.

2. **Insertion:** The middle section demonstrates an insertion mutation where an extra 'T' is added. The sequence changes from TACGCTGAC to TTACGCTGAC. This affects not just one triplet but cascades down the sequence, impacting all following triplets by altering their grouping.

Student view

Overview (/study/ap 422-cid-755105/o

3. **Deletion:** The bottom portion shows the effect of a deletion mutation where the initial 'T' in the sequence is removed, changing the sequence from TACGCTGAC to ACGCTGAC. This also affects all subsequent triplets, similar to the insertion.

The diagram also contains small blocks representing nucleotides, each labeled with a letter (A, T, C, G), and explains how these mutations cause changes in the triplet codes.

[Generated by AI]

Frameshift mutations can be caused by either insertions or deletions as these processes alter the reading frame of codons. This results in alterations to the amino acid sequence coded for by the DNA sequence. Since the genetic code is read in codons, the addition of even one nucleotide can disturb the grouping of codons. As a result, the mRNA transcript produced from the mutated DNA sequence will have a different codon sequence. This could potentially lead to changes in the resulting protein's amino acid sequence during translation. This shift can significantly impact the protein's structure and function.

Imagine you have the sentence 'THE CAT AND DOG ARE BIG'. Each three-letter word in this sentence represents a codon. If for some reason, the 'C' was deleted from the word 'CAT' and the letters all needed to shift to the left, we would now have the sentence 'THE **ATA NDD OGA REB IG',** which is nothing like the original sentence. If each of the words in the first sentence were codons, coding for a specific amino acid, this shift would have a big consequence on the polypeptide being made. This one deletion caused a frameshift mutation in which all of the codons that come after it have become altered (**Figure 2**).

Student view

Overview (/study/ap 422-cid-755105/o

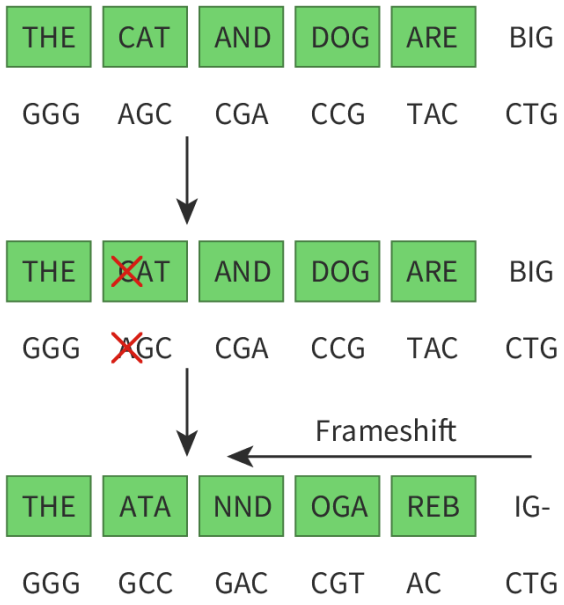


Figure 2. The effect of a frameshift location on both a sequence of nucleotides and on a simple sentence of three-letter words.

More information for figure 2

The image is a diagram illustrating the effect of a frameshift mutation on a sequence of words and corresponding codons. It consists of three horizontal sequences. The first sequence displays six three-letter words: THE, CAT, AND, DOG, ARE, BIG. Below each word are nucleotide triplets: GGG, AGC, CGA, CCG, TAC, CTG respectively.

The second sequence shows a frameshift due to the deletion of 'C' from 'CAT', resulting in a shift to: THE, ATA, NND, OGA, REB, IG-. The corresponding nucleotide sequence changes to GGG, GCC, GAC, CGT, AC, CTG, illustrating how codons are altered.

Arrows indicate the shift and the location of the deleted content, with a marked 'X' on the deleted letter 'C'. The term 'Frameshift' is labeled with an arrow pointing from the second to the third sequence, indicating the effect of the frameshift on the sequence of words and nucleotides.

[Generated by AI]

Student view

Overview (/study/ap 422-cid-755105/o

Depending on this new sequence of codons, the sequence of amino acids in a polypeptide may be altered, affecting its structure. This may lead to a protein taking a different shape, possibly losing its functionality (see subtopic B1.2 (/study/app/bio/sid-422-cid-755105/book/big-picture-id-43531/)). For example, if an active site of an enzyme is altered, it will no longer be able to bind to its substrate and catalyse the reaction (see subtopic C1.1 (/study/app/bio/sid-422-cid-755105/book/the-big-picture-id-43208/)).

It is very likely that polypeptides may stop working, either through frameshift changes or through major insertions or deletions in which many nucleotides are inserted or deleted, respectively. The severity of the consequences of mutations depends on the size and location of the mutation in the DNA sequence. The consequences of mutations will be discussed further in the next section (D1.3.4–7 (/study/app/bio/sid-422-cid-755105/book/causes-and-consequences-of-gene-mutations-id-45759/))

Watch **Video 1** to visualise and understand the different types of mutations better.

Video 1. Mutations.

Try the simulation activity below to explore the different types of mutation.

Activity

- **IB learner profile attribute:** Inquirer

Student view

Overview (/study/ap 422-cid-755105/o

- **Approaches to learning:** Research skills — Using search engines and libraries effectively
- **Time required to complete activity:** 20 minutes
- **Activity type:** Individual and pair activity

In this simulation, you will be given the chance to mutate a gene in any way you like.

Instructions

1. Open the Mutations (https://www.labxchange.org/library/items/lb:LabXchange:f1ec1b5b:lx_simulatio simulation to start.
2. Click on 'Start simulation'.
3. To see what the original protein will look like with the DNA sequence not edited press 'Show protein'. Take a screenshot so you can use it for comparison.
4. Click 'Reset' and then 'Edit DNA'.
5. Edit the DNA by either performing SNPs by editing just one or by mutating a larger sequence of DNA.
6. Click 'Show protein' and take a screenshot.
7. Repeat for at least three different mutations.

Once you are done, look at your screenshots and compare their structures. Discuss the following questions with your partner.

1. Did all mutations in the DNA sequence cause change in the protein structure?
2. What occurred to the overall structure of the protein?
3. What impact would these changes possibly have on the function of proteins?

5 section questions

D1. Continuity and change: Molecules / D1.3 Mutations and gene editing

Student view

Causes and consequences of gene mutations

Overview (/study/ap 422-cid-755105/o

D1.3.4: Causes of gene mutation D1.3.5: Randomness in mutation

D1.3.6: Consequences of mutation in germ cells and somatic cells D1.3.7: Mutation as a source of genetic variation

Learning outcomes

By the end of this section you should be able to:

- Recall that gene mutations can be caused by mutagens and by errors in DNA replication or repair.
- Explain that mutations can occur anywhere in the base sequences of a genome.
- Explain the effects of gene mutations occurring in germ cells and somatic cells.
- Recognise that gene mutation is the original source of all genetic variation.

