NEAR EAST UNIVERSITY

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DEPARTMENT OF MEDICAL GENETICS

THE ETHNIC DISTRIBUTION OF SICKLE CELL TRAIT IN NIGERIAN STUDENTS IN NORTHERN CYPRUS

MSc. THESIS

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Nicosia

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DABBAH MAIMA GBASSAY NIGERIAN STUDENTS IN NORTHERN CYPRUS THE ETHNIC DISTRIBUTION OF SICKLE CELL TRAIT IN MSc. THESIS 2023

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MSc. THESIS

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Approval

We certify that we have read the thesis submitted by **DABBAH MAIMA GBASSAY** titled **"THE ENTHIC DISTRIBUTION OF SICKLE CELL TRAIT IN NIGERIANS IN NORTHERN CYPRUS"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Medical Biology and Genetics

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DECLARATION

I hereby declare that all of the information contained in this paper was gathered and presented in a manner that is compliant with academic regulations and ethical standards of behaviour. I further declare that, in accordance with these rules and standards of behaviour, I have properly attributed and referenced all information and outcomes that are not my own and are not unique to this work.

DABBAH MAIMA GBASSAY

…../…../…2023...

Day

DEDICATION

This study is dedicated to my mom (CELIA G. NAH), MOM, without you, I would not be where I am today. Words cannot convey how much I owe you for the guidance you have shown me for your wisdom, your wit, your knee insight, and your keener intelligence. Hence, from kindergarten to university, you have always supported and stood by me. Again, wanting to see me becoming better, you give me all the immense support, both moral and financial. Thanks mom let God bless you in all your endeavors as I work to support you and take care of you when the time is right.

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Again, many thanks to my parents Mr. and Mrs. Gbassay Pabai who God used to bring me onto this earth, thanks again for allowing God to used you to bring me into this world,and thanks for all your supports.

Nevertheless, I want to thanks my dearest mom (Celia G.Nah) for her unlimited support to see me achieve my studies, love you mom forever. I'm grateful for the full support you have been giving me from kindergarten days to university days. Let the almighty God richly bless you mom. Again, my thanks and heart felt gratitude goes to Mr. Melvin Alfred Tokpah all throughout the semester up to my thesis work. Let God bless you for your great help in helping me. Besides, all thanks and appreciation go to my spiritual parents, (Rev. and Dr.Mot. Davis) for all their prayers. Finally, my appreciation goes to my friends and colleagues I meet during my work and studies. May God reward each one that had contributed to this work.

DABBAH MAIMA GBASSAY

ABSTRACT

The Ethnic Distribution of Sickle Cell traits in Nigerians' Students in Northern Cyprus

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MSc. DEPARTMENT OF MEDICAL GENETICS
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AIM:

This study was conducted to investigate The Ethnic Distribution of Sickle cell Traits in Nigerians students in Northern Cyprus.

BACKGROUND:

Sickle cell trait (SCT) is a congenital condition caused by the inheritance of a single allele of the abnormal haemoglobin beta gene, *HBS.* Carriers of SCT are generally asymptomatic, and they do not manifest the clinical and haematological abnormalities of sickle cell anemia (SCA). Among the carrier states seen in neonates, newborn screening for sickle cell trait (SCT) is the only one of them. However, there isevidence that they display certain symptoms when they are put under duress. It is not known whether or if SCT has a negative effect on the outcomes of pregnancies, particularly for women who come from developing countries where nutritional deficits are widespread.

Despite the fact that sickle cell trait (SCT) is significantly more common than other heterozygous circumstances for rare recessive diseases, sickle cell disease is one of the most common monogenetic disorders that may be found anywhere in the globe. Because of how widespread this problem is, getting reproductive counseling is absolutely necessary. In addition, it would appear that SCT is a risk factor for a variety of clinical sequelae, some of which are not found in other carrier states, such as extreme exertional injury, chronic renal disease, and venous thromboembolism. It would be helpful for genetic counselors to have more information on these clinical outcomes so that they may make more informed recommendations to patients who possess the sickle trait. The millions of people who carry the SCT gene and them

children are entitled to the benefits of modern and precise medicine, but in order to receive these benefits, additional research and clinical efforts are required.

METHOD:

In order to conduct this research on sickle cell trait, DNA samples were taken from the blood bank as well as the laboratory at the Near East University Hospital (NEUH). In light of the fact that it was approved by the NEU scientific advisory board.

100 Nigerians were selected at random to have 2.5-milliliter tubes of ethylenediaminetetraacetic acid (EDTA) containing their venous peripheral blood taken into them. Isolating genomic DNA from whole blood was accomplished with the use of a Hibrigen DNA extraction test kit (Hibrigen Biotechnology LTD, Gebze, Turkey).

This experiment was carried out in the medical genetics laboratory of Near East University. In accordance with the predetermined procedures, DNA was extracted from each of the samples and then purified. Hibrigen DNA extraction test kit - (Hibrigen Biotechnology LTD, Gebze, Turkey).

In order to amplify DNA, a PCR product consisting of two times TaqMan, a master mix, dNTPs, $Mgcl_2$, probe, PCR buffer, and deionized water was utilized. For the PCR gradient, an applied biosystems thermal cycler PCR, Himedia Insta Q96 plus Real-Time PCR machine (India) was utilized as the instrument of choice. On the screen of a computer was displayed the output from a bioimaging machine.

RESULTS:

For the purpose of this investigation, the blood samples of one hundred (100) individuals who had reportedly visited the hospital were collected.

These samples were examined to determine the sickle cell trait status of each individual. The mean age of the study group was 19.9±4.71. 50% of the study population was male with a mean age range of 29.4±4.53 and 50% was female with a mean age range of 30.5±4.91 and a P-value of 0.458 and an F-value of 0.560

We found that the expected value of individuals with normal haemoglobin (*AA*) was 56 and the observed value is 51 (51%) of normal hemoglobin cells, the observed valueis lower than expected. The value for *AS* is higher than expected 47 (47%) was observed rather than 37 which means more individuals possess the traits than expected. The carrier individuals are higher than expected. One (1%) of the study group is

observed as having the disease while the expected was 6 (6%) and the observed values for A and SS are 0.75% and 0.25% respectively.

CONCLUSION:

Distribution is not consistent with Hardy Weinberg's law at the level of significance is less than 0.05. Nigerian frequency is 1 in 45 so the results are consistent with previous studies which is perfect and urges preventive approaches in Northern Cyprus as well as awareness for Nigerian students in Cyprus.

Keywords: *HBB*, *HbSS*, sickle cell trait, Sickling, sickle cell disease,

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LIST OF ABBREVIATION

SCD: Sickle Cell Disease

Hb: Human Haemoglobin

HbA: Adult Human Haemoglobin

HbF: Woman Fetal Hemoglobin

HbA_1 : Hemoglobin Subunit Alpha 1

HbA_2: Hemoglobin Subunit Alpha 2

Hbs: Embryonic Hemoglobin

HBB: Human Subunit Beta Gene

HbAIc: Glycosylated Hemoglobin

DNA: Deoxyribonucleic Acid

Dde1: Dopachrome Tautomerase Distal Enhancer

Glu: Glutamic Acid

Val: Valine

G6PDH: Glucose-6-Phosphate Dihydrogenase

RFLP: Restriction Fragment Length Polymorphism

BPG: Biphosphoglycerate

$MetAP_2$: Methionine Aminopeptidase

SARS-COV-2: Severe Acute Respiratory Syndrome Corona Virus 2

PCR: Polymerase Chain Reaction

AS: Sickle Cell Carrier (Heterozygous)

SS: Sickle Cell (Homozygous)

bp: Base Pair

CHAPTER I:

Introduction

1.1.1. Hemoglobin and Human Blood System

Hemoglobin is an important component of the respiratory system because it transports oxygen to the body's tissues for cellular processes as well as carbon dioxide, which is then returned to the lungs (Brundha & Priyadharshini, 2019). Haemoglobin has a powerful Hemoglobin strongly binds to oxygen but has less affinity to only a moderate pull-on carbon dioxide, organic phosphates, hydrogen ions, and chloride ions in arterial blood. Similarly, it has a moderate pull-on chloride ion (Giardina, 2022). The backward representation of these interconnected affinities is manifested within the veins. Haemoglobin, a protein primarily responsible for carryingoxygen in the blood, was bestowed with the designation of "honorary enzyme" by Jacques Monod. This classification was intended to highlight and emphasize the extraordinary characteristics and capabilities of hemoglobin. An enzyme is typically defined as a biological catalyst that accelerates chemical reactions in living organisms.However, haemoglobin does not possess the typical enzymatic activity associated withtraditional enzymes. Instead, it serves a vital function in the transport of oxygen fromthe lungs to various tissues throughout the body. Monod's decision to label haemoglobin as an "honorary enzyme" was a deliberate choice to shed light on the remarkable properties of this protein. Although it does not possess the typical enzymatic functions, hemoglobin exhibits several noteworthy qualities that set it apart. One of the remarkable properties of haemoglobin is its ability to bind and release oxygen in response to changes in oxygen concentration. This characteristicallows it toefficiently absorb oxygen in the lungs, where oxygen levels are high, and release it inoxygen-depleted tissues. This dynamic behavior is crucial for facilitating effective oxygen transport and delivery to cells. Additionally, hemoglobin-demonstrates an allosteric nature, meaning its oxygen-binding affinity can be modulated by factors such as pH, carbon dioxide levels, and the presence of other molecules. This regulation enables hemoglobin to adapt to different physiological

conditions and optimize oxygen transport in various tissues and organs. Moreover, haemoglobin exhibits a high degree of specificity in binding to oxygen, ensuring that it predominantly binds to oxygen molecules and no other gases present in the blood. This specificity contributes to the efficiency and accuracy of oxygen transport. Overall, Monod's designation of haemoglobin as an "honorary enzyme" served as a means of drawing attention to the extraordinary properties and functions of this crucial protein involved in oxygen transport within the human body. Hemoglobin exhibits enzyme-like behavior attributed to the presence of an active site known as heme, a substrate (oxygen), and inhibitors (hydrogen ions) (Hu et al., 2021). Analyzing the properties of hemoglobin is helpful in understanding the function of hemoglobin as well as pulmonary physiology.
(Telen et al., 2019).

