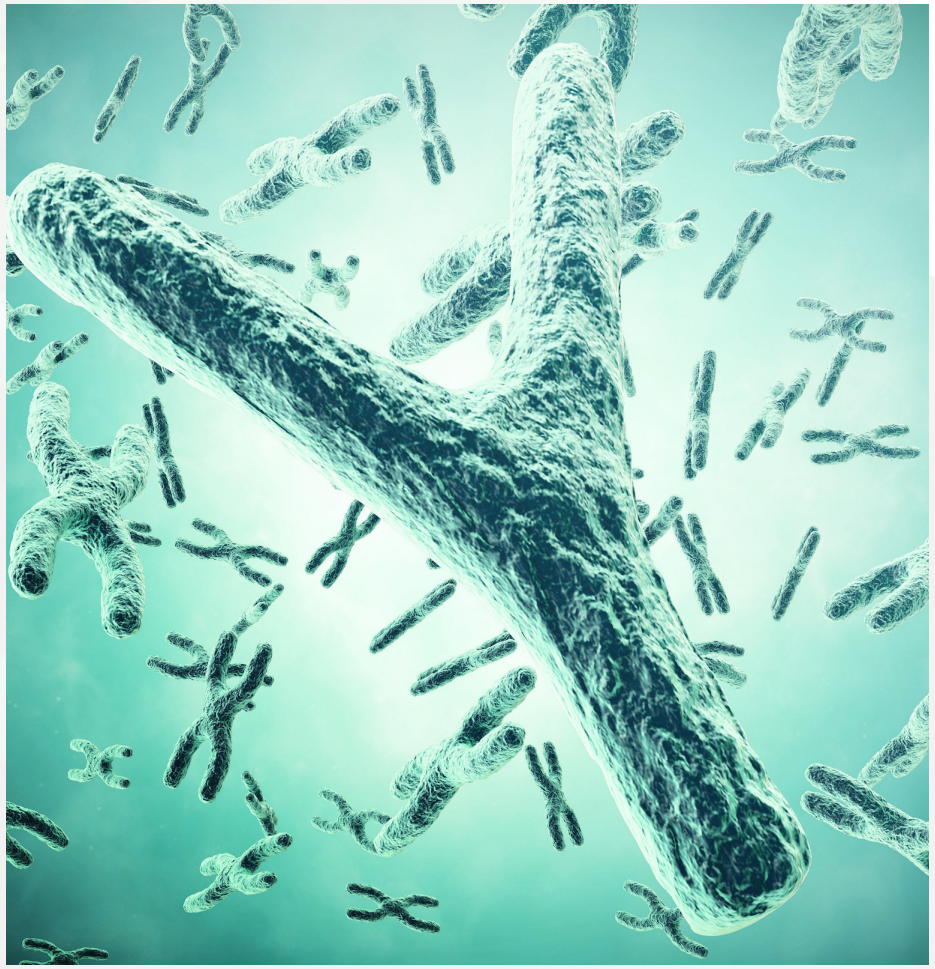

Article 1
Scientific document for use with Question 8
Risk of heart failure may increase with age due to Y chromosome loss
2025 May Exam