The study of mutations and their impact on DNA, proteins and organisms is a crucial area of research in genetics and molecular biology. What causes these gene mutations and what are their consequences? In this section, you will learn about the causes, randomness and consequences of gene mutation.

Causes of gene mutation

A gene mutation is a change in the DNA sequence of a gene that can result in altered proteins that may potentially lead to disease. Gene mutations can occur by errors in DNA replication or repair which may be triggered by mutagens. Mutagens are agents that can cause mutations. There are two types of mutagens: chemical mutagens and radiation.

Chemical mutagens are chemicals that cause mutation and include mustard gas, nitrous acid, ethyl and methyl methane sulfonate (EMS and MMS), ethyl urethane and formaldehyde. **Interactive 1** provides more detailed information about these mutagens.

Student view

Overview (/study/ap 422-cid-755105/o

- **Mustard gas**
- **Nitrous acid**
- **Ethyl urethane**
- **EMS and MMS**
- **Formaldehyde**

Interactive 1. Types of Chemical Mutagens.

Mutagens are also present in the form of radiation. Ultraviolet (UV) radiation from the Sun and ionising radiation from X-rays (**Figure 1**), gamma rays and radioactive isotopes can lead to many errors in DNA replication (see subtopic D1.1 (/study/app/bio/sid-422-cid-755105/book/big-picture-id-43546/)). Radiation exposure can cause various types of damage to DNA, such as single-strand breaks, double-strand breaks and chemical modifications to DNA bases, potentially leading to cancer and other health problems. These damages have the potential to disrupt the process of DNA replication.

For instance, if a single-strand break occurs in the DNA template strand during replication, it can impede the movement of the replication fork. This interruption disrupts the continuity of the template strand, resulting in replication errors or the halt of replication machinery. Double-strand breaks are more severe and can completely halt DNA replication. If not properly repaired, these breaks can lead to the loss of genetic material, which significantly impacts the stability and integrity of replicated DNA.

Radiation-induced chemical modifications to DNA bases can also interfere with replication. These modifications alter the properties of base pairing, leading to mispairing during replication and the introduction of errors in the replicated DNA.

Student view

Overview (/study/ap 422-cid-755105/o

Figure 1. X-ray exposure is a type of ionising radiation that may lead to DNA mutations. A lead protective coat or apron is worn by patients to minimise their exposure to harmful radiation during X-ray examinations.

Credit: BanksPhotos, Getty Images

Randomness in mutation

Mutations can occur randomly anywhere in the base sequences of a genome due to errors during DNA replication or repair, exposure to mutagens such as radiation or chemicals, or other random events.

Certain bases in DNA have a higher probability of mutating than others. This susceptibility is primarily due to the chemical properties of the bases and their vulnerability to different mutagenic agents. For example, cytosine has a relatively higher mutation rate compared with the other bases. This is because cytosine can undergo a spontaneous chemical reaction called deamination, where it loses an amino group, resulting in the conversion of cytosine to uracil (**Figure 2**).

Student view

Overview (/study/ap 422- cid- 755105/o

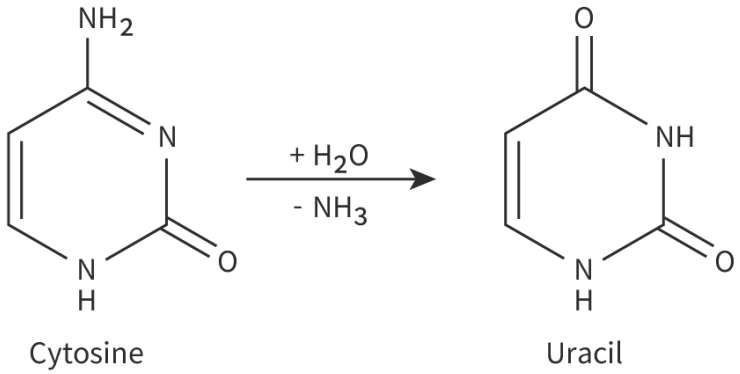


Figure 2. The deamination process converts the nucleotide cytosine to uracil.

More information for figure 2

This is a diagram showing the chemical process of deamination where cytosine is converted to uracil. On the left, there's a molecular structure of cytosine displaying rings with labeled atoms: NH2 group attached. An arrow indicating a chemical reaction points to the right, showing H2O added and NH3 removed. On the right, the molecular structure of uracil is displayed, which lacks the NH2 group, reflecting the change during the process. The structures are labeled accordingly with 'Cytosine' and 'Uracil'.

[Generated by AI]

Uracil is typically found in RNA but not in DNA. If not repaired, uracil in DNA can lead to errors during DNA replication and potentially cause mutations. Although some bases have a higher probability of mutating than others, there is no natural mechanism known for deliberately changing a particular base to alter a trait.

The occurrence and frequency of mutations can vary among different species, populations and individuals. Several factors can influence mutation rates, including the fidelity of DNA replication machinery, exposure to mutagens (such as UV radiation or certain chemicals) and DNA repair mechanisms. Additionally, genetic variability within a population contributes to the diversity of mutations, as different individuals may carry unique sets of genes that can increase or decrease the likelihood of mutation occurrence.

Student view

Overview (/study/ap 422-cid-755105/o

Environmental conditions can also impact the frequency and types of mutations. For example, exposure to mutagenic agents or stressful environmental factors can increase mutation rates. Exposure to mutagenic agents, including UV radiation, chemicals, ionising radiation, carcinogens and certain viral infections, can increase the likelihood of DNA damage and mutations. These environmental conditions pose risks of genetic alterations that may contribute to the development of cancer, genetic disorders and other health complications.

Additionally, certain environmental conditions may favour the selection and accumulation of specific mutations that provide advantages in those particular environments. For example, the ability to digest lactose, the sugar found in milk (**Figure 3**), varies among human populations. In most mammals, the production of the lactase enzyme, which is responsible for breaking down lactose, decreases after infancy. This leads to lactose intolerance in adulthood for many individuals worldwide.

Figure 3. People that are lactose intolerant have trouble digesting the lactose in milk.

Credit: Daniel Hurst Photography, Getty Images

Student view

Overview (/study/ap 422-cid-755105/o

However, in populations with a long history of dairy farming and milk consumption, a genetic mutation that causes lactase persistence has emerged. This mutation allows individuals to maintain lactase production and digest lactose throughout their lives.

One example of lactase persistence is observed in populations of European descent. Historically, dairy farming played a significant role in European agriculture, with milk and dairy products being important dietary components. The ability to digest lactose beyond infancy provided a selective advantage in these populations, allowing individuals to continue consuming milk as a source of nutrition throughout their lives.