Ingram was the first person to show that a variation in one of the 287 amino acid residues in hemoglobin was associated with sickle cell anemia in 1957 (Poluri et al., 2021). This discovery has laid the foundation for a molecular understanding of diseases by providing the first-ever evidence that a point mutation in a structural gene can result in the alteration of a single amino acid in the corresponding encoded protein. Is caused due to a change in a single amino acid. (Zhang et al., 2021). The sickle cell gene, as it became prevalent in malaria-endemic regions across the globe, served as a compelling demonstration of the evolutionary phenomenon of natural selection (Beri et al., 2021). People who have the sickle cell trait have a higher chance of surviving of *falciparum malaria* than those who do not have the trait. The reason behind this phenomenon can be attributed to several factors. Firstly, individuals with the sickle cell trait exhibit a lower parasite count during falciparum malaria infections (Williams et al., 2005). This reduction in parasite load can contribute to a milder manifestation of the disease and, consequently, a higher chance of survival. Additionally, sickle cell trait carriers have a reduced risk of developing cerebral malaria, a severe complication characterized by the involvement of the central nervous system. Cerebral malaria can result in life-threatening complications and long-term neurological damage. However, individuals with the sickle cell trait have a decreasedsusceptibility to cerebral malaria, further enhancing their survival prospects during falciparum malaria infections (Williams et al., 2005). Haemoglobin is an iron-containing oxygen-transport metalloprotein that is found in the erythrocytes of nearlyall vertebrates (Ahmed et al., 2020). The fish family Channichthyidae is an exception

(Gruss et al., 2023). The respiratory system, particularly the lungs, plays a crucial role in the uptake of oxygen from the environment. Simultaneously, the oxygen-binding protein known as hemoglobin, present within the bloodstream, facilitates the efficient delivery and distribution of oxygen to various tissues and organs within the body (Messerli et al., 2020). At the site of release, the oxygen becomes available, thereby enabling the occurrence of aerobic respiration Aerobic respiration subsequently generates energy through metabolic processes, thereby providing the necessary fuel for the physiological functions of an organism. In healthy persons, the content of hemoglobin in the blood can range from 12 to 20 grams per 100 millilitres (ml), (Sachdev et al., 2023). It was found that in mammals, the chromoprotein accounts for over 96% of the dry weight (by weight) of red blood cells and approximately 35% of the overall weight (including water), This means that chromoprotein makes up the majority of the weight of red blood cells. Because hemoglobin has the ability to bind oxygen at a rate of 1.34 ml, the oxygen-carrying capacity of blood is improved by a factor of seven (Simon et al., 2019). In mammals, each molecule of hemoglobin is capable of transporting four oxygen molecules to various parts of the body simultaneously (Premont et al., 2020). Furthermore, hemoglobin plays a crucial rolein facilitating the transport of various gases, including carbon dioxide, in the body. For instance, a specific type of hemoglobin called Carbamino haemoglobin is responsible for transporting a significant portion of the total respiratory carbon dioxide (approximately 20 to 25% of the total) (Cenzi et al., 2018). In this molecule, CO2 binds to the heme protein. Nitric oxide, an important regulatory chemical, is carried by the molecule that is banded to a thiol group in the globin protein. Nitric oxide is released at the same time as oxygen (Tejero et al., 2019).

According to the literature, it is also possible to see hemoglobin in cells that are not RBCs or their precursors. Numerous additional types of cells, such as macrophages, alveolar cells of the lungs, retinal pigment epithelium, hepatocytes, mesangial cells of the kidney, endometrial cells, cervical cells, and vaginal epithelial cells contain haemoglobin, (Wiedemann, 2022). In addition to its function as a transporter of oxygen, hemoglobin in these tissues also performs the roles of an antioxidant and a regulator of iron metabolism (Ucar et al., 2022). The binding of glucose to hemoglobin can lead to elevated levels of haemoglobin A1c, particularly in situations where there is an excess of glucose present in the bloodstream (Chenet al., 2022). These gases include carbon dioxide, nitric oxide, hydrogen sulfide

and sulfide, according to a study carried out by Mishra et., al., (2021). A variant of the molecule called leghaemoglobin is utilized to safeguard anaerobic systems, such as the nodules found in leguminous plants responsible for nitrogen fixation, from the detrimental effects or inactivation caused by oxygen exposure (Shumaev et al., 2022). Hemoglobinemia is a medical condition that is defined by an excessively high concentration of hemoglobin in the plasma of the blood.

There are around 200 different forms of hemoglobin that have been discovered. It is recommended that the word "variant" can be used instead of "abnormal" because the majority of hemoglobins are not associated with sickness (Liddy et al., 2022). The Professor Herman Lehmann of Cambridge University in England and his "musketeers" from all over the world were responsible for the discovery of many of these different kinds of hemoglobins. Moreover, as additional information was acquired, a correlation emerged between the stereochemical structure-function relationships of differenttypes of hemoglobin and the clinical symptomatology (Kanipakam et al., 2021).

1.1.2. The role of haemoglobin

Oxygen, which is produced as a result of photosynthesis in plants, is required for all living organisms. (Valerian et al., 2022). The haemoglobin in the lungs is responsible for transporting oxygen to the tissues and organs of the body than it is used in cellular respiration and other metabolic activities to produce energy and maintain the health of the cells (Dzal et al., 2015). In various organisms, including nearly all vertebrates, certain invertebrates, and all other taxonomic groups, the presence of the molecule hemoglobin (Hb) is a common feature within the erythrocyte cells.

Hemoglobin is widely recognized as one of the molecules that hold paramount significance in the fundamental biological processes across diverse forms of life.

The primary physiological function of this organ pertains to the facilitation of oxygen transportation from the pulmonary system to various regions of the organism, thereby enabling its utilization in the process of aerobic respiration, a metabolic pathway that leads to the generation of energy.

It has been demonstrated that in addition to carrying oxygen, haemoglobin is capable of binding to a variety of other gases (De Franca Lope et al., 2021). Carbon dioxide (CO2), nitrogen oxide (NO), carbon monoxide (CO), and a few other gases are included in this category.

Banks et al. (2016) reported the identification of in vitro interactions between the bisphenol 3,4-quinone metabolite and specific molecular entities, namely HHB, HAS, and Cytc. The measurement of glycosylated hemoglobin, also known as *(*HbA1c*),* is widely used as the gold standard for monitoring long-term changes in blood glucose levels (Ladewig et al., 2017). Glycosylated hemoglobin is produced when glucose binds to hemoglobin at high concentrations. Hemoglobin is a complex molecule that serves multiple functions within the body. Some of these functions include the transport of oxygen throughout the body, the metabolism of nitric oxide, metabolic reprogramming, redox balance, pH regulation, and catalysis (for example, alkyl hydroperoxidase, nitrite reductase, (NO) dioxygenase, monoxygenase,esterase, and lipoxygenase) (Gardner, 2012). According to Boes et al. (2017), premature RBCs are the source of Hb, which is a conjugated oxygen transporter metalloprotein found in the bone marrow. Polymerized heme and globin make up its parts in this structure.

Pellegrin et al. (2021) have provided compelling evidence through the utilization of state-of-the-art technology, revealing the presence of hemoglobin not solely within the erythrocyte, but also on the surface of the progenitor red blood cell. Dao et al. (2018) have identified several nonerythroid cell types that exhibit the presence of hemoglobin. These cell types include macrophages, alveolar cells in the lungs, retinal pigment epithelium cells, mesangial cells in the kidneys, hepatocytes in the liver, endometrial cervical alveolar cells, epithelial cells in the vagina, as well as A9 dopaminergic neurons located in brain tissues. This diverse range of cell types underscores the broad distribution of hemoglobin beyond erythroid cells in various anatomical sites and physiological contexts. According to Tsivgoulis et., al., (2020) research, Hb can be expressed by the epithelial cells that make up rabbit cervicovaginal tissue. Hemoglobin and its peptides have a role in immunity against infection of the vaginal epithelium (Sommerstein et al., 2020).

The tetramer protein known as human hemoglobin (HHb) is found in the erythrocytes of vertebrates. It has the ability to bind to a wide variety of various substances, such as herbicides, medicines, and insecticides (Bhunia et al., 2022).

Proteins, including globin, are composed of polymers known as amino acids, which serve as the fundamental structural units (Wade, 2021). These globin chains are available in a number of different types, the most common of which are gamma, beta, alpha, and delta According to Dasauni et al. (2022), a healthy human individual will possess a pair of alpha chains alongside two additional chains. Das et al. (2020) revealed that the composition of each Hb molecule consists of four distinct subunits, with each subunit capable of associating with a specific polypeptide chain in one of five unique configurations, denoted as alpha, beta, gamma, and so forth.

Hemoglobin A, for instance, is encoded by a number of different hemoglobin genes (such as *HBA1*, *HBA2*, and *HHB*, which each code for a distinct subunit of hemoglobin). This kind of hemoglobin makes up between 95 and 100 percent of an adult's total *HB* content. Olufemi et al. (2011) established that the numerical designation "22" corresponds to the molecular representation of human fetal hemoglobin (HBF), a terminology commonly employed in scientific discourse. There are a few key ways in which *HB F* diverges from adult hemoglobin. Hemoglobin A2, also referred to as *HB A*2, is a variant of hemoglobin that is uncommon in adults The construct denoted by "22" consists of two alpha (α)-chains along with two beta (β)-chains (22). During the initial trimester of pregnancy, an alternative form of embryonic hemoglobin (HB) becomes evident within the maternal bloodstream,referred to as 22. This variant encompasses two alpha (α)-chains and two gamma (γ)- chains (Weatherall, 2019). Moreover, human erythrocytes harbor HB-S in the configurations of HB-Gower I and HB-Gower II, both comprising four quaternary structures composed of two alpha (α)-chains, two zetas (ζ)-chains, two epsilon (ε)- chains, and two gamma (γ)-chains (Brittain, 2002). *HBS* are found in the form of *HB*-Gower I and *HB*-Gower II in human erythrocytes. Hemoglobin *A*3, also known as *HBA*3, is a variation of Hemoglobin *A* that is found more frequently in old RBCs. The glycosylated form of hemoglobin, also known as *A1C* (*HB A1C*; glycosylated *HB*), comprises between three and five percent of total *HB* in healthy individuals. However, this percentage can rise up to between six and fifteen percent in those who have type 2 diabetes mellitus (Zhao et al., 2022).

