Genomics

Name

Module

Module Code

Introduction

Genetics can be viewed as a branch of biology which involves the study of genes. Researchers in genetics are concerned with genetic variation and heredity among other functions of the genes. Mutations of a single of multiple genes may lead to various diseases. Some of the genetic disorders include cystic fibrosis, Tay-Sachs disease, phenylketonuria and colour-blindness among others. There are various causes of gene mutations including low frequency due to chemical instability of purine and pyrimidine bases and errors that occur during the replication of DNA. Gene mutation may also occur due to environmental issues like exposure to ultraviolet radiations and chemical carcinogens. The current analysis evaluates sickle cell anaemia which among the most common disease that arises from genetic code. Various elements of the disease including signs and symptoms of the disease, the characteristics of the gene linked to the disease, the type of mutation that results in the disease, and characteristics of the inheritance of the disease will be evaluated.

Summary of the disease

Sickle cell anaemia, commonly referred to as sickle cell disease is a genetic disease of the red blood cells (Hoppe et al., 2017). Normally the red blood cells are disc-shaped which gives them the ability to travel in the blood vessels. However, sickle cell disease make the red blood cell have an abnormal sickle shape making them sticky and rigid. This condition makes it difficult for the red blood cells to move freely in the veins therefore leading to being trapped in the small vessel. Such sickle shaped block the blood from reaching the body parts which may lead to tissue damage or pain (Ware & Dertinger, 2021).

Sickle cell disease arise due to single base pair point mutation in the Beta globin gene. This phenomena contributes to substituting the amino acid valine for glutamic acid in the chain. According to the Centre for Disease Control and Prevention (CDC), sickle cell disease

is a group of inheritance disorders of the red blood cell (CDC, 2020). Accordingly, the sickle cell disease leads to a constant shortage of red blood t cells. There are different symptoms of sickle cell disease including anaemia episodes of pain swelling of hands and feet, frequent infections, delayed growth and development of a child and vision problems.

The phenotypic variation attributed to clinical presentation is a specific feature of sickle cell disease (Kato et al., 2018). Typically, sickle cell is characterized by disorders of different body system including chronic and acute complications that present. This aspect leads to reduction of foetal haemoglobin due to failure of oxygen to circulate optimally in the body tissues. The inheritance of haemoglobin S is the common form of sickle cell disease and this proportion varies according to different genotypic parameters and geographical location. Therefore, sickle cell disease is a critical genetic disorder considering it contributes to alteration in an individual's phenotypic and physiological parameters.

Function of the Gene linked to sickle cell disease

Haemoglobin beta gene is associated with the development of sickle cell disease. Mutations in haemoglobin beta gene found on chromosome 11 contributes to alteration of red blood cell (Menzel & Thein, 2019). The function of the gene is to provide instructions for making beta-globin proteins. Beta globin is a sub unit of hemoglobin located in the red blood cells. In adults, hemoglobin is made up of four protein subunits including two beta-globin subunits and two subunits of Alpha globulin. Each of these protein subunit is bound to an iron containing molecule known as heme.

The function of haemoglobin beta Gene is to provide instruction for protein synthesis referred to as beta-globin (Rullo et al., 2019) .The current genetic component is therefore, important in protein synthesis and formation of polypeptide chains in adult hemoglobin. Mutations in beta globin lead to sickle cell anaemia whereas the absence of beta chain leads

to Beta 0 thalassemia. The active production in the amount of detectable beta-globin leads to beta globin thalassemia. The Beta Globin gene is a dependent interim genetic component with different complex upstream regulatory elements that are designed to produce insignificant proportion of the total protein before enucleation of the red blood cell.

Mutations in the HBB gene

The haemoglobin beta gene is a critical determinant of the integrity of red blood cells (Cai et al., 2018). This implies that mutations in the gene leads to developing sickle cells and consequently challenges attached thereto. These mutation are also responsible for several serious hemoglobinopathies as evident in beta thalassemia and sickle cell anaemia. Hemoglobinopathies are a set of different health conditions that are responsible for the production of insufficient haemoglobin or low haemoglobin levels. The epidemiology of sickle cell therefore arises with the mutations in the beta gene which is responsible for the integrity of red blood cells.