Creativity, activity, service

Strand: Service
Learning outcome: Demonstrate engagement with issues of global significance

To raise awareness of the detrimental effects of smoking within your community, take the initiative to organise a public health campaign. Cigarette smoke contains numerous chemical mutagens that can induce mutations in DNA. This campaign can encompass various components aimed at educating individuals about the risks associated with both first-hand and second-hand smoking.

You could arrange informational sessions or workshops that provide comprehensive knowledge about the health consequences of smoking. These sessions could cover a range of topics, including the adverse effects that smoking may have on the respiratory system, cardiovascular health and the increased susceptibility to different types of cancers. By inviting experts or healthcare professionals to speak at these sessions, participants can gain access to accurate and up-to-date information.

You could also create displays or exhibitions that visually depict the negative effects of smoking. These displays can incorporate infographics, statistical data and personal stories to portray the impact of smoking.

To extend the reach of your campaign, you could use social media platforms to spread awareness. You could create engaging content such as informative articles, videos and testimonials to share with a broader audience.

Overview (/study/ap 422-cid-755105/o

By undertaking these activities, you can play an active role in promoting awareness of the harmful effects of smoking, both within your community and beyond.

Consequences of mutation in germ cells and somatic cells

Gene mutation is the original source of all genetic variation. Gene mutations can occur in either:

- somatic cells: all the cells in the body EXCEPT for germ cells
- germ cells: cells that give rise to eggs or sperm.

Mutations in somatic cells can cause diseases during a person's lifetime. For example, a mutation in a somatic cell can possibly cause cancer, leading to uncontrolled cell growth and division. While mutations that are acquired only in somatic cells may have an effect on an individual during their own lifetime, luckily they are not passed on to their offspring. Mutations can only be inherited and passed on to one's offspring if the mutation occurs in the germ cells that give rise to the gametes (the eggs or sperm).

Mutations in germ cells may alter the chromosome number or the gene sequence in the gametes. Mutations that are passed onto offspring are considered to be inherited mutations. They can have various effects on individuals, including causing genetic disorders and increasing their susceptibility to certain diseases.

Mutation as a source of variation

Variation refers to the natural diversity that exists among individuals within a species, encompassing differences in traits, characteristics and genetic makeup. Mutation serves as a fundamental source of genetic variation, contributing to the diversity observed within and among populations of living organisms. These mutations can have various effects on an organism, including being neutral, silent, harmful or beneficial.

Student view

- **Neutral and silent mutations** are those that do not significantly affect the organism. Neutral mutations typically occur in non-coding regions of the genome or in regions that do not alter the function of essential genes. Silent mutations, on the

Overview (/study/ap 422- cid- 755105/o

other hand, occur in the coding sequence of a gene but do not alter the amino acid sequence of the resulting protein due to the degeneracy of the genetic code (see subtopic D1.2 (/study/app/bio/sid-422-cid-755105/book/big-picture-id-43547/) and section D1.3.1 (/study/app/bio/sid-422-cid-755105/book/gene-mutations-id-43806/)). Since they have no discernible impact, neutral and silent mutations are often passed on through generations without any significant effect on the organism or the population.

- **Harmful mutations** have negative consequences on an organism. They can cause diseases, developmental abnormalities, or reduce the organism's fitness and survival. Harmful mutations are typically selected against in natural selection because individuals with these mutations are less likely to survive, reproduce and pass on the mutations to future generations.
- **Beneficial mutations** are rare but can provide advantages to an organism and increase its fitness in a particular environment. These mutations can enhance an organism's ability to adapt to changing conditions, improve its reproductive success, or provide resistance to diseases or environmental stressors. Beneficial mutations can become advantageous if they provide an organism with a selective advantage, allowing individuals carrying these mutations to outcompete others in their population and increase their representation in subsequent generations. Over time, the frequency of beneficial mutations in a population can increase, leading to the evolution of new traits or even new species. There is more to learn about the importance of such mutations in subtopic D4.1 (/study/app/bio/sid-422-cid-755105/book/the-big-picture-id-43238/).

Nature of Science

Aspect: Observations

Commercial genetic tests provide individuals with information about their potential health and disease risks. Although this can be advantageous for informed health decisions, it can also pose significant challenges, including difficulties with interpreting the results without expert guidance.

An example of this challenge is present with carrier screening tests. This is a type of test an individual can perform to see if they are a carrier of a genetic disease.

Student view

Overview (/study/ap 422-cid-755105/o

Usually carrier screening tests are available through various healthcare providers such as genetic counsellors and doctors, but nowadays some companies even provide direct-to-consumer testing options that enable individuals to order a test kit online and provide a blood or saliva sample at home. It's important to note that direct-to-consumer testing may not include the same level of pre- and post-test counselling and support as testing ordered through a healthcare provider.

The interpretation of these results without professional assistance could lead to misinterpretations, anxiety and inappropriate medical decisions. Furthermore, genetic test results may uncover sensitive information that could affect not only the individual but also their family members. Therefore, it is essential to have comprehensive genetic counselling to assist individuals in understanding the implications of genetic test results. This includes assessing their personal and familial risk factors and providing support for informed health decisions.

Try the data analysis activity below to help with your understanding of mutagens.

Activity

- **IB learner profile attribute:** Thinker
- **Approaches to learning:** Thinking skills — Reflecting at all stages of the assessment and learning cycle
- **Time required to complete activity:** 20 minutes
- **Activity type:** Individual and pair activity

A study was done to investigate the effects of chronic radiation exposure on human cells. The researchers exposed human cells to low doses of ionising radiation over a period of several weeks. Some of the data they obtained can be found in **Figure 4**. Dose rates of ionising radiation are in Gy/h (Gray per hour). Error bars represent the uncertainty associated with a data point.