The constituent amino acids, commonly referred to as aaas, involved in the synthesis of hemoglobin can exhibit species-specific variations. These distinctions become increasingly evident when comparing organisms that diverged from a common ancestor in the more distant past. For example, chimpanzees, bonobos, and

humans possess intact Alpha and Beta globin protein chains within their hemoglobin. However, this is not the case for chimpanzees. Notably, humans and gorillas exhibit slight disparities between their Alpha- and Beta-globin chains, differing by a single amino acid. As the evolutionary divergence between species increases, so do the observed differences in the amino acid sequences of these globin chains.

Zaldvar-López et al., (2017) state that the process of making hemoglobin involves two primary stages: the production of globin and the production of heme. Theproduction of hemoglobin depends on two other processes, known respectively as globin synthesis and heme synthesis. Harteveld et al. (2022) state that the gene for Alpha-globin (*HBA*1) is located on chromosome 16p13.3, and the gene for *B*eta-globin (*HBB*) is located on chromosome 11p15.4. Within the cytoplasm of erythrocytes, the molecular mechanisms of transcription and translation govern the initiation of globin synthesis. Numerous studies have shown that heme stimulates the production of globin by increasing gene transcription. Tan et al., (2023) state that the cytoplasm and mitochondria of erythrocytes are the primary sites of heme metabolism.

1.1.3. Structure of Hemoglobin

According to Ahmed et al. (2020), the hemoglobin molecule is a multi-subunit globular protein that contains heme. Heme is an iron (Fe) ion complex core that is bound by a heterocyclic ring that is not a protein.

The porphyrin ring is made of four pyrrole molecules connected cyclically over a bridge of methane. When iron is in its ferrous state, the porphyrin ring complexes with iron metal to create an iron metal-porphyrin complex (Cook et al., 2017). The ferrous iron that serves as the oxygen-binding site may be found at the geometric center of the ring, exactly in the middle of four nitrogen atoms that are all aligned in the same plane (Kovalskii et al., 2022). The globular protein comprises a distinctive constituent distinguished by the existence of a tetrahedral configuration of Alpha and Beta polypeptide chains (specifically Alpha 1, Alpha 2, Beta 1, and Beta 2). As reported by Amanullah et al. (2022), hemoglobin consists of 141 and 146 amino acid monomers, which are present in both the Alpha- and Beta-globin chains. Notably, both the Alpha- and Beta-globin chains incorporate histidine, positioned at residue 87 and 92, correspondingly, within each chain. Between the heme and each of the four histidines, there is a covalent bond found. Iron-porphyrin complexes have a role in the primary function of hemoglobin, which acts as an oxygen transporter in the blood (Ru et al.,

2023). This is because oxygen binds to iron as the blood circulates through the lungs and the tissues of the body. The vast majority of the amino acids that make up hemoglobin are located in the shorter portions of the protein that are not helical and are joined to one another in order to make the alpha helix (Wang et al., 2023). Hydrogen bonds play a role in the stabilization of the helical sections of this protein. They do this by attracting molecules that are close by and bending the polypeptide chain into a certain shape.

1.1.4. Importance of hemoglobin

Hemoglobin, a protein that is found in red blood cells and contains iron, has two distinct functions within the body. In the first place, it assists in the transportation of oxygen from your lungs to the other parts of your body (Mohanto et al., 2022). Second, it is responsible for transporting carbon dioxide from the cells of the body to the lungs so that it can be exhaled. Hemoglobin, which is responsible for giving red blood cells their characteristic contains around 70 percent of the iron that is found in human body (Dybas et al., 2022). There are many different types of hemoglobin found but the most prevalent ones are: Hemoglobin *A*, often known as *HGBA*, is the kind of hemoglobin that is most commonly seen in adults (Akinbosede et al., 2022). *F*(*HGBF*): This type of hemoglobin, also referred to as fetal hemoglobin, is present in fetuses as well as neonates (Sheth et al., 2021). In contrast to adult hemoglobin, whichhas two beta chains, fetal hemoglobin has two gamma chains. Adult hemoglobin onlyhas two beta chains (Calle, et al., 2020). Because fetal hemoglobin has a higher affinity for binding oxygen than adult hemoglobin does, it is able to pull oxygen from the blood

of the mother even if the blood has a lower oxygen content. According to Turk et al. (2019), this exerts beneficial effects on the prenatal development of the fetus within the maternal organism. When a baby is born, all of the fetal hemoglobin has been replaced by adult hemoglobin. This process is complete by the time the baby is delivered (Gilmartin et al., 2020). The presence of a high oxygen concentration in the pulmonary environment induces the hemoglobin molecules to bind oxygen (Okniska et al., 2022). Because there is a reduced concentration of oxygen in functioning tissues, hemoglobin is responsible for the release of oxygen. The "cooperative" binding that occurs between hemoglobin and oxygen results in a marked increase in the activity's overall efficiency (Nikinmaa et al., 2019). This lends credence to the hypothesis that subsequent oxygen binding is enhanced by the first binding of the molecule. The same is true for oxygen; the liberation of one molecule of oxygen prepares the door for the release of other molecules with a structure very similar to itsown (Shadrack et al., 2021). This indicates that hemoglobin is capable of respondingnoticeably more rapidly to the oxygen demands that are placed on working tissues. The ease with which hemoglobin binds oxygen is influenced by a number of factors, including the plasma pH, plasma bicarbonate levels, and atmospheric oxygen pressure (particularly at higher altitudes) (Bellelli et al., 2020). When the molecule 2,3- disphosphoglycerate (2,3-DPG) binds to hemoglobin, it lowers the protein's affinity for oxygen, which in turn increases the amount of oxygen that may be released (Arez, 2019). The molecule known as hemoglobin is made up of four distinct proteins (Sebastiano et al., 2021). Acclimatized individuals have a higher capacity to transport molecules as a result of a higher quantity of 2,3-DPG in their blood (Mallet et al., 2023). At Hb values of less than 5.0 g/dL (50 g/L), one runs the risk of developing heart failure and passing away; at Hb values of more than 20 g/dL (200 g/L), one runs the risk of developing blood pressure issues (Chawla et al., 2020). Protein can be foundin' the spleen, liver, and bone marrow, in addition to the muscles (Muchtar et al., 2022).If an excessive amount of iron is withdrawn from the store without being replaced by food, the iron storage can become depleted, which can result in a decrease in hemoglobin levels (Cook, 2005). After giving blood, the majority of people's hemoglobin levels return to normal somewhere between six and twelve weeks afterward (Browne et al., 2020).

The physiological impact of these changes on the structure and biochemistry of hemoglobin could range from being completely insignificant to having a significant

influence (Dzhalilova et al., 2020). Hemoglobin is a heterotetramer composed of globin subunits, each of which is a member of the same chemical family as the others (Seyedarabi et al., 2019). The kinetic of HbO2 binding and release have been optimized for this role, and they are capable of being adjusted over an individual's lifetime in response to changes in physiology and metabolism (Weber et al., 2022). The range of normal hemoglobin levels for men is 135 to 170, whereas the normal range for women is 120 to160 (Munro et al., 2023).

1.1.5. Biochemistry of Hemoglobin

Hemoglobin, also known as hemoglobin, is a protein that contains iron and is present in the blood of many different species. It is located in the red blood cells (erythrocytes) of vertebrates, and its primary job is to transport oxygen throughout the body. The relationship between hemoglobin and oxygen is both unstable and reversible (Omar et al., 2020). Oxyhemoglobin is a pigment that, when oxygenated, has a beautiful red color; when it has been deoxygenated, it has a blue purple color (Fenk, et al., 2022). The bone marrow is where the production of hemoglobin for red blood cells takes place (Barger, 2022). Transferrins are proteins that salvage iron from oxidized hemoglobin and deliver it to the bone marrow after dead red cells. This process takes place after the red cells have died (Ravingerová et al., 2020). It is recycled so that it can be used in the production of new RBCs, and any leftover hemoglobin is transformed into bilirubin, which is the yellow-brown pigment that is responsible for the characteristic hue of bile (Culliton et al., 2021). In the tetrahedral structure of each hemoglobin molecule, there is a core globin group that is surrounded by four heme groups (Chu et al., 2021). The iron atom that is found in heme is linked to a porphyrin, which is a ring-shaped organic complex and accounts for just 4% of the total mass of the molecule (Vanin, 2021). Along the path that blood takes from the lungs to the rest of the body, oxygen atoms are attached to and bound by the atom of iron. As a result of the presence of four iron atoms in each molecule of hemoglobin, the molecule has the ability to bind four molecules of oxygen. The formation of globin involves the joining of two different pairs of polypeptide chains (Saeed et al., 2021).

People who have sickle cell anemia, a severe genetic form of anemia in which the cells become crescent-shaped in the lack of oxygen, have a variant form of hemoglobin known as hemoglobin S (Kumar et al., 2022). This form of hemoglobin

can only be seen in people with sickle cell anemia. The abnormal cells that have the shape of a sickle die off too quickly and have the potential to become lodged in microvessels, which can impede blood flow and lead to damage to the tissue (Veluswamy et al., 2020). Sickling is primarily an African trait, but it can also be found in people of Middle Eastern, Mediterranean, or Indian origin (Bays et al., 2022).