DATE 06.04.2025

Dr. Thusitha Gajanayake
www.tulipdust.com

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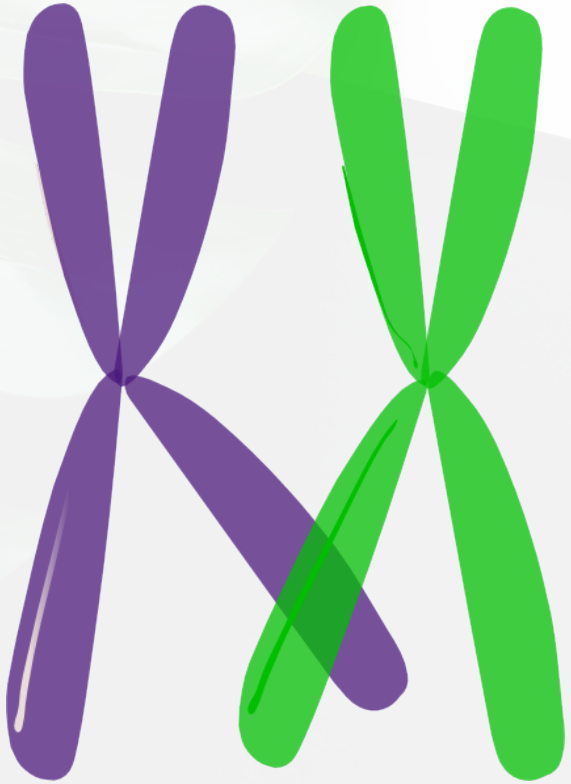
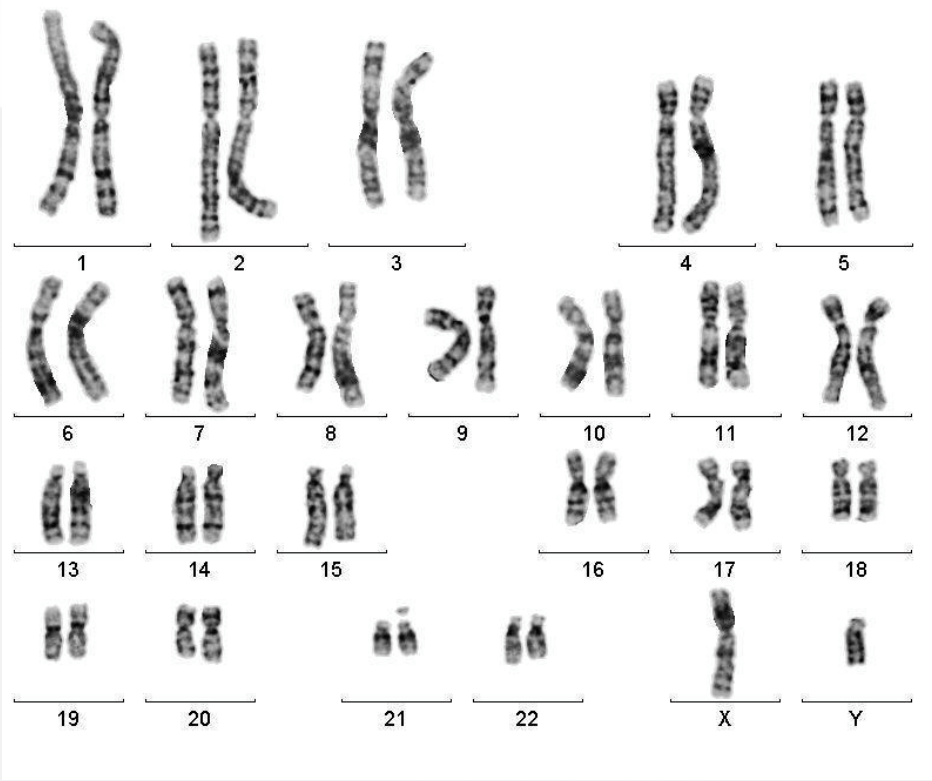
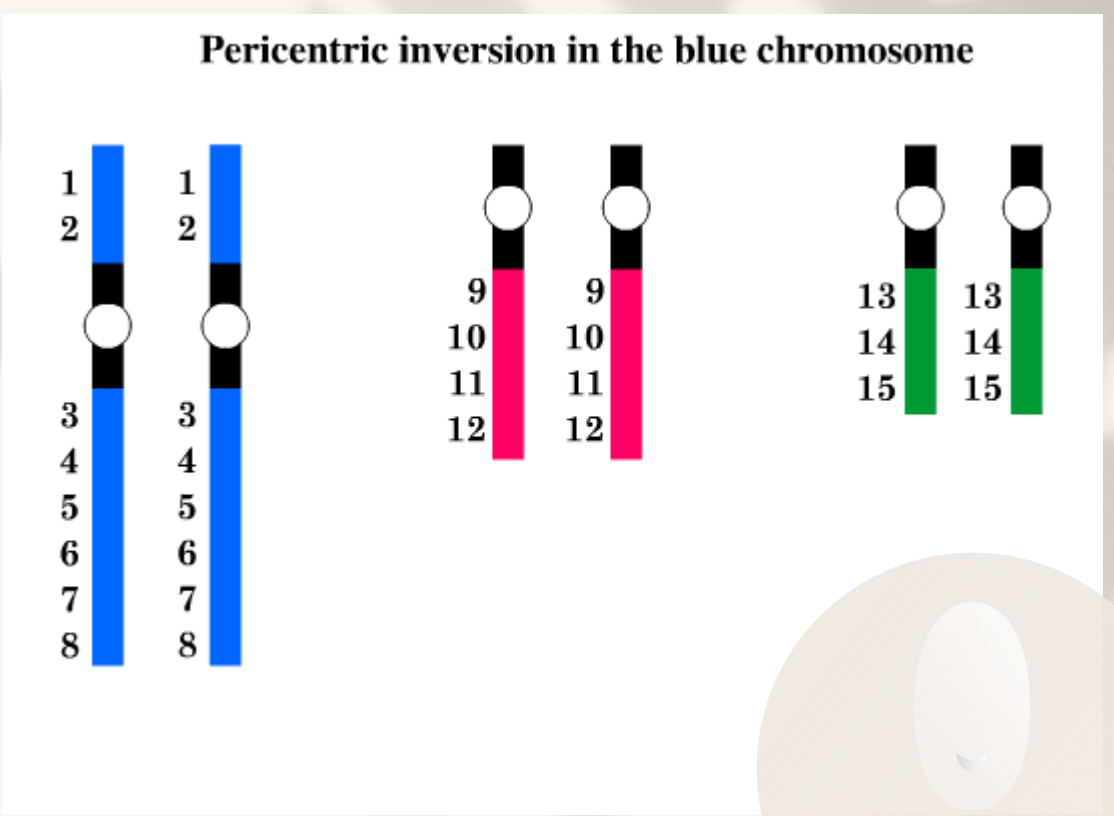




Respiration, Internal Environment, Coordination, and Gene Technology.

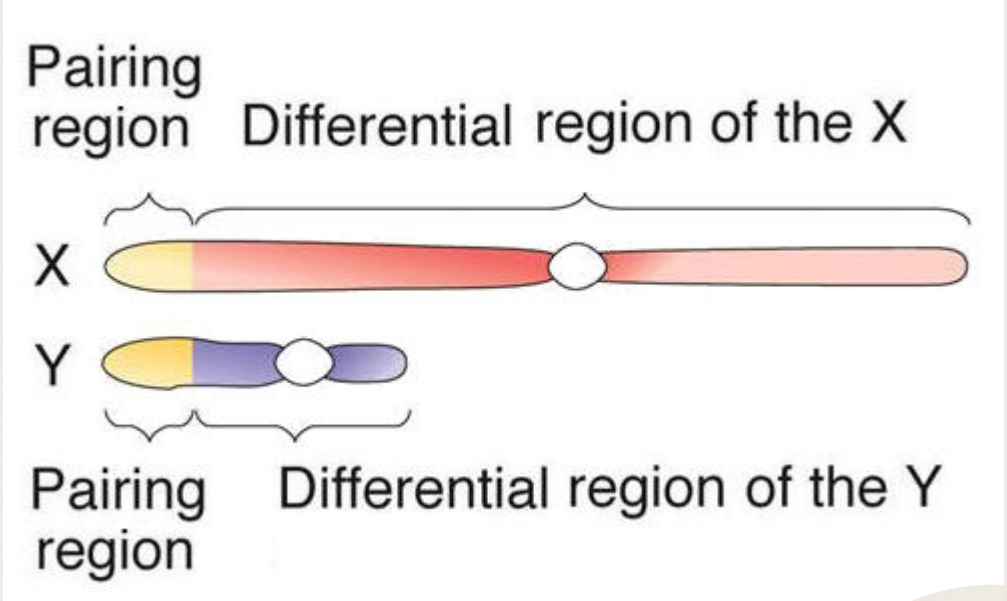
Background knowledge chromosome inversion

A chromosomal inversion is a genetic mutation where a segment of a chromosome breaks off, rotates 180 degrees, and reattaches to the same chromosome, but in the reverse orientation. This reversal of the DNA sequence can occur within a single chromosome or between different chromosomes. There are two main types of inversions: paracentric and pericentric.