Student view

Overview (/study/ap 422- cid- 755105/o

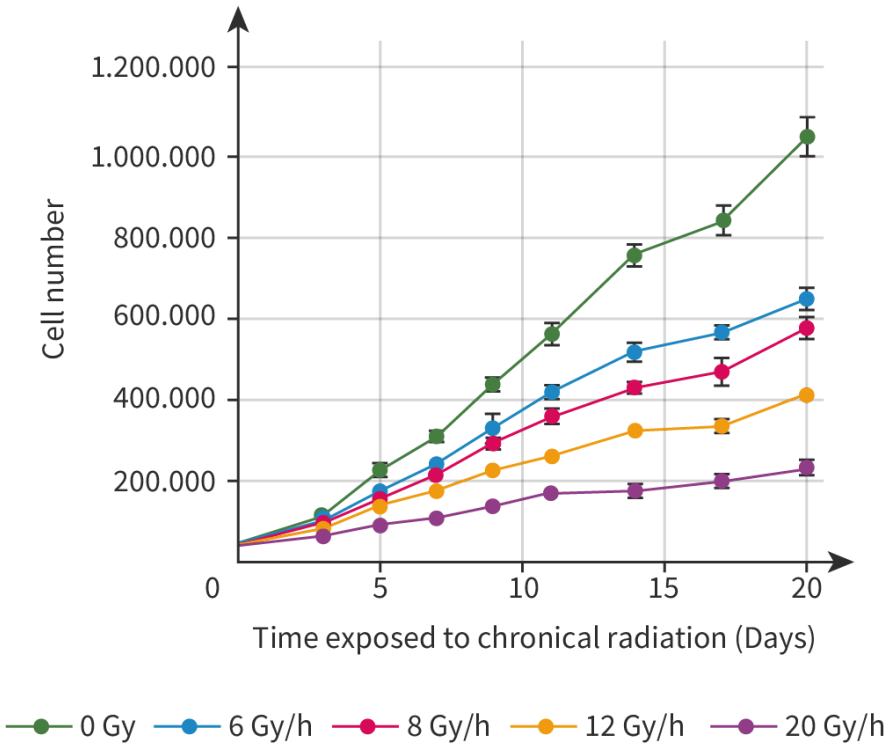


Figure 4. Effect of radiation on cell number.

More information for figure 4

The graph depicts changes in cell number relative to time and radiation dose levels, measured in Gray per hour (Gy/h), over a period of 0 to 20 days. The X-axis represents the time exposed to chronic radiation in days, while the Y-axis represents the cell number, ranging from 0 to over 1,200,000.

There are five lines in the graph, each representing a different dose rate:

1. **0 Gy/h:** Signified by green circles. This line shows the highest increase in cell number, reaching over 1,000,000 by 20 days.
2. **6 Gy/h:** Represented by blue squares. This line shows a moderately high increase, exceeding 800,000 cells by 20 days.
3. **8 Gy/h:** Indicated by pink triangles. This line follows a similar trend to the 6 Gy/h dose, ending just below 600,000 cells.
4. **12 Gy/h:** Shown by orange diamonds. The increase in cell number is smaller, peaking around 400,000 by 20 days.
5. **20 Gy/h:** Illustrated by purple hexagons. This line shows the least cell growth, stabilizing slightly above 200,000 cells.

Overall, the graph demonstrates a decrease in cell growth with increasing radiation dose, with error bars indicating the uncertainty at each data point.

[Generated by AI]

Student view

Overview (/study/ap 422- cid- 755105/o

1. State the relationship between cell number and time exposed to chronic radiation.
2. Compare cell number counts for 0 Gy and 20 Gy/h.
3. Calculate the percentage difference in cell number at day 20 for 6 Gy/h and 20 Gy/h
4. Suggest a reason for the reduction in cell numbers with increased dosage.

5 section questions

D1. Continuity and change: Molecules / D1.3 Mutations and gene editing

Genetic engineering (HL)

D1.3.8: Gene knockout (HL) D1.3.9: CRISPR sequences and enzyme Cas9 in gene editing (HL)

D1.3.10: Conserved or highly conserved sequences in genes (HL)

Higher level (HL)

Learning outcomes

By the end of this section you should be able to:

- Outline that gene knockout is a technique for investigating the function of a gene by changing it to make it inoperative.
- Explain the use of the CRISPR sequences and the enzyme Cas9 in gene editing.
- Describe the hypotheses for conserved or highly conserved sequences in genes.

Imagine a world where scientists can edit genes with precision, like editing a sentence in a book. With the presence of new technology, called CRISPR, this world is becoming reality, revolutionising the field of biotechnology. CRISPR allows scientists to make targeted changes to DNA, the blueprint of life, opening up a world of possibilities for treating genetic diseases, creating disease-

Student view

Overview (/study/ap 422-cid-755105/o

resistant crops and even engineering new organisms. With CRISPR, scientists can envision a future where we can reshape the very building blocks of life itself.

You can learn more about CRISPR applications in this article (https://www.labiotech.eu/best-biotech/crispr-applications-gene-editing/).

CRISPR and gene knockout are two powerful techniques that have revolutionised genetic engineering. Genetic engineering refers to the process of altering the DNA of an organism in order to introduce new characteristics, remove unwanted traits or modify existing ones. In this subtopic, you will learn about these techniques and about how knowledge of conserved sequences between species is essential to advancements in science.

Gene knockout technique

Gene knockout is a technique in which a specific gene is intentionally removed or changed in some way so that the expression of it is permanently prevented. This genetic engineering technique is used to understand the role of specific genes on an organism's development, physiology or disease susceptibility.

One example of a gene knockout study, which has played a critical role in cancer research, is the p53 (p stands for protein) gene knockout in mice. Researchers observed that there was a significantly higher prevalence of cancerous growths in mice when the p53 gene, on chromosome 17, was inactive. It was concluded and supported by several additional studies, that the p53 gene is important for inhibiting tumour development in many tissues as it prevents cells from dividing uncontrollably and thus forming tumours (**Figure 1**).

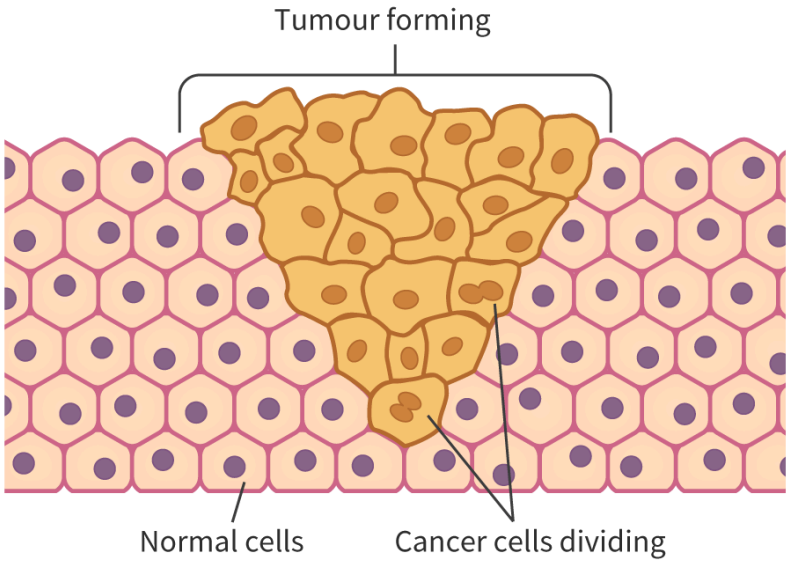


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Figure 1. The absence of p53 increases the incidence of tumour growth.