The mutation process begins with the GAG to GTG base pair point mutation. This aspect leads to the substitution of the hydrophilic amino acid (glutamic acid) to a hydrophobic valine (Carlice-dos-Reis et al., 2017). This process occurs in the sixth position of the beta chain of haemoglobin known as haemoglobin S (HbS). The red blood cells containing HbS or this mutant haemoglobin with a combination of others abnormal alleles undergo polymerization when exposed to environmental conditions and become rigid. This righty poses a threat to the red blood cells as they may haemolyse due to an increased density. This process affects blood flow and wall integrity. The increased density and rigidity of the RBC'c leads to tissue-ischemia, vaso-occlusion, haemolysis and infarction.

These characteristics indicate that a single point mutation in globin beta gene leads to a defective haemoglobin that polymerises upon exposure to a de-oxygenated environment contributing to the formation of sickle cells. This disorder is also characterised by abnormality in adhesive characteristics of red blood cells, peripheral blood mononuclear cells and platelets. These components stick to the to the sickle cells red blood cells. The beta globin mutation makes the sickle gene pleiotropic (Kalkan et al., 2020). This mutation also leads to variations in phenotypic expression associated with the complexity of cell environment and genetic interactions. The polymerization of sickle cells in a de-oxygenated environment is attributed to different factors in situ. First, the inheritance of alpha thalassaemia and the foetal haemoglobin are critical factors in this aspect. On the other hand, these factors contribute to the formation of a defective red blood cells in situ. Other genetic factors are the genetic variations in the BCL11A, HBB loci and HBS1L-MYB among others. These genetic variations are responsible for suppressing gamma chains and production of foetal haemoglobin. The produced foetal haemoglobin is an important component in suppressing sickle cells polymerization due to the its ability to reduce concentration of HbS. Haemoglobin S is also rich in oxygen retention potential and therefore, ability to ameliorate the sickle cell disease's haemolytic and vaso-occlusive pathology.

According to Menzel and Thein (2019), there are nearly 400 gene mutations in the globin beta gene leading to beta thalassemia. Most of these gene mutations involve the structural change in the single DNA building block near or within the haemoglobin beta gene. Some of the mutations leads to insertions or deletions in the haemoglobin beta gene nucleotide. The end results is the reduction in production of beta-globin reduction. Mutations of the gene leading to sickle cells is therefore, a critical factor in epidemiology of the disease.

Inheritance characteristics

Sickle cell disease is an inherited condition that follows an autosomal recessive patterns (Vucak et al., 2018). This implies that the inheritance pattern is not gender dependent and both parents must carry the genetic mutations. This aspect imply that even if one parent is symptomatic, he or she must carry such genetic mutations for the children to be affected. If both parents carry a single gene mutation, there is a 25% chance that the offspring's will develop the disease or a 50% chance that such offspring's will develop asymptomatic conditions of sickle cells. The inheritance of a homozygous haemoglobin S, referred to as sickle cell anaemia is the most significant form of sickle cell disease (Uçucu, 2021). However, the inheritance dynamics are influenced by different factors such as the environment and geographical locations. Also, the inheritance of sickle cell traits is dependent on the specific genetic components. For instance, individuals with HbS S sickle cell disease inherit two sickle cell genes S one from either parent. This is the most severe form of sickle cell commonly referred to as sickle cells anaemia. Inheritance of HbS C sickle cell disease arises due to a sickle cell gene S from one parent and the other one from an abnormal haemoglobin C. This type of sickle cell disease manifests as a mild form among the offspring's.