Background knowledge
Do all the genes in Y has on X

- No, not all genes present on the Y chromosome are also found on the X chromosome. The Y chromosome contains unique genes that are not present on the X chromosome. While some genes in areas called pseudoautosomal regions are shared, the vast majority of genes on the Y chromosome are unique to it.



Do both X chromosomes express genes ?

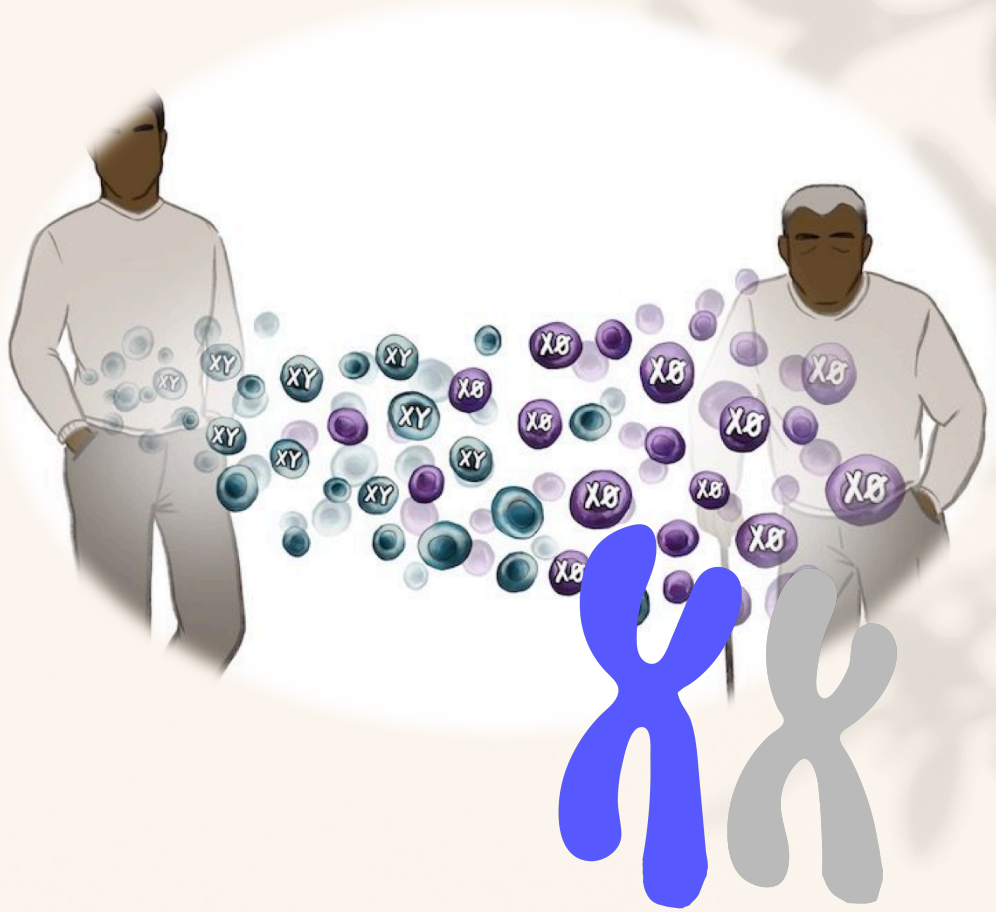
- In female mammals, only one of the two X chromosomes is actively expressed in each cell. This process, called X-chromosome inactivation (XCI), ensures that females don't have a double dose of X-linked genes, which would be detrimental to their development. While one X chromosome is inactivated, it's not completely silent and can still influence gene expression on the active chromosome.

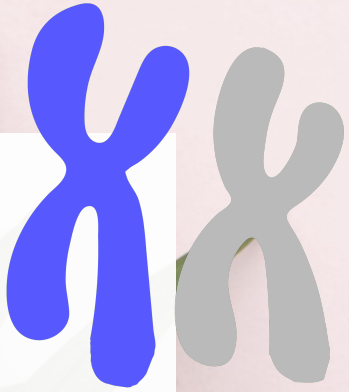
In **chorionic villus sampling**, a small sample of embryonic tissue is taken from the developing placenta. This makes a much bigger sample of fetal tissue available for examination. The cells can be tested for a wide range of genetic abnormalities. This diagnostic technique can be carried out much earlier in the pregnancy, so that if a termination is necessary it is physically less traumatic for the mother. The results are also available more rapidly than for amniocentesis.

There are two disadvantages to chorionic villus sampling.

- There is a 0.5–1% risk that the embryo may spontaneously abort after the tissue sample is taken, though the risk of miscarriage at this stage of pregnancy is high anyway.
- All paternal X chromosomes are inactivated in fetal placental cells so any problems in the genes on that chromosome cannot be detected by this technique.

1. The immune cells of many older men lose their Y chromosomes, and this may contribute to men having a higher rate of heart disease than women. Health risks from Y chromosome loss have long been suspected, but evidence from animals and people now adds more support to the idea – and may suggest a treatment for the damage caused to the heart.