More information for figure 1

The image is a diagram illustrating the progression from normal cells to tumor formation. It shows a regular pattern of hexagon-shaped, pink cells labeled as "Normal cells" with darker central circles, representing nuclei, spread evenly across the image. In the center, an irregular cluster of larger yellowish cells is labeled "Tumour forming." These cells differ in shape and size, indicating cancerous division. Arrows point to these cells with the label "Cancer cells dividing," highlighting their uncontrolled growth compared to the surrounding normal cells. The diagram visually contrasts the appearance and growth patterns of normal and cancerous cells.

[Generated by AI]

The use of knockout organisms as models in research helps scientists understand the role that specific genes play, ultimately leading to potential treatments. In addition to mice, there are many other organisms that are used for knockout studies.

Theory of Knowledge

When considering the use of knockout mice in scientific research, an intriguing question arises:

Do we tend to exaggerate the objectivity of scientific facts and the subjectivity of moral values when evaluating the ethical implications of such experiments?

A library of knockout organisms, e.g. mouse and zebrafish knockout libraries, are available for researchers to use as models in research. These libraries are a collection of organisms that have been genetically modified to have one or more of their genes ‘knocked out’ or disabled (**Figure 2**). They provide a valuable resource for investigating the roles of genes in various biological processes and diseases.

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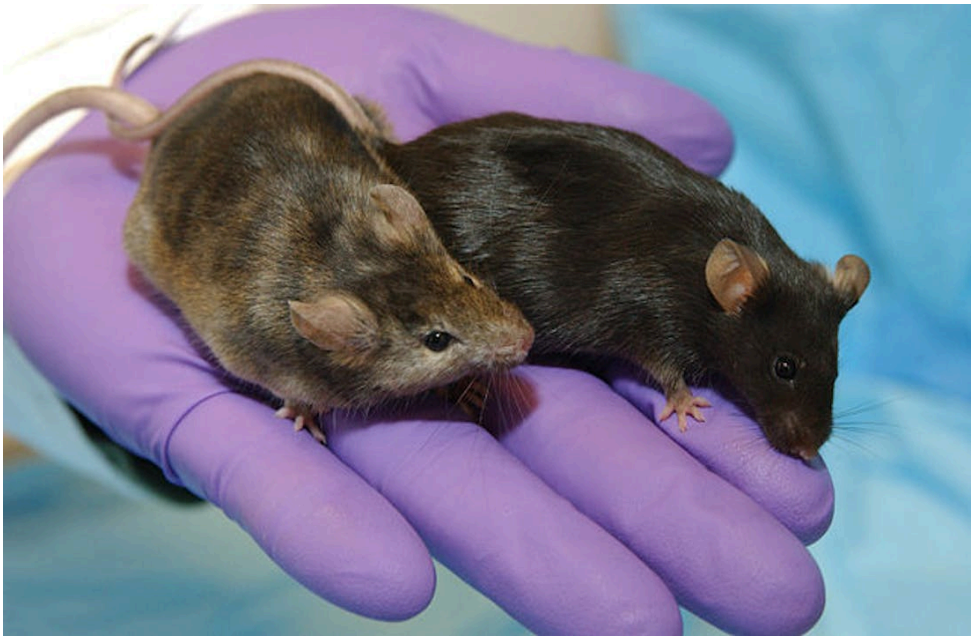

Figure 2. Mice are common organisms that are used in scientific studies.

Source: Knockout Mice5006-300 (https://commons.wikimedia.org/wiki/File:Knockout_Mice5006-300.jpg) by Maggie Bartlett, NHGRI. is in the Public domain

Use of CRISPR sequences and the enzyme Cas9 in gene editing

The CRISPR-Cas9 system comprises multiple components, including:

- the enzyme Cas9, which can be used to cut DNA at specific target sites on a chromosome
- CRISPR, which stands for **C**lustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats. CRISPR are specific regions of DNA that are found in bacteria and contain short, repeated sequences and unique spacer sequences that are incorporated, usually from viral DNA encountered by the bacteria.

CRISPR-Cas9 system occurs naturally in bacteria

Bacteria employ the CRISPR-Cas9 system as a means of self-defence against invading foreign DNA, such as viruses. By incorporating short segments of foreign DNA into their own genome as ‘spacers’, bacteria can create a molecular record of previous infections. This allows the bacterium to identify and destroy similar foreign DNA in future encounters using the CRISPR-Cas9 system.

1. When foreign DNA is encountered that matches a CRISPR spacer, a corresponding short RNA molecule (known as CRISPR RNAs, or crRNAs) identifies and binds to specific viral sequences.

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2. It then guides Cas9, an endonuclease enzyme, to the target DNA enabling it to make precise cuts in the DNA.
3. This results in a double-strand break that can be repaired through various mechanisms by the cell's DNA repair machinery. These repairs however are, in many cases, error prone.

Theory of Knowledge

To what extent should we trust the scientific community to use gene editing technologies responsibly?

How have scientists made use of the CRISPR-Cas9 mechanism?

Scientists have adapted this natural system for use in genetic engineering by creating single guide RNAs (sgRNA) to target specific genes for modification or deletion. The sgRNA molecule is designed to specifically target and bind to a particular DNA sequence of interest, guiding the Cas9 enzyme to that location and enabling it to make precise cuts in the DNA, resulting in a double-strand break. Once the break has been made at a specific location in the DNA, scientists can add, delete or modify the DNA sequences at that point (**Figure 3**).