1.1.6. Hemoglobin Pathophysiology

Continuous autoxidation of hemoglobin (Hb) results in the generation of superoxide, which then dismutates into hydrogen peroxide (H2O2) and is capable of fueling further oxidative reactions (Liu et al., 2022). When present in the microcirculation and subjected to hypoxic conditions, autoxidation manifests itself in a manner that is particularly severe for unstable dimers formed at lower Hb concentrations (Bou-Fakhredin et al., 2022). The red blood cell (RBC) possesses an intricate antioxidant system that is intended to fight against oxidative processes (Mahmood et al., 2021). Whether they result from the hemolysis of RBCs or the infusion of blood substitutes that are based on Hb, the oxidative responses of extracellular hemoglobin cannot be entirely neutralized by the antioxidant system that is now accessible (Alayash, 2021). In the presence of imbalanced H2O2, ferrous and ferric Hbs undergo oxidation, which results in the production of Fe (IV)-ferrylHb and OxyferrylHb, respectively (Rifkind et al., 2015). The reaction between FerrylHb and hydrogen peroxide results in the formation of heme breakdown products as well as free iron. In addition to Fe (IV), OxyferrylHb also consists of a free radical that is ableto take part in a variety of different oxidative processes. Autoxidation of hemoglobin results in the creation of Fe (III)Hb, which easily releases heme and is another cause of oxidative stress (Rifkind et al., 2015). These oxidation products have the potential to contribute to oxidative reactions that take place in the plasma, particularly after the Hb dimers with a lower molecular weight have been taken up by cells and tissues (Buehler et al., 2020). "The proinflammatory action of heme and oxyferryl increases their potential for oxidative stress"(Vona et al., 2021). These oxidative processes can make clinical problems worse, including atherosclerosis, renal failure, sickle cell disease, and malaria, to name just a few of the disorders that fall into this category. Because haemolytic anemia causes an increase in hemolysis, there is a significant cause for concern over the potentially hazardous effects of Hb released from extracellular spaces (Ballas et al., 2021). Both the diseases themselves and the treatments for them can

make haemolysis worse (Takahashi et al., 2020). Blood transfusions are required when the number of red blood cells in the blood lowers dramatically as a result of haemolysis or blood loss (Park et al., 2020). Therefore, it is of the uttermost importance that the blood that is being transfused does not further elevate the extracellular Hb level, regardless of whether it is the blood that has been banked RBCs or blood that has been retrieved from the patient by an Autologous Blood Recovery System (Voss et al., 2021).

1.2. Hemoglobinopathies

The spectrum of genetic conditions known as hemoglobinopathies is caused by mutations in the globin chains of the hemoglobin molecule (Yu, 2022). Hemoglobinopathies are a category of disorders that are passed down through families and are characterized by inadequate or abnormal synthesis of the hemoglobin molecule (De La Fuente-Gonzalo et al., 2019). These diseases are brought on by mutations in a single gene, and they are frequently inherited as autosomal co-dominant traits (Veterinary Team, 2021).

Hemoglobinopathies are a catch-all word that encompasses all hereditaryforms of hemoglobin abnormalities (De Moraes Pinto Luciano et al., 2023). Thalassemia syndromes and structural hemoglobin variants are the two most frequent forms of hemoglobin that are not functioning properly. The most prevalent types of thalassemia are α- and β- while the most common structural hemoglobin variants are *HBS*, *HBE*, and *HBC* (Kohne, 2011). There are a great number of subtypes and hybrids that can be found within each category. Hemoglobinopathies can present themselves clinically in a broad variety of ways, ranging from a minor form of anemia called hypochromic anemia to a moderate form of the haematological disease to a severe form of anemia thatrequires transfusions and involves multiple organs throughout the patient's lifespan, inaccordance with the findings of (Sharma et al., 2021). Every year, there are around 320,000 newborns who are diagnosed with hemoglobin abnormalities that are severe enough to require medical treatment (Nisha et al., 2020). Roughly eighty percent of the world's infants are welcomed into the world in developing nations (Thavy et al., 2009). There are solid estimates that suggest that roughly 5.2% of the world's population, which translates to more than 360 million people, contain genes for polymorphisms in hemoglobin. The beta-thalassemia carrier rate is approximately

1.5% across the world (Office of the Regional Director for Southeast Asia of the World Health Organization).

1.3. Sickle Cell Diseases & Traits

Sickle cell disease, often known as SCD, is a common inherited blood disorder that can cause serious health complications. The most common form of anemia is known as sickle cell anemia (Fadelmula et al., 2020). The occurrence of an abnormality in the hemoglobin protein, a crucial component of erythrocytes responsible for oxygen transport, is documented to cause distinctive morphological distortions, resulting in a sickle-shaped appearance (Erhabor et al., 2019). Clinical manifestations of sickle cell disease (SCD) typically manifest during the early childhood stage, approximately between five to six months of age among the majority of affected individuals (Badr et al., 2022).

Notably, symptoms associated with sickle cell anemia include anemia, sickle cell crises characterized by severe pain episodes, edema in the extremities, susceptibility to bacterial infections, and the risk of stroke, as revealed by the study findings (Sherif et al., 2019). With advancing age, individuals with SCD may experience chronic pain (Phillips et al., 2023). In high-income nations, the average life expectancy for individuals with SCD typically ranges from 40 to 60 years (Badr et al., 2022).

The diagnosis of sickle cell disease (SCD) is assigned to individuals who inherit two mutated alleles of the HBB gene, the primary genetic determinant responsible for hemoglobin synthesis (Persaud et al., 2019). The SCD gene is situated on chromosome 11 (Menzel et al., 2019). The distinct variations occurring in each hemoglobin gene lead to the emergence of diverse hemoglobin subtypes (Bhatia et al., 2023). Notably, individuals with SCD exhibit an increased susceptibility to episodes triggered by elevated temperatures, stress, dehydration, or high altitudes, as documented in the literature (Zolaly et al., 2019). A person who has the sickle cell trait, often known as a carrier, has one faulty copy of the gene but, in most cases, doesnot exhibit any signs of the condition (Xu et al., 2019). Sickle cell disease (SCD)can be diagnosed through blood testing, and in some countries, newborn babies are routinely screened for the disorder. It is possible to perform prenatal testing and diagnosis (Christopher et al., 2021). Patients suffering with sickle cell disease may benefit from the use of pain medication, folic acid supplements, pain management, and immunizations for the prevention of infection (Oteng-Ntim et al., 2021). Other

treatment options include receiving blood transfusions and taking the medication hydroxycarbamide, often known as hydroxyurea (Ansari et al., 2016). SCD can be cured in a very small percentage of individuals through the process of transplanting bone marrow (Patel et al., 2020).

As of the year 2015, the number of individuals living with sickle cell disease in the world was approximately 4.4 million, and another 43 million people had sickle cell trait (Abraham et al., 2019). It is believed that more than 80% of all cases of sickle cell disease are found in Sub-Saharan Africa (Esoh et al., 2021). In addition to the people who are native to sub-Saharan Africa but reside in other areas of the world, people from some sections of India, Southern Europe, West Asia, and North Africa have mutations in the *HBB* gene (Akinyemi et al., 2021). In the year 2015, an estimated 114,800 fatalities were ascribed to sickle cell disease (SCD) based on documented data (Felli et al., 2021). The initial medical depiction of SCD was first documented in 1910 by James B. Herrick, an American physician (Akinsete, 2022). The elucidation of SCD's hereditary transmission was subsequently accomplished in 1949 by E. A. Beet and J. V. Neel (Doerfler et al., 2021).

Individuals who possess sickle cell trait (SCT) harbor a single mutated hemoglobin beta gene within their genetic makeup (Bruno et al., 2022). The presence of dual defective alleles of the hemoglobin beta gene is the distinguishing factor between sickle cell disease (SCD) and sickle cell trait (Arishi et al., 2021). Notably, individuals carrying sickle cell traits generally experience a higher quality of life compared to those affected by sickle cell disease, as they remain unaffected by symptoms related to sickling (Ricardo Santos De Almeida, 2019). Moreover, individuals with sickle cell trait do not exhibit an elevated risk of mortality when compared to the general population. Consequently, attention is directed toward the assessment and management of sickle cell trait, with a specific emphasis on the collaborative efforts of interdisciplinary teams in delivering quality care to affected individuals (Ashorobi, 2022). The benign nature of sickle cell trait implies its minimal influence on an individual's overall health. However, instances have been documented wherein complications attributable to the trait status have arisen (Key et al., 2010). Consequently, patients possessing sickle cell trait who develop any of these disorders may not be entirely benign and may necessitate comprehensive therapeutic interventions (Ochocinski et al., 2020).

Steeck (2003) posits that the SCT syndrome is generally regarded as non-life-threatening, although conflicting accounts exist. The occurrence of the "SCT" (or ECAST) has been observed in military personnel as well as elite athletes in the civilian domain (Gibson et al., 2016). Yang et al. (2020) suggest that intense physical exertion has been linked to rhabdomyolysis and fatalities. The precise role of sickle cell trait as an underlying cause in such situations remains unclear, and the onset of acute complications can often be averted through adequate hydration, oxygenation, and avoidance of extreme temperatures (Lowe et al., 2019). Clinically, the sickle cell trait is most significant when it is discussed in the context of genetic counseling and family planning as seen in the (NHS screening programme and the Sickle Cell Disease Association of America) (Leeming, 2022).