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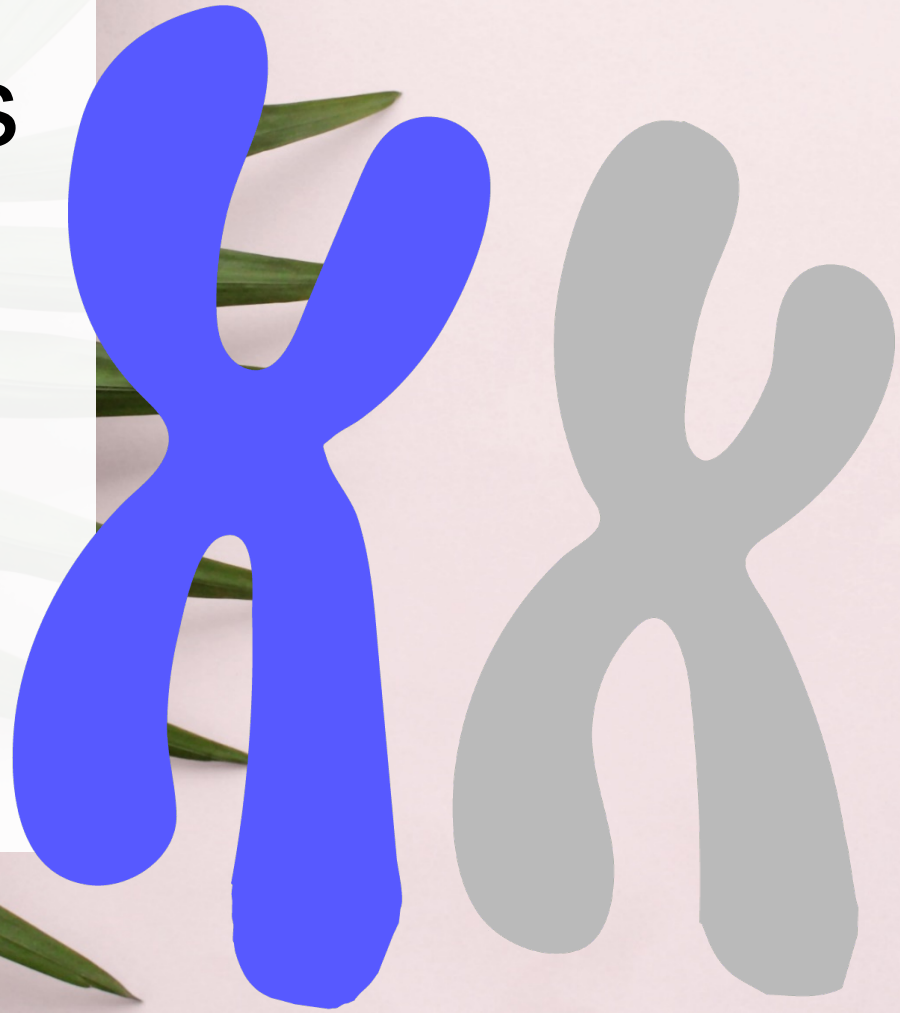
Why is Y chromosome loss occurring mostly in immune cells ? (2)

Model Answer

Y chromosome deletion occurs more frequently in immune cells, as the **Y chromosome does not participate in any functions within immune cells** and **has a high rate of division.**

2. DNA is packaged into chromosomes, with the cells of most men and transgender women carrying one X and one Y, and those of most women and transgender men carrying two Xs – although some people have other combinations, such as XXY or XYY. It was discovered several decades ago that in some people born with XY chromosomes, a proportion of the immune cells have no Y chromosome, a phenomenon that becomes more common with increasing age. For instance, 40 per cent of 70-year-old men have no Y in at least some of the immune cells found in their blood

Explain why certain individuals possess different combinations, such as XXY or XYY.(2)



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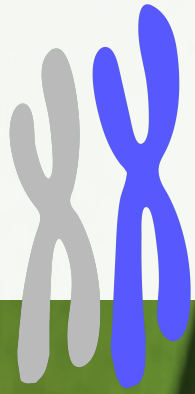
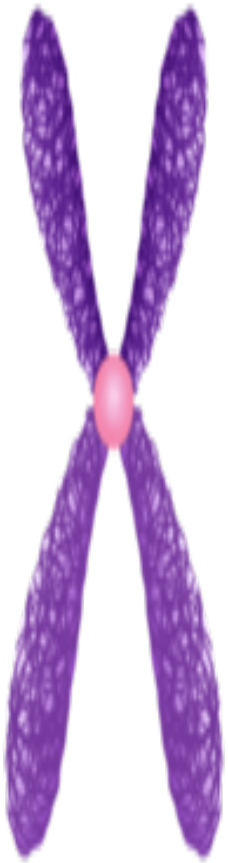
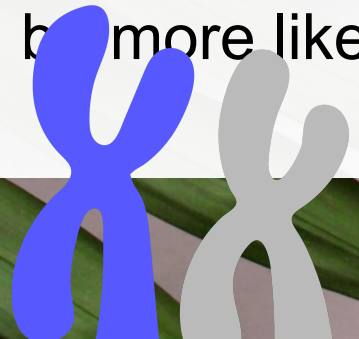
During meiosis, homologous chromosomes fail to separate properly, resulting in one cell receiving an extra chromosome while the other cell lacks it.

This occurs when an egg cell with two X chromosomes (XX) is fertilized by a sperm cell with a Y chromosome, or when a sperm cell with both X and Y chromosomes fertilizes a normal X egg.



3. The reasons for this are unclear, but it could be because the Y chromosome is small and carries relatively few genes apart from those involved in sex determination and sperm production, so the **stem cells that produce immune cells** can survive if they happen to lose their Y when replicating their DNA. If they lose any other chromosomes, however, the cells would b more likely to die.