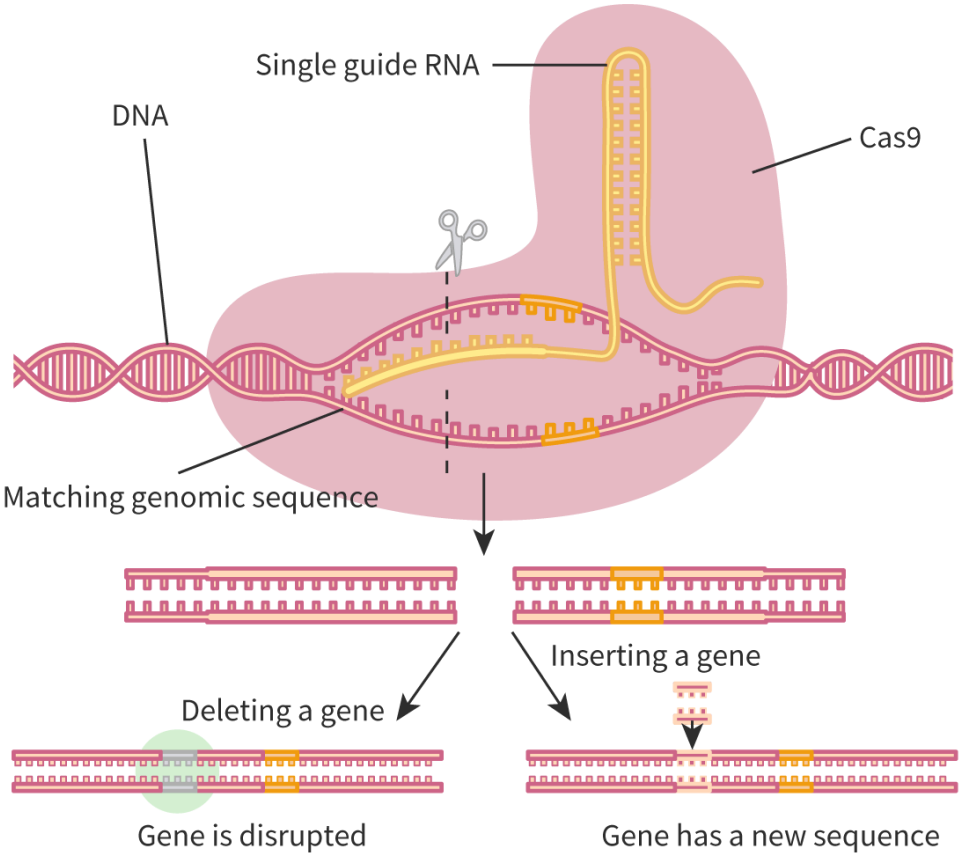

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Figure 3. The CRISPR-Cas9 system has the ability to alter genes.

More information for figure 3

The diagram represents the CRISPR-Cas9 system, illustrating the process of gene editing. At the center, a DNA double helix is shown intertwined with an RNA strand labeled "Single guide RNA (sgRNA)," indicating its role in guiding the Cas9 enzyme to the correct location on the DNA. The Cas9 enzyme is depicted as a pink blob enveloping part of the DNA and sgRNA, with a scissor symbol to signify its function in cutting the DNA. Once the DNA is cut, an arrow points downwards indicating three possible outcomes: disruption, deletion, or insertion.

On the left, the term "Matching genomic sequence" is shown, which denotes the DNA section targeted by the sgRNA. Below this, the top left box labeled "Deleting a gene" shows a section of the DNA where a segment has been removed. In the middle, the box labeled "Gene is disrupted" highlights a section where an interruption has occurred in the genomic material. Finally, on the right, "Inserting a gene" shows templates and a newly inserted sequence into the DNA. Below this, the box labeled "Gene has a new sequence" shows the modified DNA with an added segment.

Overall, the diagram depicts the localization and guided cutting action of CRISPR-Cas9 on the DNA, illustrating the outcomes of deletion, disruption, or insertion of gene sequences.

[Generated by AI]

Watch **Video 1** to learn more about the ability of the CRISPR-Cas9 system to edit genes.

Video 1. CRISPR: Gene editing and beyond.

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Uses and applications of CRISPR-Cas9 system

The CRISPR-Cas9 technology has shown success in genetic research, biotechnology and agriculture. Here are some of the applications of CRISPR-Cas9 system:

1. **Gene therapy:** CRISPR-Cas9 technology offers promising prospects for treating genetic disorders. By precisely correcting disease-causing mutations in a patient's cells, it has the potential to provide effective solutions for conditions like sickle cell anaemia.
2. **Agriculture:** CRISPR-Cas9 has the ability to transform crop breeding practices, introducing precise genetic modifications to enhance desirable traits. This powerful tool can improve crop yield, nutritional content and disease resistance, contributing to the advancement of agricultural practices.
3. **Disease modelling:** CRISPR-Cas9 can be utilised to create animal models that simulate human diseases, aiding in the comprehensive study of their mechanisms and potential therapies. By introducing specific mutations or deleting genes in animals, researchers gain valuable insights into disease progression and potential treatment strategies.
4. **Genetic engineering of microorganisms:** CRISPR-Cas9 technology can make precise modifications to the genetic material of bacteria, yeast or other microorganisms. By doing so, the CRISPR-Cas9 system can enhance these microorganisms' ability to produce valuable compounds such as pharmaceuticals, biofuels and enzymes. This targeted genetic manipulation allows for the creation of efficient microbial factories that can contribute to sustainable production processes.

Despite its successes, the CRISPR-Cas9 system also raises ethical and safety concerns, particularly regarding the editing of human embryos or the genetic modification of entire species.

Nature of Science

Aspect: Science as a shared endeavour

The CRISPR technology holds great promise for medical applications such as treating genetic disorders and developing new therapies. However, there are several ethical concerns associated with the potential uses of CRISPR that must be addressed before implementation of this technology on a large scale.

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One of the significant concerns is the possibility of using CRISPR for genetic enhancement or selection, which raises ethical and moral issues. There is also a risk of off-target effects where CRISPR could unintentionally modify genes other than the targeted ones, leading to unforeseen consequences.

To address these ethical concerns, scientists and policymakers worldwide are working to establish regulatory frameworks for the application of genome editing technologies like CRISPR. Nonetheless, the regulations in different countries vary, leading to the need for international cooperation to harmonise regulation laws.

International organisations, such as the World Health Organization (WHO) and the International Summit on Human Gene Editing, are working towards developing global guidelines for the responsible use of genome editing technologies. Scientists and policymakers have the accountability of ensuring the responsible application of genome editing technologies that benefit society while minimising risks and ethical concerns.

Conserved and highly conserved sequences in genes

Conserved sequences are those that remain identical or similar across a species or group of species, while highly conserved sequences remain similar over long periods of evolution (see subtopics A4.1 (/study/app/bio/sid-422-cid-755105/book/the-big-picture-id-43246/) and D4.1 (/study/app/bio/sid-422-cid-755105/book/the-big-picture-id-43238/)). Species that have close evolutionary relationships usually share a high degree of gene sequence homology.

Conserved or highly conserved sequences in genes help provide clues about the function and importance of these sequences in the evolution of species. One hypothesis for the evolution of these sequences is functional constraints. Functional constraints refer to the selective pressures that prevent the accumulation of mutations that disrupt the function of a gene or its products. Mutations that alter the structure or function of a protein can have detrimental effects, particularly if the protein is involved in essential cellular processes. As a result, these mutations are less likely to persist in a population over time. Highly conserved genes therefore have critical roles in the organism's survival. The second hypothesis is the hypothesis of slower rates of mutation and suggests

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that natural selection pushes mutation rates down to a lower limit set by the power of random genetic drift rather than by intrinsic physiological limitations. This results in reduced levels of replication, transcription, and translation.

The HBA gene, which codes for the haemoglobin alpha chain, is an example of a highly conserved sequence between organisms. Scientists can align DNA, mRNA or amino acid sequences from different organisms in order to see how closely conserved the sequences are (**Figure 4**).