On the other hand, various complications, such as high-altitude splenic infarction, venous thromboembolism, and renal damage, have been gradually linked to SCT (Waters et al., 2022). The latter cohort exhibits an elevated susceptibility to renal medullary cell carcinoma, haematuria, and nephropathy (Goldsmith et al., 2012). Gupta et al., (1991) conducted research indicating a heightened risk of hyposthenuria, characterized by the inability to concentrate urine, among patients diagnosed with sickle cell trait. The distinctive vulnerability of the medullary organ arises from a culmination of factors, notably hypoxia, acidosis, and sluggish blood flow (Adebayo et al., 2021). A study published in EBio Medicine (Osei-Hwedieh et al., 2016) demonstrates that human SCT red cell samples, when stored for extended durations, exhibit reduced resistance both in vitro and in vivo within a mouse model. While these findings may not be deemed groundbreaking, they underscore the necessity for further research, particularly in regions with a higher prevalence of the SCT genotype, including investigations into the utilization of SCT red cells for transfusion purposes (Gibson et al., 2016).

Sickle cell disease (SCD), characterized by aberrations in hemoglobin, a crucial protein responsible for oxygen transportation to the body's tissues within red blood cells, has been documented in the scientific literature since its initial discovery in 1910 (Inusa et al., 2019; Triantafyllou et al., 2020). Notably, sickle cell disease was first recorded in African medical literature during the 1870s, and in contemporary times, certain African tribes employ tattoos to identify individuals as "Ogbanje" (Children who come and go), reflecting the high infant mortality rates observed among sicklers (Onyedikachi, 2021). It is a genetic blood disorder that is produced by a

change in the beta-globin chain, especially a change from thymine (T) to adenine (A) at codon 6 (from GAG to GTG), which results in the amino acid valine being replaced for glutamate (Gln) at position 6 (Cortabarria et al., 2021). This change in the beta-globin chain causes sickle cell anemia. Sickle cell anemia is a form of inherited blood disorder that is characterized by irregularly shaped red blood cells and rapid hemolysis This condition is inherited in an autosomal recessive manner, being transmitted across successive generations. Individuals who are heterozygous for the trait of sickle cell (sickle cell carriers) rarely exhibit severe anemia, in stark contrast to those who are homozygous for the trait (Houwing et al., 2019). Sickled red blood cells (HbS) are more rigid than normal red blood cells (*HBA*), which causes micro-vascular occlusion and, eventually, a "crisis" characterized by episodes of severe pain, increased susceptibility to secondary infections, leg ulcers, bone infarcts, and other infarcts with tissue death potentially occurring in almost all organs (skin, liver, spleen, bone, kidneys, retina, and CNS (Egesa et al., 2022). Due to their structural composition, red blood cells are prone to damage, leading to the characteristic anemia observed in this disorder (Cao et al., 2021). The bone marrow strives to compensate for the deficiency by generating additional red blood cells; however, the rate of production falls short of the pace at which these cells are being destroyed. Sickled red blood cells only function for 10 to 20 days but healthy red blood cells can function for 90 to 120 days (Weigand et al., 2022). In most cases, signs of sickle cell anemia first appeared in childhood (Kirkham et al., 2021). Symptoms of sickle cell anemia can range from minor to severe, depending on the person who has the condition (Meier et al., 2021). *HBS* is the most common form of hemoglobinopathy, and it has the potential to be lethal. There are many other kinds of hemoglobinopathies, the most prevalent of which thalassemia in addition to the less common variants (Kohne, 2011).

More than 300,000 newborns are diagnosed with hemoglobinopathy every year (Wonkam, 2023). Among them, the most commonly observed hemoglobinopathy is sickle cell anemia. This figure represents approximately five percent of the global population. The condition is predicted to impact 4.4% of live births around theworld, with the highest incidence rates being seen in Africa, Southeast Asia, and the Americas (Hillert et al., 2020). The prevalence of sickle cell trait ranges from 10% to 45% throughout different parts of Sub-Saharan Africa (Siransy et al., 2023). This range is due to the fact that the trait is more prevalent in some areas than others. The prevalence of heterozygous disease symptoms among Nigerians spans a range of 20

to 30 percent, as reported in a study by Spira et al. (2022). According to the literature, there are roughly 160 million people living in Nigeria, and approximately 2% to 3% of them have sickle cell anemia, (Ataga et al., 2022). Oxidative stress happens when there is an excess of oxidants, like free radicals or reactive oxygen species (ROS), and a deficit of antioxidants in the body (Nakai & Tsuruta, 2021). The generation of reactive oxygen species (ROS) is an unavoidable by-product of normal intracellular catabolism (Zeng et al., 2023). This process employs oxygen as a terminal electron acceptor (oxidant), which in turn leads to ROS synthesis. Even in healthy individuals this process creates intermediates of reactive oxygen species (ROS) such as superoxide (O2•), hydrogen peroxide (H2O2), and hydroxyl radicals (OH2) (Andrés et al., 2022). These ROS include superoxide, hydrogen peroxide, and hydroxyl radicals. The increased oxidative stress that is observed in SCD is hypothesized to beassociated to microvascular dysfunction, Vaso occlusion, and organ damage.

Increased intravascular hemolysis, damage caused by ischemia and reperfusion, and chronic inflammation are all factors that contribute to the high rate of reactive oxygen species (ROS) generation that is seen in SCD (Avondt et al., 2019). Excessive levels of cell-free hemoglobin with its catalytic action on oxidative reactions, the characteristic recurrent ischemia-reperfusion injury, a chronic pro-inflammatory state, higher autoxidation of sickle hemoglobin (*HBS*), increased xanthine oxidase activity in sickle cell disease aortic endothelium, and a higher number of leukocytes that produce twice the number of reactive oxygen species all contribute to the Antioxidant enzymes and compounds are key defensive mechanisms against reactive oxygen species (ROS) (Onyedikachi, 2021). Some examples of antioxidant enzymes and chemicals include reduced glutathione (GSH), ubiquinols, uric acid, vitamins C and E, flavonoids, and carotenoids. Antioxidant enzymes are responsible for the neutralization and elimination of free radicals (Akbari et al., 2022). Antioxidant enzymes are responsible for the conversion of hazardous oxidative products into hydrogen peroxide (H2O2) and, eventually, water (Andrés et al., 2022). This conversion is a multi-step process that requires cofactors such as copper, zinc, manganese, and iron. Antioxidants that aren't enzymes are powerful because they halt the proliferation of free radicals in the body. The administration of antioxidant minerals and nutrients, such as zinc, vitamins C and E, flavonoids, and carotenoids, to individuals with sickle cell disease (SCD) did not yield clinically significant ameliorative effects in terms of reduced hemolysis, as evidenced by a study conducted

by Islam et al. (2023). Recent investigations conducted by Tantawy et al. (2023) have demonstrated that patients with SCD exhibit notably elevated levels of antioxidant enzymes, including glutathione peroxidase (GPx) and superoxide dismutase (SOD), in comparison to healthy controls. These findings were unveiled by researchers hailing from the United Kingdom and the United States (Biswal et al., 2019). Noteworthy antioxidant enzymes consist of copper, zinc, and manganese superoxide dismutases (SODs), along with their extracellular counterparts (Saxena et al., 2021). Mitochondrial manganese superoxide dismutase, known as Mn-SOD, serves as a pivotal enzyme responsible for regulating the toxicity of dioxygen within the organelle, which endures heightened oxidative stress levels, as elucidated by García-Caparrós et al. (2020). Holley et al. (2011) have reported that a structural mutation within the coding sequence of the Mn-SOD gene, specifically a substitution of thymine with cytosine at the -9 position of the signal peptide, results in the alteration of valine to alanine. More precisely, the valine residue undergoes a conversion from GTT to GCT. Notably, this signal peptide is subsequently removed during the maturation process, an observation of significance since it plays a critical role in directing the enzyme to the mitochondria, as highlighted by Alvarez et al. (2021).

1.4. Etiology and Epidemiology

1.4.1. Sickle cell trait Etiology

As per the findings presented by Nyffenegger et al. (2022), the principal causative factor behind the sickle cell trait is an anomalous variant of hemoglobin called sickle hemoglobin or *HB S*. Sickle cell anemia, on the other hand, arises from a mere substitution of a single amino acid within the beta-globin chain. This mutation manifests as a single-base alteration in the beta-hemoglobin chain, wherein the adenine (A) at codon 6 is replaced by thymine (T) due to the mutation, as documented by Zarkada et al. (2022). Consequently, the resulting amino acid, glutamic acid, undergoes a conversion to valine. Red blood cells containing valine-type hemoglobin undergo sickling when exposed to an environment with diminished oxygen levels. Individuals with sickle cell trait exhibit heterozygosity, signifying that they inherit the HBS gene from one parent and the HBA gene from the other, as indicated by Xu et al. (2019).

1.4.2. Epidemiology of sickle cell

People of African descent and those whose ancestors originated in the tropics and subtropics, where malaria is prevalent, are more likely to have the sickle cell trait than people of other racial or ethnic backgrounds In the United States, the sickle cell trait is observed in approximately 9% of African Americans, which equates to a population of around 3 million individuals. Conversely, the prevalence among Caucasians is significantly lower, at a mere 0.2%. Notably, sub-Saharan Africa is home to an estimated one-third of the global population, totaling 300 million individuals, who possess the sickle cell trait, as posited by Boateng et al. (2019). Geographical regions with a higher incidence of malaria exhibit a greater prevalence of the sickle cell trait. Gibson et al. (2021) estimate that the occurrence rate can rise as high as 66% in Saudi Arabia and up to 25% in specific parts of Africa. With the influx of a substantial number of immigrants from high-prevalence regions such as Africa and the Middle East, both sickle cell disease and the sickle cell trait are anticipated to experience increasing prevalence in Western countries.

According to Hernigou et al. (2020), the prevalence of sickle cell disorder ranges from five to seven percent among the general population. Sickle cell disorder, which is the most prevalent form of hemoglobinopathy worldwide, primarily affects Sub-Saharan Africa and Asia, as stated by Shukla et al. (2019). In various regions of Sub-Saharan Africa, the occurrence of "sickle cell trait" varies between ten and forty-five percent, as reported by Olupot et al. (2022). The carrier prevalence of sickle cell trait in Nigeria falls within the range of 20 to 30 percent, according to Nieswand et al. (2020). Onyedikachi (2021) indicates that approximately 2 to 3 percent of Nigeria's population, which exceeds 160 million people, are affected by sickle cell disorder. A recent study conducted in Benin City, south-central Nigeria, by Therese (2019) estimated the prevalence of sickle cell disorder to be 2.39 percent, based on an extensive retrospective analysis.