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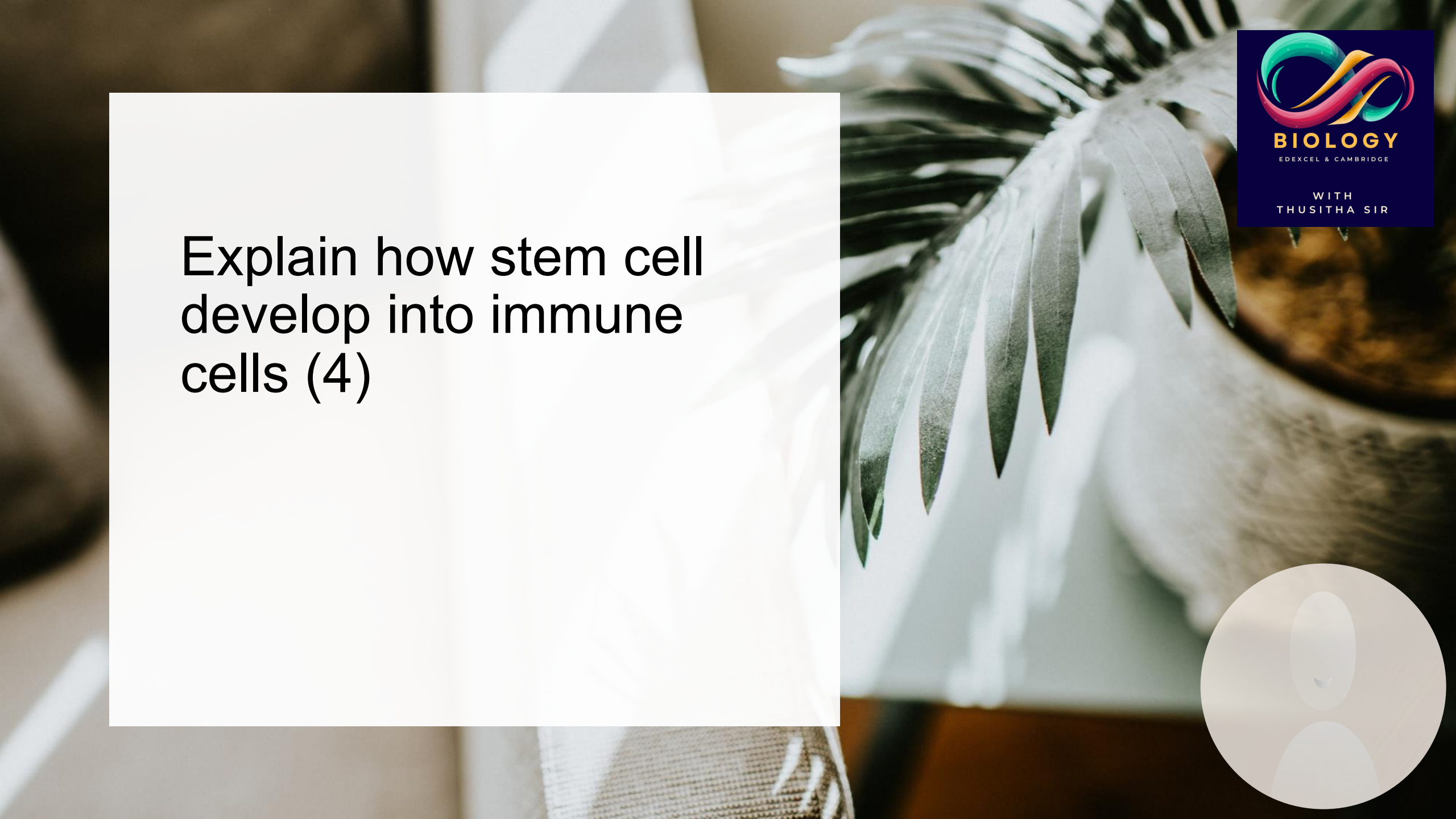
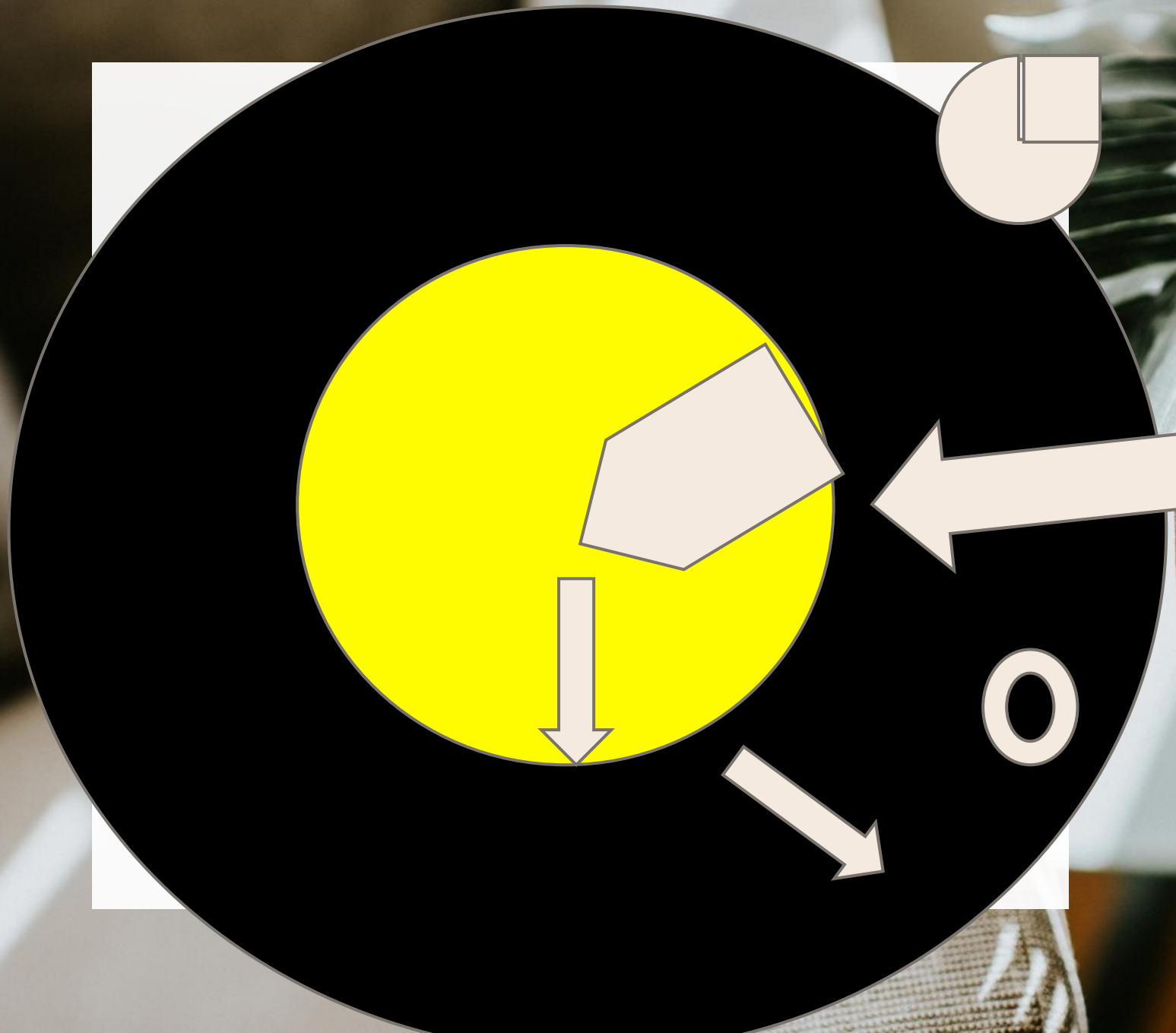
Explain how stem cell develop into immune cells (4)