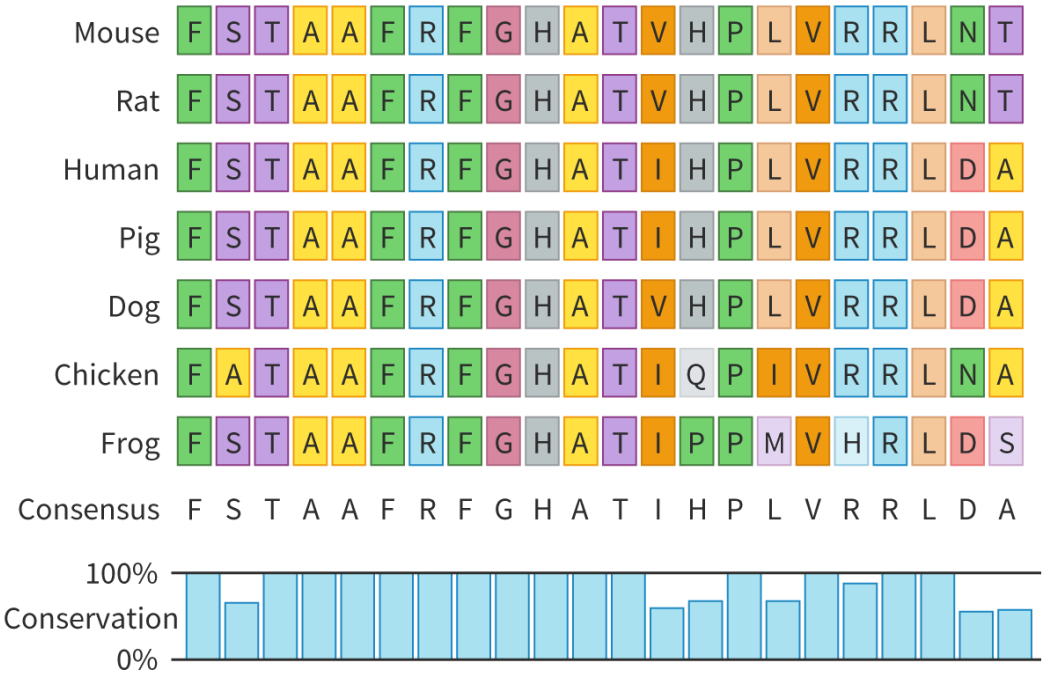

Figure 4. Amino acid sequence alignment between different species for the HBA protein.

More information for figure 4

The image displays an amino acid sequence alignment of the HBA protein across multiple species, including Mouse, Rat, Human, Pig, Dog, Chicken, and Frog. Each row represents the protein sequence from a different species, with a series of colored boxes indicating the presence of specific amino acids at each position. Below these sequences, a consensus sequence is displayed, highlighting the most common amino acid at each position across all species. Further below, a bar graph illustrates the conservation level at each position, with bars indicating higher conserved positions. This visualization helps compare the degree of conservation of the HBA protein among various organisms.

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Try the activity below to compare the DNA sequence of a conserved gene between organisms.

Activity

- **IB learner profile attribute:** Thinker
- **Approaches to learning:** Thinking skills — Experimenting with new strategies for learning
- **Time required to complete activity:** 30 minutes
- **Activity type:** Pair activity

Clustal Omega is a free online tool designed to facilitate the comparison of nucleotide and amino acid sequences. It offers the ability to compare multiple sequences simultaneously, allowing for the construction of multiple alignments.

This tool is particularly useful in the field of bioinformatics and molecular biology, as it enables researchers and scientists to analyse genetic information efficiently and accurately. These alignments can reveal conserved regions and aid in the identification of evolutionary relationships between genes or proteins. By highlighting similarities and differences, researchers can gain valuable insights into the structure, function and evolution of genes and proteins.

Task

The CHRNE gene is responsible for encoding the cholinergic receptor epsilon, a crucial protein involved in transmitting signals within the nervous system. The ability to compare these nucleotide sequences from different organisms aids in understanding the genetic variations and similarities across different species.

In this activity, you will try Clustal Omega for yourselves.

You will input plain text files containing nucleotide sequences for the CHRNE gene and compare them.

Follow this link (https://old-ib.bioninja.com.au/standard-level/topic-3-genetics/31-genes/sequences.txt) to plain text files that contain the nucleotide sequence for the CHRNE gene from different species

Instructions

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1. Go to Clustal Omega: Multiple Sequence Alignment (https://www.ebi.ac.uk/jdispatcher/msa/clustalo) to start.
2. Change the input sequence type to the relevant one (Protein, DNA, RNA).
3. Paste the CHRNE sequences in the space provided.
4. Make sure that the species name is preceded by a forward arrow (e.g. '>Human').
5. Once you have added all sequences, scroll down and click 'Submit'.
6. Analyse the sequence alignment by observing where the nucleotides are the same between species and where they are different. You can read more about how to interpret sequence alignment here (https://www.labxchange.org/library/items/lb:LabXchange:5b84cc84:l
7. Once you are done, complete the following questions and share your answers with your teacher.

Questions

1. How does Clustal Omega help in identifying similarities and differences between DNA sequences?
2. What can multiple sequence alignments reveal about the genetic variations among different species?
3. What are conserved regions in DNA sequences and why are they important?
4. How can the comparison of DNA sequences using Clustal Omega aid in understanding evolutionary relationships?
5. Can you identify any functional domains within the CHRNE gene using the sequence alignment results from Clustal Omega?
6. What are some potential applications of Clustal Omega and DNA sequence comparison in the field of molecular biology and bioinformatics?

5 section questions

Student view

D1. Continuity and change: Molecules / D1.3 Mutations and gene editing

Summary and key terms

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- Single-nucleotide polymorphisms (SNPs) occur when one nucleotide is replaced by another nucleotide in the DNA sequence. Synonymous substitutions are known as neutral mutations as they do not change the amino acid sequence due to the degeneracy of the genetic code while nonsynonymous substitutions change the amino acid sequence which can affect the structure and function of a protein.
- Frameshift mutations can be caused by either insertions or deletions as these processes alter the reading frame of codons. This results in alterations to the amino acid sequence coded for by the DNA sequence. Insertions occur when one or more nucleotides are added to the DNA sequence. Deletions occur when one or more nucleotides are removed from the DNA sequence.
- A gene mutation is a change in the DNA sequence of a gene that can result in altered proteins that may potentially lead to disease. Gene mutations can occur by errors in DNA replication or repair which may be triggered by mutagens. Mutagens are agents that can cause mutations and there are two types: chemical mutagens and radiation.
- Mutations can occur randomly anywhere in the base sequences of a genome due to errors during DNA replication or repair, exposure to mutagens such as radiation or chemicals, or other random events. Although some bases have a higher probability of mutating than others, there is no natural mechanism known for deliberately changing a particular base to alter a trait.
- Gene mutation is the original source of all genetic variation. Mutations in germ cells can be passed onto offspring and affect their traits while mutations in somatic cells can only have an impact on the individual during their lifetime and cannot be passed on to their offspring.
- Mutations can have various effects on an organism, including being neutral, beneficial or harmful. Neutral mutations are those that do not significantly affect the organism, harmful mutations have negative consequences on an organism and beneficial mutations are rare but can provide advantages to an organism and increase its fitness in a particular environment.