1.5. Patho and Histo-physiology

1.5.1. Pathophysiology of Sickle Cell Disease

In contrast to sickle cell illness, sickle cell trait only rarely results in a vaso-occlusive crisis. Henry et al. (2021) observes that individuals harbouring the sickle cell trait may exhibit clinical manifestations resembling those of individuals with sickle cell anemia under circumstances that promote the formation of sickle cells.

Truong et al. (2022) identify several contributing factors to the occlusion of capillaries, including severe hypoxia, deviations in body temperature (either low or high), heightened sympathetic output, dehydration, elevated levels of 2,3-DPG, and the release of inflammatory cells. The occlusion occurs as a result of the sickling of red blood cells induced by hemoglobin S (HbS).

This is especially noticeable in the bones. Sickling is just one of the mechanisms that contribute to enhanced adherence of red blood cells. Other mechanisms include interactions between inflammatory cells and platelets (Conran & De Paula, 2020). This could take place in the limbs, the kidneys, the heart, the lungs, the abdomen, or any of the other abdominal organs (Lee et al., 2022). Ischemia, or lack of blood flow, is a risk factor for organ damage, and repeated blows can increase the risk of ischemia. The inflexibility of red blood cells is crucial to the development of sickle cell disease as a pathological process (Gurkan et al., 2021). Due to their great elasticity and biconcave disc form, red blood cells are able to bend and twist so that they can pass through tiny blood channels (Recktenwald et al., 2021). Red blood cells are more likely to become sickled when there is a low oxygen tension in the blood. Sickle cell disease is characterized by recurrent episodes of sickling, which damage the cell membrane and reduce the cell's flexibility (Boisson et al., 2022). These cells do not revert to their natural shape when normal oxygen tension is reinstated since it does not cause that to happen (Krentz et al., 2021). These blood cells do not bend, therefore anytime they come into contact with a blood vessel that is too narrow, they obstruct the flow of blood and induce ischemia. The true cause of the anemia caused by this condition is hemolysis, which can be defined as the death of red cells as a result of their shape (Qiang, et al., 2023). The rate at which new red blood cells can be produced by bone marrow is a lot slower than the rate at which existing ones are being destroyed. The lifespan of sickle red blood cells is roughly 10 to 20 days, which is significantly shorter than the 90 to 120 days that healthy cells have (Pretini et al., 2019).

The pathophysiology and effects of SCD, which were initially identified a century ago, have been the subject of extensive research (Esoh et al., 2002). The polymerization of *HBS* within erythrocytes beneath circumstances of a lack of oxygen pH, and cells lack of water results in the characteristic "sickle" shape of erythrocytes (Fellows et al., 2012). In its dynamic interaction with the vascular endothelium, this sickle causes episodic microvascular occlusion, ischemia, and reperfusion, vascular

and inflammatory stress, and increased production of adhesion molecules, inflammatory cytokines, and vascular oxidases (Soliman et al., 2020).

Chronic haemolysis also causes anemia, hypoxia, cholelithiasis, weariness, intolerance to exercise, and hypercoagulability. pulmonary hypertension development, ischemic strokes, endothelial nitric oxide depletion, and vasculopathy (Chakravorty et al., 2015). ADORA2B is a G-protein-coupled adenosine receptor, and recent research revealed the crucial role of hypoxia in multi-organ damage through an increase in the substance signaling in genetically modified sickle mice (Chakravorty et al., 2015). The etiology of pain in sickle cell disease (SCD) remains incompletely understood, asnoted by Vogel et al. (2018). Nociceptive impulses arising from cellular responses to tissue infarction, swelling, and ischemia-reperfusion injury activate peripheral sensorynerve receptors, as elucidated by Uhelski et al. (2019). However, neuropathic pain and heightened sensitivity to mechanical touch have also been frequently reported. Recently, it was discovered that the latter phenomenon is attributable to increased primary afferent signals transmitted to the central nervous system via the transient receptor potential vanilloid-1 (TRPV1) in genetically modified sickle mice, as described by Zhen et al. (2022).

1.5.2. Histopathology

Individuals who possess the sickle cell trait exhibit red blood cells that appear morphologically normal when observed under a microscope under resting conditions, as evidenced by Hoeger et al. (2020). Nevertheless, upon exposure to oxidative stress, these red blood cells undergo a transformative process, assuming the characteristic morphology of drepanocytes, commonly referred to as sickle cells. Sickling might become so severe due to the increase in the number of reticulocytes

1.6. Importance of Sickle Cell Traits

The sickle cell trait is distinguished by its clinical insignificance and its minimal impact on the overall quantity of blood cells within the body.

This is an important distinction. It would appear that there has been a significant rise in the occurrence of this characteristic across the entirety of Africa, India, and the Middle East; it offers around a thirty percent reduction in the risk of contracting malaria. Sickle-cell trait reduction has also been seen in patients who maintain abnormally high levels of fetal hemoglobin in adulthood. These individuals

have been studied extensively. There is a good chance that fetal haemoglobin protects against sickling. There is a positive correlation between elevated levels of fetal haemoglobin and the prevalence of sickle cell disease (Walter et al., 2022). According to the results of whole-genome sequencing, it is possible to trace back all sickle-cell variants to a single haplotype that served as their ancestor (Mikhaylova et al., 2021). It is believed that this haplotype first appeared in the Sahara Desert during the Holocene Wet Phase, which occurred approximately 7,300 years ago. The Arabian/Indian, Beninese, Cameroonian, Central African Republic/Bantu, and Senegalese variants are the five unique sickle cell variants that have been discovered as having descended from this ancestral haplotype. A sixth designation has been kept aside for atypical sickle-cell haplotypes (Shriner et al., 2017). Because of their association with greater *HBF* levels, some of these variations have important implications for clinical practice. For instance, Senegalese and Saudi-Asian types of the disease typically cause less severe symptoms (Green et al., 1993).

1.7. Differential Diagnosis

It is possible to differentiate sickle cell trait from other types of sickle cell illness, as well as beta-thalassemia major and beta-thalassemia minor (Vincent et al., 2016). The diagnosis of SCD is made possible by an examination of hemoglobin, which is frequently carried out using either electrophoresis of protein or high-performance liquid chromatography (Kanter et al., 2015). The most prevalent variant of SCD, *SS*, causes individuals to produce no *HBA* but primarily *HBS* along with varying quantities of *HBF* and *HBA*2, whereas SCD causes individuals to largely create *HBS* and *HBC* (Arishi et al., 2021). In more complex situations, DNA-based techniques are frequently employed to confirm the diagnosis of SCD (Mbayabo et al., 2022).

1.8. Treatment and Gene therapy

In contrast to numerous developed and developing countries, parents residing in the United States have the advantage of accessing prenatal genetic testing, as outlined by Strnadová et al. (2022). Furthermore, the screening for the sickle cell trait is mandated for all newborns prior to hospital discharge across all fifty states. The study conducted by Segbefia et al. (2021) demonstrates that the sickling test is a straightforward and dependable method for detecting this condition.

A drop of blood is transferred to a microscope slide and prepared for inspection at this point (Rabanel et al., 2020). If sickling is observed during the physical examination, the diagnosis can be confirmed through the use of hemoglobin electrophoresis (Devanesan, A. et al., 2021). The relative abundance of the various forms of hemoglobin in a particular sample can be determined by the use of hemoglobin electrophoresis (Ilyas et al., 2020). Patients that have sickle cell trait also have normal hemoglobin A in their blood, but they also have abnormal hemoglobin S. In most cases, medical treatment is not required for patients who carry the sickle cell trait (Hoeger et al., 2020). Initiation of treatment for sickle cell trait patients is contingent upon the presence of symptoms, including those associated with the trait, as highlighted by Ding et al. (2020). In order for clinicians to promptly commence therapy upon symptom manifestation, it is crucial for them to possess knowledge regarding the diverse complications that may arise from the trait. Reports indicate that the primary therapeutic objectives for sickle cell disorder usually revolve around the avoidance and management of symptoms, as stated by Brousse et al. (2014). The management of “sickle cell” disease complications at an early stage is crucial. This includes acquiring transcranial Doppler ultrasounds on a regular basis to detect and treat pulmonary hypertension, detect and treat consequences and damage to the many organs and systems linked with this condition, prevent stroke, and detect and treat pulmonary hypertension (Houwing et al., 2019). Commercially accessible preventive therapies such as “hydroxyurea, P-selectin inhibitors” like “crizanlizumab”, and “hemoglobin oxygen-affinity modulators” like “Voxelotor” are also available (Runge et al., 2022). In SCD, hydroxyurea increases total and fetal hemoglobin, lowering erythrocyte gelation and sickling (Dimitrova et al., 2023). Some of the more recent medications being investigated for the medical management of SCD include decitabine/THU (NCT01685515), DNMT1 inhibitors (LBH589/Panobinostat) (NCT01245179), agents attacking carbon monoxide delivery (Sanguinate NCT02411708), and phosphodiesterase 9 inhibitors (IMR-687 (NCT04053803). Nonionic block copolymer surfactants like Poloxamer and Vepoloxamer are used to try and prevent vaso-occlusion (Cisneros,2020 & Thein,2018). P2Y2 inhibitors, such as prasugrel and ticagrelor (NCT02482298), as well as medications that affect the activation of “neutrophils and monocytes, intravenous immunoglobulin (NCT01783691), simvastatin (NCT03599609), anti-factor Xa (rivaroxaban)

(NCT02072668)", and antioxidants decrease the effects of oxidative stress (N-acet (Tebbi, 2022).