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MS POINTS

Mark Scheme (Results) October 2023 Pearson Edexcel International Advanced Level In Biology (WBI15) Paper 01 Unit 5: Respiration, Internal Environment, Coordination and Gene Technology

- **fibroblasts respond to {mechanical / chemical stimuli / TGF-beta / transcription factor} (1)**
- **causing {a change in gene expression / switching genes on / differential gene expression} (1)**
- **due to {epigenetic modification / histone modification / DNA methylation} (1)**
- **{active / switched on} genes are transcribed (into mRNA) (1)**
- **translation (of mRNA) occurs (at the ribosome) (1)**
- **(resulting in) formation of proteins needed for {differentiation / specialisation} {of fibroblasts / to myofibroblasts} (1)**

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4. Loss of this Y chromosome in immune cells correlates with higher rates of health problems, including heart disease, cancer and Alzheimer's disease. But it was unclear whether Y loss causes these conditions or if faulty DNA replication is behind both Y loss and the health issues, says Lars Forsberg at Uppsala University in Sweden

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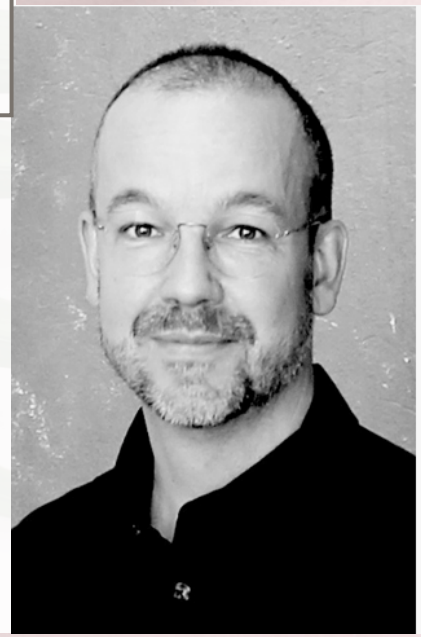
5. To find out, Forsberg and his colleagues **used the CRISPR gene-editing technique to remove the Y chromosome from about two-thirds of the immune cells of male mice to mimic the phenomenon.** These mice developed heart problems once they got to about 1 year of age, precipitated by their heart muscle becoming scarred. “We show causality,” says Forsberg. “We can see that losing the Y chromosome in the blood causes disease in the heart.”



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CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) gene editing is a powerful tool that allows scientists to precisely modify DNA sequences in living cells.

1 Targeting the DNA: CRISPR uses a guide RNA molecule that is designed to match a specific DNA sequence in the target gene.

2. Cutting the DNA: Once the Cas9 protein is guided to the target DNA sequence, it acts like molecular scissors, creating a double-stranded break at that location.

4. Editing the Gene: By carefully controlling the DNA repair pathways, scientists can add, remove, or alter genetic material to achieve specific changes in the genome.

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6. The researchers also looked at how Y chromosome loss affected men in a large ongoing medical study called UK Biobank, which tracks participants' health over time. They found that the more immune cells without a Y that the men had at the time of their enrolment, the higher their risk of dying from any type of heart disease over the following 12 years. For instance, men who had lost the Y chromosome in more than 40 per cent of their immune cells had a 31 per cent higher risk of dying from any circulatory disease during the study period. **Scarring of heart muscle can contribute to some common types of heart disease, such as heart failure, says Forsberg.**

Scarring refers to the replacement of healthy heart muscle tissue with scar tissue after an injury, most commonly a heart attack. This scarring can reduce the heart's ability to pump blood efficiently, leading to heart failure and other complications.

Q Explain how scarring contribute to heart failure ?

- Scars reduces heart muscles
- Left ventricle contraction force decrease
- Less cardiac output

Q Explain how scarring of heart muscle detected.

Use ECG

Scar tissue, which replaces damaged heart muscle, can disrupt the heart's electrical signals, leading to changes in the ECG waveform.

7. Further work on the mice uncovered clues about how immune cells cause heart scarring. When the animals were dissected, immune cells lacking a Y chromosome were found to have infiltrated heart muscle, **triggering the release of an inflammatory signalling molecule called transforming growth factor beta**

Q Explain how transforming growth factor beta cause scarring

Immune cells lacking the Y chromosome can contribute to heart damage by promoting scar tissue builds up in the heart muscle. Specifically, macrophages, a type of white blood cell, without the Y chromosome can stimulate cells in the heart to produce more connective tissue, resulting in increased scarring.