Higher level (HL)

- Gene knockout is a technique in which a specific gene is intentionally made inoperative to study its function. This technique is used to investigate the effects of removing a particular gene on an organism's development, behaviour, physiology and disease susceptibility.

Student view

Overview (/study/ap 422-cid-755105/o

- CRISPR is a specific region of DNA that is found in bacteria that contains short, repeated sequences and unique spacer sequences that are incorporated from foreign DNA encountered by the bacteria. Bacteria employ the CRISPR-Cas9 system as a means of self-defence against invading foreign DNA, such as viruses. By incorporating short segments of foreign DNA into their own genome as ‘spacers,’ bacteria can create a molecular record of previous infections. This allows the bacterium to identify and destroy similar foreign DNA in future encounters using the CRISPR-Cas9 system.
- When foreign DNA is encountered that matches a CRISPR spacer, a corresponding short RNA molecule (known as CRISPR RNAs, or crRNAs) identifies and binds to specific viral sequences. It then guides Cas9, an endonuclease enzyme, to the target DNA enabling it to make precise cuts in the DNA. This results in a double-strand break that can be repaired through various mechanisms by the cell's DNA repair machinery.
- Conserved sequences are those that remain identical or similar across a species or group of species, while highly conserved sequences remain similar over long periods of evolution. Species that have close evolutionary relationships usually share a high degree of gene sequence homology.

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Key terms

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Review these key terms. Do you know them all? Fill in as many gaps as you can using the terms in this list.

1. _____ occur when one nucleotide is replaced by another nucleotide in the DNA sequence.
2. _____ substitutions are known as neutral mutations as they do not change the amino acid sequence due to the degeneracy of the genetic code.
3. _____ mutations can be caused by insertions or deletions, which alter the reading frame of codons.
4. _____ are agents that can cause mutations. Mustard gas and nitrous acid are types of _____ mutagens.
5. Mutations in _____ can be passed onto offspring and affect their traits.
6. _____ mutations are those that do not significantly affect the organism. _____ mutations can cause diseases, developmental abnormalities, or reduce the organism's fitness and survival. _____ mutations are rare but can provide advantages to an organism and increase its fitness in a particular environment.
7. [HL] _____ is a technique in which a specific gene is intentionally made inoperative to study its function.
8. [HL] Bacteria employ the _____ as a means of self-defence against invading foreign DNA, such as viruses.
9. [HL] The _____ molecule is designed to target and bind to a particular DNA sequence of interest, guiding the _____ enzyme to that location and enabling it to make precise cuts in the DNA resulting in a double-strand break.
10. [HL] _____ sequences are those that remain identical or similar across a species or group of species.

chemical | Beneficial | sgRNA | Cas9 | Gene knockout | Neutral | Harmful | germ cells | SNPs | Synonymous | Conserved | CRISPR-Cas9 system | Frameshift | Mutagens

Check

Student view

Checklist

What you should know

After studying this subtopic you should be able to:

- Explain that gene mutations are structural changes to genes at the molecular level.
- Outline the consequences of base substitutions.
- Outline the consequences of insertions and deletions.
- Recall that gene mutations can be caused by mutagens and by errors in DNA replication or repair.
- Explain that mutations can occur anywhere in the base sequences of a genome.
- Explain the effects of gene mutations occurring in germ cells and somatic cells.
- Recognise that gene mutation is the original source of all genetic variation.

Higher level (HL)

- Outline that gene knockout is a technique for investigating the function of a gene by changing it to make it inoperative.
- Explain the use of the CRISPR sequences and the enzyme Cas9 in gene editing.
- Describe the hypotheses for conserved or highly conserved sequences in genes.

- **IB learner profile attribute:** Thinker
- **Approaches to learning:** Thinking skills – Experimenting with new strategies for learning
- **Time required to complete activity:** 60 minutes
- **Activity type:** Individual activity

Gene mutations may occur through single nucleotide polymorphisms (SNPs) but how are these polymorphisms even detected? In this simulation, you learn how scientists identify SNPs and will be taken through a series of steps and questions to understand the complexity of the process.

Your task

Design the simplest experiment that can determine if your test subject has inherited a particular SNP that affects bitter taste.

1. Open the Experimental Design (https://www.labxchange.org/library/items/lb:LabXchange:c89bc1ea:lx_simulation:1) simulation to start.
2. Click ‘Start simulation’ and click on ‘Level 1’ and then ‘Start simulation’.
3. Complete all sections and be sure to complete the questions in the problem solving, results and reflection sections.
4. Then complete the following questions and share your answers either written or verbally with your teacher.

Questions

1. What can the identification of polymorphisms tell us about individuals or populations?
2. What is the purpose of PCR in the detection of polymorphisms?
3. Explain the principle behind gel electrophoresis and its role in analysing single nucleotide polymorphisms.

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4. How does gel electrophoresis help in visualising and distinguishing different DNA fragments?

Reflection

Section Student... (0/0) Feedback Print (/study/app/bio/sid-422-cid-755105/book/reflection-id-46892/print/) Assign

Teacher instructions

The goal of this section is to encourage students to reflect on their learning and conceptual understanding of the subject at the end of this subtopic. It asks them to go back to the guiding questions posed at the start of the subtopic and assess how confident they now are in answering them. What have they learned, and what outstanding questions do they have? Are they able to see the bigger picture and the connections between the different topics?

Students can submit their reflections to you by clicking on 'Submit'. You will then see their answers in the 'Insights' part of the Kognity platform.

Reflection

Now that you've completed this subtopic, let's come back to the guiding question introduced in The big picture (/study/app/bio/sid-422-cid-755105/book/the-big-picture-id-43250/).

- How do gene mutations occur?
- What are the consequences of gene mutation?

With these questions in mind, take a moment to reflect on your learning so far and type your reflections into the space provided.

You can use the following questions to guide you:

- What main points have you learned from this subtopic?
- Is anything unclear? What questions do you still have?

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- How confident do you feel in answering the guiding questions?
- What connections do you see between this subtopic and other parts of the course?

⚠ Once you submit your response, you won't be able to edit it.

0/2000

Submit

Rate subtopic D1.3 Mutations and gene editing

Help us improve the content and user experience.

☆ ☆ ☆ ☆ ☆

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