Individuals with sickle cell disorder frequently have steady-state normal neutrophil and monocyte counts in addition to platelet counts. Acute incidents typically result in an increase in these values. The association between Neutrophia and the seriousness of sickle cell disorder have been mentioned in several studies (Yousif 2022). Neutrophil interactions with erythrocytes and endothelium result in an upregulation of the production of cytoadhering molecules, such as P- and E-selectins. P-selectin is upregulated in endothelial cells and platelets during the "pathogenesis of vaso-occlusion and pain crises" associated with sickle cell disease (Morikis et al., 2022; Moussa et al., 2022). Increasing the proportion of "nicotinamide adenine dinucleotides in sickle cell erythrocytes through oral administration ofpharmaceutical-grade l-glutamine (USAN, glutamine has been shown to reduce oxidative stress and may lessen episodes of pain that is linked to sickle cell disease (Niihara et al., 2018). It was found that L-glutamine and hydroxyurea have been approved by the Food and Drug Administration for the treatment of "sickle cell" disorder in Americans. Along with other generally advised immunizations, vaccination against pneumococcal, meningococcal, and influenza lowers the risk of developing serious infections (Lee, 2020; Cannas et al., 2019).

Due to the potential for vaso-occlusive crises, severe chest syndrome, post-operative infections, congestive heart failure, and organ failure, surgery for sickle cell disease carries are at higher risk of death as a result, extensive pre-operative care, such as transfusions or exchange transfusions, is needed (Stephens & Gillick, 2020; Valikhani et al., 2021).

Treatment for sickle cell disease on a genetic basis is now possible with the recent advancements in human genome engineering tools, especially the gene-editing technique CRISPR/Cas9 (Bhattacharjee et al., 2022). Additionally, these advancements have enhanced our comprehension of the molecular mechanisms governing mammalian erythropoiesis and globin shifting. It's critical to comprehend the genetics and transcription factors that affect fetal hemoglobin synthesis or suppression (Menzel et al., 2019). Thanks to developments in genetic engineering, it is now possible to genetically reprogram patient-derived hematopoietic stem and progenitor cells as well as induced pluripotent stem cells. The globin gene may be used in ex vivo gene therapy to treat this condition. Clinical trials have been

conducted on this right now, with a lot of success and positive outcomes. When it comes to the treatment of sickle cell disorder, gene therapy combines with the use of Lent Globin and autologous transplantation of hematopoietic stem and progenitor cells that have been infected with the BB305 lentiviral vector, which encodes a modified- -globin gene that results in the anti-sickling hemoglobin, HbAT87Q. According to a recent finding, a single dose of Lent Globin causes most erythrocytes to continue producing HbAT87Q, which reduces haemolysis and completely resolves severe vaso-occlusive episodes (Han et al., 2023; Haltalli et al., 2021). Another method is to use gene editing to correct flawed DNA where it naturally exists. For instance, the patient's own *BCL11A* gene is disrupted to cause the production of fetal hemoglobin. (Demirci et al., 2020). The use of a patient's own stem cells for genetic therapy has been investigated, myeloablative conditioning has been shown to be a huge problem in the study. Additionally, even though gene therapy holds great promise, it is expensive it has some disadvantages (Charlesworth, 2022; Russell, 2021). Following gene therapy for sickle cell disease, reports of acute myeloid leukemia have been made (Goyal, 2022; Jones,2021).

1.9. Future Therapies

Despite, several studies are ongoing, it has been stated that Decitabine, 5-azacytidine, and short-chain fatty acids like butyrates are among the promising medications that have been shown to modulate Hb F production in addition to Hydroxyurea (Pace, 2021; Lopez, 2022). According to the findings of recent studies specific pathophysiological processes in SCD, such as abnormal membrane cation transport systems, increased/stimulated red cell-endothelial adhesiveness, endothelial activation and vasospasm, cellular dehydration, prooxidant state, and hypercoagulability in SCD, their therapeutic efficacy is developed (Adewoyin 2015; McKinney, 2017). Clotrimazole and Senicapoc (ICA 17043), a clotrimazole analogy, have been shown to reduce red cell dehydration and hemolytic rate, and they are well tolerated in SCD patients (Shmukler et al., 2019). By blocking the KCL cotransporter, magnesium salts are also observed to lessen red blood cell dehydration. Magnesium sulfate infusion has been shown to shorten hospital stays for VOC patients (Than et al., 2017). In addition to the aforementioned, there is ongoing contemplation regarding the utilization of distinctive monoclonal antibodies designed to impede red cell-endothelial adhesion. Furthermore, deliberation is underway regarding the potential

employment of anti-P-selectin and heparin to restore the equilibrium of hypercoagulable conditions. Additionally, aspirin and warfarin are being considered as means to diminish the viscosity of whole blood, while Flocor is being explored for its potential to normalize hypercoagulable states (Adewoyin, 2015). By increasing NO bioavailability, inhaled nitric oxide and its precursor L-arginine have been shownto be helpful in acute vasoocclusive crises and other ischaemic complications (Bazer, 2022; Matte, 2019).

Gene therapies theoretically provides a great hope for the treatment of the disease However, research is still ongoing in this area to find a vector to transfer the functional beta globin gene efficiently (Abraham & Tisdale, 2021).

1.10. Statement of the Problem

Sickle cell disease (SCD) is a prevalent hereditary blood disorder that affects millions of individuals worldwide, particularly those of African descent. In Nigeria, SCD poses a significant public health challenge, with high morbidity and mortality rates. However, the ethnic distribution and prevalence of sickle cell traits among Nigerian students studying in Northern Cyprus remain largely unexplored. The problem addressed by this thesis is the limited knowledge regarding the ethnic distribution of sickle cell traits among Nigerian students in Northern Cyprus. Despite the growing number of Nigerian students in Northern Cyprus, there is a lack of comprehensive research on the prevalence of sickle cell traits and the associated genetic variations specific to this population. Understanding the ethnic distribution of sickle cell traits is crucial for several reasons. Firstly, it enables the identification of individuals at risk and facilitates the implementation of appropriate preventive measures and healthcare interventions. Secondly, considering the potential impact on reproductive choices, knowledge of sickle cell trait prevalence can help educate and counsel Nigerian students and their families regarding the importance of genetic testing and informed decision-making. Lastly, this research contributes to the existing body of knowledge on sickle cell traits and provides valuable insights for policymakers and healthcare providers in Northern Cyprus. Thus, this thesis aims to investigate the ethnic distribution of sickle cell traits among Nigerian students in Northern Cyprus, with a focus on understanding the prevalence rates, genetic variations, and associated health implications. By addressing this research gap, the findings of this study will contribute to enhancing the healthcare services and support systems available to

Nigerian students with sickle cell traits in Northern Cyprus, ultimately promoting their overall well-being and academic success.

1.11. Purpose of the Study

The purpose of this study is to investigate and understand the ethnical distribution of sickle traits among Nigerian students in Northern Cyprus. Sickle cell disease (SCD) is a hereditary disorder that affects the structure and function of red blood cells, primarily prevalent in individuals of African descent. As Nigerian students form a significant portion of the international student community in Northern Cyprus, this research aims to shed light on the prevalence and distribution of sickle cell traits within this specific population.

The objectives of this study include Prevalence Assessment: To determine the prevalence of sickle cell traits among Nigerian students in Northern Cyprus, as well as the distribution of genotypes associated with SCD. Ethnicity and Sickle Cell Traits: To explore the relationship between the ethnic backgrounds of Nigerian students and the occurrence of sickle cell traits within this population. Health Implications: To investigate the potential health implications of sickle cell traits in Nigerian students and identify any challenges they may face while studying abroad in Northern Cyprus. Awareness and Education: To assess the level of awareness and knowledge among Nigerian students in Northern Cyprus regarding sickle cell disease and the importance of genetic screening.

Support and Mitigation Strategies: To propose recommendations and strategies to support Nigerian students with sickle cell traits in Northern Cyprus, including access to healthcare, counseling, and educational resources. Comparative Analysis: To compare the prevalence and distribution of sickle cell traits among Nigerian students in Northern Cyprus with relevant studies conducted in Nigeria and other international student communities.

By achieving these objectives, this study aims to contribute to the existing literature on sickle cell disease and expand our understanding of the ethical distribution of sickle cell traits among Nigerian students in Northern Cyprus. The findings will not only provide valuable insights into the health profile of this specific population but also help inform healthcare policies, support services, and educationalinitiatives to ensure the well-being and academic success of Nigerian students with sickle cell traits in international study environments

1.12. Significance of the Study

The finding of this study will help in revealing the prevalence of SCT in the population of Nigerian students and will create awareness among other foreigners to take necessary precautions when they go back to their respective countries.

In conclusion, although some studies have been conducted to analyze the ethnic distribution of sickle cell disease in the Nigerian Population. This research aims to investigate the ethnic distribution of sickle cell disease in Nigerian Students in Northern Cyprus.

CHAPTER II:

Literature Review

2.1. Theoretical framework

The identification of the ethnic distribution of sickle cell traits among Nigerian students in Northern Cyprus is a significant research area due to its implications for public health, genetic counseling, and the provision of appropriate healthcare services. This theoretical framework aims to provide a structured approach for examining the prevalence and distribution of sickle cell traits among Nigerian students in Northern Cyprus, considering the ethnic diversity within the Nigerian population and the geographical context of Northern Cyprus. To determine the prevalence of sickle cell traits among Nigerian students in Norther Cyprus. To analyze the ethnic distribution of sickle cell traits among Nigerian students in Northern Cyprus.

This theoretical framework provides a systematic approach to studying the ethnic distribution of sickle cell traits among Nigerian students.

2.2.Related Research

According to recent research conducted by Oyedeji et al. (2023), over 66% of the estimated 120 million individuals worldwide affected by sickle cell disease reside in Africa. Imalingat et al. (2022) further assert that this condition afflicts nearly 1000 children in Africa each day, making it the most prevalent hereditary acquired illness on the continent. Disturbingly, these studies indicate that more than half of these children succumb to severe anemia before attaining the age of five. The mortality toll in Africa stands at 338,403 individuals (Erhabor et al., 2019).