Individuals with HbS beta thalassemia disease inherit one sickle cell gene S from one parent and the other gene from beta thalassemia (Cai. Inheritance of HbS beta 0-thalassemia leads to a severe form of sickle cells compared to those with HbS beta + thalassemia. The other significant type of sickle cell inheritance is the HbSD, HbSE and HbSO. Individuals with these types of inheritance take a single gene S and one from an abnormal type of haemoglobin (Either D, E or O). It's also possible for offspring to inherit one single cell gene from one parent and a normal gene from the other parent. This condition is referred to as sickle cell trait inheritance (SCT) (Ware & Dertinger, 2021). In this case, an individual inherits gene S and a normal gene A. Individuals with this type of inheritance do not show

any signs of sickle cells disease and may live a normal life but pass these traits to the offspring. Also, this inheritance may lead to uncommon health problems related to sickle cells traits. Therefore, the inheritance modalities of sickle cells is a critical determinant of pathophysiology and epidemiology of the disease.

Conclusion

Sickle cell anaemia is a genetic disease of the red blood cells. The disease alters the red blood cells adversely affecting their ability to travel in the blood vessels. The research has demonstrated that sickle cell anaemia occurs due to mutation of the haemoglobin beta gene found on chromosome 11. Sickle cell disease is an inherited condition that follows an autosomal recessive patterns. Genetics play a vital role in the passage of the disease from one individual to the other. As demonstrated in the analysis, if both parents carry a single gene mutation, there is a 25% chance that the off-springs will develop the disease or a 50% chance that such offspring's will develop asymptomatic conditions of sickle cells.

References

Cai, L., Bai, H., Mahairaki, V., Gao, Y., He, C., Wen, Y., ... & Cheng, L. (2018). A universal approach to correct various HBB gene mutations in human stem cells for gene therapy of beta‐thalassemia and sickle cell disease. *Stem cells translational medicine*, *7*(1), 87-97.

Carlice-dos-Reis, T., Viana, J., Moreira, F. C., Cardoso, G. D. L., Guerreiro, J., Santos, S., & Ribeiro-dos-Santos, Â. (2017). Investigation of mutations in the HBB gene using the 1,000 genomes database. *PloS one*, *12*(4), e0174637.

CDC. (2020, 12 14). What is Sickle Cell Disease? Retrieved from Centers for Disease Control and Prevention: https://www.cdc.gov/ncbddd/sicklecell/facts.html

Hoppe, C., Jacob, E., Styles, L., Kuypers, F., Larkin, S., & Vichinsky, E. (2017). Simvastatin reduces vaso‐occlusive pain in sickle cell anaemia: a pilot efficacy trial. *British journal of haematology*, *177*(4), 620-629.

Kalkan, B. M., Kala, E. Y., Yuce, M., Alpaslan, M. K., & Kocabas, F. (2020). Development of gene editing strategies for human β-globin (HBB) gene mutations. *Gene*, *734*, 144398.

Kato, G. J., Piel, F. B., Reid, C. D., Gaston, M. H., Ohene-Frempong, K., Krishnamurti, L., ... & Vichinsky, E. P. (2018). Sickle cell disease. *Nature Reviews Disease Primers*, *4*(1), 1-22.

Menzel, S., & Thein, S. L. (2019). Genetic modifiers of fetal haemoglobin in sickle cell disease. *Molecular diagnosis & therapy*, *23*(2), 235-244.

Rullo, R., Di Luccia, A., Ciani, E., & Pieragostini, E. (2019). The haemoglobin subunits alpha and beta: Old and new genetic variants in the Italian Mediterranean buffalo. *Czech Journal of Animal Science*, *64*(7), 279-290.

Uçucu, S. (2021). Difficulties in the diagnosis of Hb S/Beta thalassemia: Really a mild disease?. *Journal of Medical Biochemistry*.

Vucak, J., Turudic, D., Milosevic, D., Bilic, M., Salek, Z., Rincic, M., & Bilic, E. (2018). Genotype-phenotype correlation of β-thalassemia in Croatian patients: a specific HBB gene mutations. *Journal of pediatric hematology/oncology*, *40*(2), e77-e82.

Ware, R. E., & Dertinger, S. D. (2021). Absence of hydroxyurea‐induced mutational effects supports higher utilisation for the treatment of sickle cell anaemia. *British Journal of Haematology*.