8. Treating the mice with an antibody that blocks this growth factor reduced the harmful effects of the loss of the Y chromosome – **although it is too soon to conclude the same approach would benefit men who are losing their Y chromosomes, says Forsberg**. He is co-founder of a biotech firm called Cray Innovation that is developing a blood test to tell people if they have loss of the Y chromosome in their immune cells

Q How antibody prevent effect of transforming growth factor beta and scarring of heart

- Antibodies can prevent heart scarring by neutralizing transforming growth factor
- Antibofy is specific to transforming growth factor
- preventing transforming growth factor from binding to its receptors and initiating the signaling pathway

Q Explain why it is early to determine that the same method would be advantageous for men who are experiencing a loss of their Y chromosomes.

- Mouse research results are not always directly translatable to humans due to significant biological differences.
- Mouse has different metabolic pathways, immune responses, and drug metabolism.
- Mouse genetic is different to human

9. “This is the best evidence I have seen for a direct effect of Y chromosome loss on a physiological process,” says John Perry at the University of Cambridge. In 2019, Perry and his colleagues published work suggesting that a propensity for Y chromosome loss is caused by many genetic variants that raise the likelihood of DNA errors during cell division, which could be why loss of the Y chromosome is linked with cancer

Q How DNA error link with cancer ? (2)

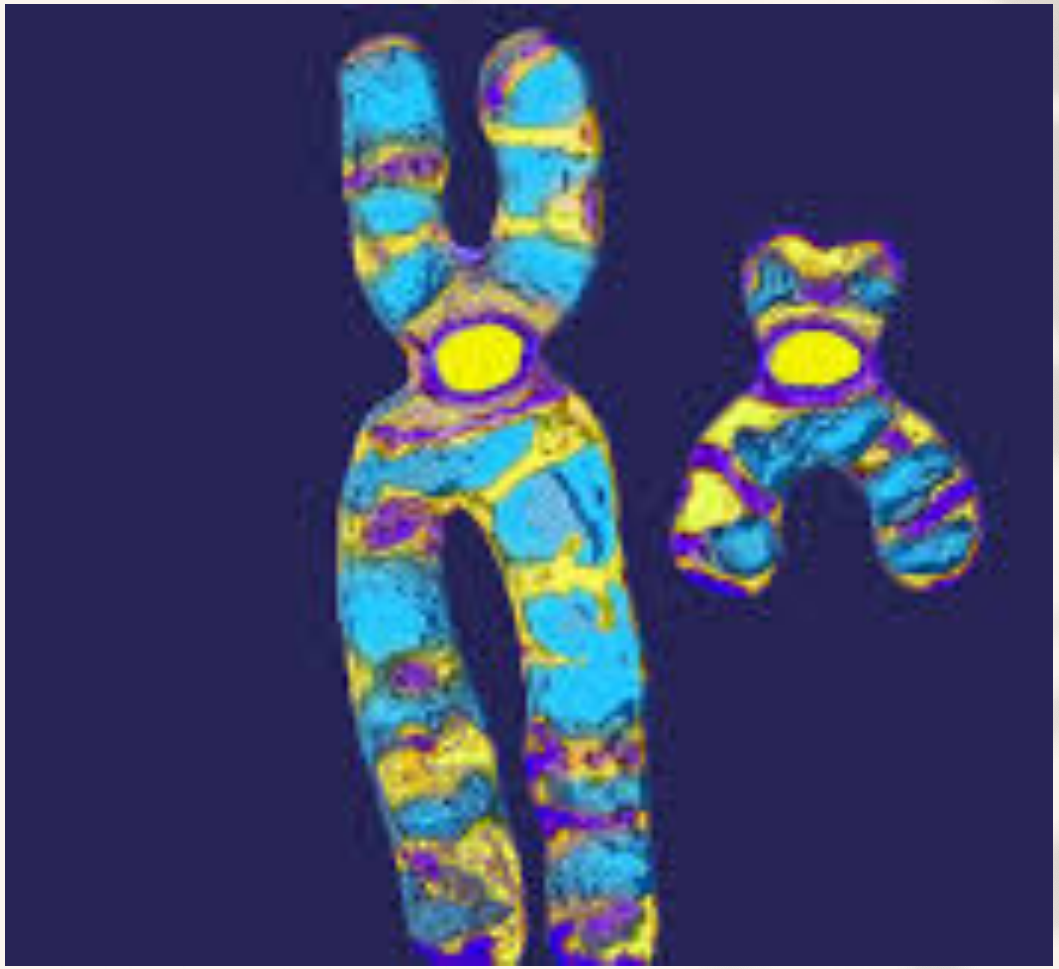
Model answer - DNA mutations are a significant driver of cancer development, primarily due to their impact on cellular processes and the accumulation of these errors over time. When DNA errors affect genes that regulate cell growth, division, and repair, they can lead to uncontrolled cell proliferation and the formation of tumors.

10. Forsberg’s team next plans to investigate whether people born with XYY chromosomes experience different effects if they lose one of their Y chromosomes

XYY syndrome, also known as Jacobs syndrome, is a genetic condition where males have an extra Y chromosome.

Article 2

Essence of man: Y size doesn’t matter



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11. There’s nothing very mach about the Y chromosome. Even though it’s what makes men male, the human Y, like its counterparts in almost all mammals, is tiny compared with its partner, the X chromosome. It’s lost hundreds of genes – and if the Y continues to lose them, it could someday wink out of existence entirely.

12. Claims of its impending demise are starting to look premature, however. Far from being a rotting husk, the modern Y, tiny though it is, is turning out to be a highly evolved and surprisingly important part of men’s wider genetic endowment, responsible for far more than just maleness.

13. It is easy to see why some biologists thought the Y was destined for oblivion: it is all on its own. **There are two copies of all other chromosomes, which are basically containers for holding genes**. Each copy acts as a backup for the other. The pairs line up and swap bits when organisms reproduce. Some offspring get landed with chromosomes full of damaged genes and are eliminated by natural selection, whereas others inherit undamaged copies and survive to reproduce.

14. Way back in the evolutionary past, there was no Y, just a regular pair of chromosomes. Sex was determined by environmental factors such as temperature. But then a gene on a single chromosome mutated in a way that made any individual that inherited it male. At first this proto-Y could still swap genes with its partner, the proto-X chromosome. About 180 million years ago – in the line of mammals that branched away from the platypus and echidna – a section of it containing the gene variant for maleness got flipped back to front. This section no longer lined up properly with the corresponding part of the proto-X, so damaged genes in this section could no longer be swapped for good ones

Beyond repair

15. Further inversions put more and more of the Y beyond repair. The X was fine because females inherit two copies that can swap parts. The Y, however, started to lose bits because men have just one copy. The human version now has just 78 genes, far less than its original 600 or so. At this rate of decay the Y ought to disappear altogether within 5 million years, as famously predicted a few years ago by Jenny Graves at La Trobe University in Melbourne, Australia

Q “The human version now has just 78 genes, far less than its original 600 or so. At this rate of decay the Y ought to disappear altogether within 5 million years” How this prediction make ?

By calculating the gene decay rate

600/ 44 mil = 14 genes per mil

78/14 = 5.5 mil

16. But there is growing reason to believe that what's left of the Y is here to stay. For one thing, even though it has lost almost all of its original set of genes, it has gained others: we now know that 61 of the human Y's 78 genes were not present before the first inversion took place. Almost all the new genes play a role in sperm production, making the Y a perfect home for them. There are often several copies of these genes, too, so there are backups.

Q
What does the research indicate about the future of the Y chromosome ? (2)

Despite predictions that the Y chromosome might disappear altogether within 5 million years due to its decay, there is growing evidence that what remains of the Y chromosome is important and has gained new genes that play a role in sperm production, suggesting it is here to stay.

17. An even stronger reason to think the Y chromosome has a bright future comes from the discovery, by Daniel Bellott at the Whitehead Institute in Boston, that its decay seems to have ground to a halt. His team compared the Y chromosomes of eight mammals – human, chimp, rhesus macaque, marmoset, mouse, rat, bull and opossum – to trace its evolutionary history. They found bursts of gene loss directly after inversions happen, followed by long periods of stability. In fact, not a single gene has been lost from the oldest part of the human Y in the past 44 million years.

- **Crossing over (recombination)**: this process occurs in prophase 1 of meiosis when large, multi-enzyme complexes 'cut and join' bits of the maternal and paternal chromatids together (see **fig E**). The points where the chromatids break are called **chiasmata**. These are important in two ways. First, the exchange of genetic material leads to added genetic variation. Second, errors in the process lead to **mutation** and this is a further way of introducing new combinations into the genetic make-up of a species.

Explain how gene loss take place during inversion in cell. (3)

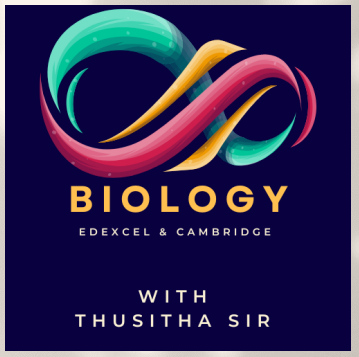
chromosomal inversions can occur during meiosis.

Prophase I

Chromosome cross over

chromosome breaks off, flips around, and reattaches in the opposite orientation.

This can loss genes if truncation happens withing the gene



New genes can arise from several mechanisms, including gene duplication, transposable element protein domestication, lateral gene transfer, gene fusion, gene fission, and de novo origination, according to Nature. One key mechanism is gene duplication, where errors in DNA replication create multiple copies of a gene. Over time, these duplicated genes can evolve and acquire new functions.

Q
How scientist claim that not a single gene has been lost from the oldest part of the human Y in the past 44 million years. (2)

Scientists determine gene stability in the oldest parts of the Y chromosome through comparisons of the human Y chromosome with those of other species. By analyzing the gene content and structure of the Y chromosome across these different lineages, they can pinpoint when genes were likely lost or gained.

18. The remaining genes may simply be too essential to lose. A team led by Henrik Kaessmann at the University of Lausanne, Switzerland, surveyed the Y chromosomes of 15 different mammal species and one bird. They found that a chromosome linked with maleness evolved three distinct times – once in birds, once in the ancestor of the platypus and echidna, and a third time in the ancestor of all other mammals. The ancestors of the three Ys each started with different kinds of genes, but to Kaessmann's surprise, all ended up with a stable set of the same sorts of genes, which is what Bellott's team also found. "You play this evolutionary game with different sets of genes, and you get the same kinds of genes retained in each case," he says. "It's always the regulatory genes that remain.

Q Why this study include a bird with 15 different mammals ? (2)

To compare the effect of gene loss on other animals apart from mammals

To find the maleness evolution in other animals

19. Why? When a gene is lost from the Y, males are left with one copy of the gene, on their single X chromosome. That means less of the protein the gene codes for gets made – roughly half the usual dosage. Evolution can fix this in males by ramping up production from the single X, but then their female descendants get a double dose from their two Xs. To keep gene output the same in the two sexes despite this difference, females have evolved to inactivate one of their two copies of most genes on the X. Perhaps the amount of protein produced by the regulatory genes retained on the Y had to be so precisely calibrated that organisms couldn't survive the awkward intermediate stage when this workaround did not yet function perfectly, suggests James Turner at the MRC National Institute for Medical Research in London. Regulatory genes are particularly vital because they control many other genes

Q How regulatory gene control other gene? (4)

- Regulatory genes control other genes by producing transcription factors
- transcription factors that bind to promoter
- Then RNA polymerase bind
- transcription factors can either activate or repress transcription of the target genes, thus influencing the amount of mRNA and ultimately the amount of protein produced by those genes

20. So important are the Y genes, in fact, that even during a man's lifetime, losing the Y in some tissues takes a toll. Chromosomes can be lost when cells divide, and men who lose the Y chromosome in their bone marrow – which happens in about 8 per cent of elderly men – have a higher risk of cancer and die an average of 5.5 years younger than other men.

Suggest a reason why it only happens in about 8 per cent of elderly men (1)

Genetic and

environment factors