According to projections, it is anticipated that by the year 2050, approximately 88% of all sickle cell disease (SCD) cases will be concentrated in the sub-Saharan Africa region. Regrettably, despite this significant prevalence, the availability of newborn screening programs remains limited (Lema, 2020; Acharya, 2023). Nigeria, with a staggering four to six million affected individuals and a prevalence of one in four Nigerians carrying the sickle cell trait, serves as the epicenter of this disorder.

Globally, the estimated number of individuals affected by sickle cell disease reaches nearly fifty million (Nwabuko et al., 2022).

Approximately 300,000 newborns worldwide undergo screening for sickle cell disease (SCD) annually. Sub-Saharan Africa accounts for over 75% of this global figure (Nwabuko et al., 2022). In Nigeria alone, as reported by Nwabuko et al. (2022), an estimated 100,000 to 150,000 infants are diagnosed with SCD each year, constituting 33% of the global SCD statistics. Consequently, Nigeria holds a pivotal position in the epidemiology of SCD on a global scale. The prevalence of SCD within Nigerian states ranges from 1% to 3% (Nwabuko et al., 2022).

The most prevalent hemoglobin variant in Nigeria is Hb-SS, while Hb-SC is sporadic and predominantly found in the southwestern region of the country (Nnoduet al., 2021).

Approximately 25% of adults in Nigeria carry the sickle cell gene, while an estimated 2.3% of the population is affected by sickle cell disorder (SCD). Africa exhibits the highest incidence rate of SCD, with 7.3 cases per 100 years of observation, as indicated by available data. Despite Nigeria having the highest prevalence of SCD worldwide, the adoption of standard-of-care protocols for SCD patients remains inconsistent and inadequate. In this environment, sickle cell disorder stands as the most prevalent non-infectious disease, with up to 25% of the population carrying the sickle cell trait (Galadanci et al., 2014)

Individuals with SCD experience chronic challenges resulting from the mutation, including anemia, infections, stroke, tissue damage, organ dysfunction, severe pain episodes, and premature mortality (Waddell et al., 2022). The debilitating effects and ongoing treatment requirements of the disease often limit access to education, employment opportunities, and a high quality of life for individuals with SCD (Oluwo et., al. (2022).

In order to increase the overall child survival rate, the “World Health Organization (WHO)” recognized sickle cell disorder in 2006 as a disease with a significant impact on public health in Africa and a high global impact (Mulumba et al.,2015). Approximately 401,000 out of 465,000 infants born annually with notable hemoglobin (Hb) disorders, which corresponds to a global count of 405,000, are afflicted with sickle cell disease (SCD) (Grosse et al., 2011). For instance, historical and scientific documentation originating from West Africa has presented comprehensive designations employed by the three main Nigerian tribes for the identification of

individuals with SCD (Alabi et al., 2022). Specifically, within the western region where they constitute the majority ethnic group, the Yorubas refer to them as "abiku," a Yoruba term signifying "sufferers" or "children that bring sadness" (Alli et al., 2016). In the Ibo tribe, the designations "Ogbanje" and "Sankara-miji" are employed. In Nigeria, SCD represents the most prevalent intrinsic condition, affecting an estimated 4 million individuals with a birth prevalence of 2%, while over 40 million people exhibit sickle cell traits (Sliwa et al., 2023).

Despite being of normal weight at birth, children with SCD experience weight loss during the first year, which gradually persists until adulthood. This is coincidentally followed by a delay in both boys' and girls' skeletal maturation, as well as a delay in the menstrual cycle for girls (Alabietal,2022).

One of the ten non-communicable diseases (NCDs) in Nigeria, sickle cell disorder has a significant effect on morbidity and mortality in children and adults (Walters et al., 2023). Nigeria exhibits the highest prevalence of sickle cell disease among African nations due to its expansive size, resulting in approximately 100,000 newborn deaths annually, which accounts for 8% of the overall infant mortality rate in the country (Onoh et al., 2020). Furthermore, it is estimated that around 24% of the Nigerian population carries the sickle cell trait (Onoh et al., 2020). The sickle cell mutation, believed to have originated from Asia and Africa, is responsible for the development of sickle cell disease (Nnodu et al., 2012). According to Qidwai (2021), sickle cell disease arises from a spontaneous mutation occurring in the beta-globin gene (HBB), affecting reproductive cells and being transmitted across generations. The beta-globin chain genes have been identified as originating from various sources, encompassing four primary African haplotypes and one Asian haplotype. Notable African haplotypes include those found in Senegal, Benin, the Bantu population (Central African Republic), and Cameroon (Fong, 2013; Bitoungui, 2015). Among these, the Bantu haplotype is associated with the most severe phenotypic manifestations.

Furthermore, an additional study highlights Uganda as having one of the highest incidences of sickle cell anemia worldwide (Hernandez et al., 2021). Recognizing the significance of this issue, the Uganda Ministry of Health conducted a comprehensive epidemiological investigation in 2013 to gain a deeper understanding of sickle cell trait (SCT) and sickle cell disease (SCD) within the country's borders (Ndeezi et al., 2016). The Uganda Sickle Surveillance Study (US3) provided valuable insights, revealing that both SCT and SCD exhibit high prevalence rates of 13.3% and

0.7%, respectively, across the nation (Kambasu et al., 2019). These findings shed light on the non-uniform distribution of the disorders at the district and regional levels, with prevalence rates ranging from 2.5% to 23.9% in different districts, as outlined in the report.

The study contributes to the understanding of the prevalence and distribution of sickle cell traits within a specific population of Nigerian students residing in Northern Cyprus. This information is crucial for healthcare professionals, policymakers, and researchers involved in managing and addressing sickle cell disease (SCD) in this particular group. By investigating the ethnic distribution of sickle cell traits, the study sheds light on the genetic variability and inheritance patterns of the disease among Nigerian students in Northern Cyprus. This knowledge aids in identifying individuals who may carry the sickle cell trait and are at risk of passing it on to their offspring. Consequently, it will help in implementing appropriate prevention and counseling strategies to reduce the incidence of SCD in future generations.

CHAPTER III:

Materials & Methods

3.1. Introduction

This chapter represents all the materials and methods that were used in the conduction of the research and provides information about the research design, participants/sample, data collection and analysis procedures as well as how the findings are analyzed.

3.2 Research Design

This research design aims to investigate the ethnic distribution of sickle traits among

Nigerian students residing in Northern Cyprus. The study utilizes a quantitative approach, making use of laboratory analysis to gain a comprehensive understandingof the sickle cell trait prevalence and associated factors within this population. The research design includes the following sections: introduction, objectives, research questions, theoretical framework, methodology, data collection, data analysis, limitations, and ethical considerations.

3.3 Study Group

The study groups are shown in table 3.2 and Figure 3.2 below. 100 Nigerianswere selected for the purpose of this study.

Table 3.1

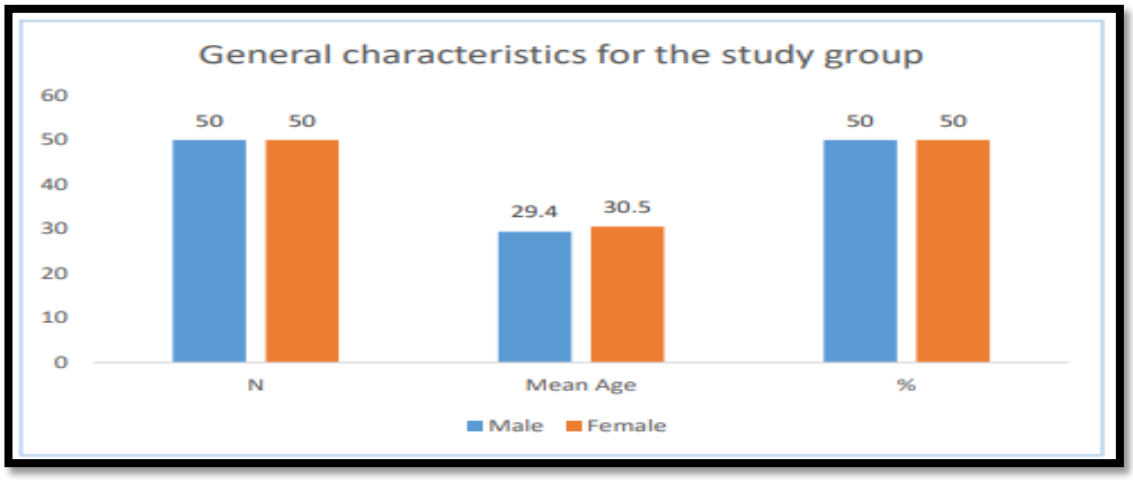
General characteristics of study group

Demography variable	N	P-Value	F-value
Age	19.9 ± 4.71	0.458	0.560
Male	29.4 ± 4.53	0.458	0.560
Female	30.5 ± 4.91	0.458	0.560

Table 3.1 and figure 3.1 provides an overview of the study group, indicating that the mean age of the entire group was 19.9±4.71. The mean age for males was 29.4±4.53,

while the mean age for females was 30.5±4.91. Statistical analysis yielded a P-value of 0.450 and an F-value of 0.560.

Figure 3.1. General Characteristics of the study group



3.4. Data collection tools/Materials

Hibrigen DNA extraction test kit - (Hibrigen Biotechnology LTD, Gebze, Turkey). The Block Heater (HB-1 (WEALTEC Corp.U.S.A)
HERAEUS PICO 17 Centrifuge (Thermo Electron Corporation),
ColumbiaVortex machine (VELP SCIENTIFICA), Europe

3.5. Data collection procedure

In order to conduct this research on sickle cell trait, 100 Nigerians' venous peripheral blood was taken into 2.5-milliliter tubes. The samples were taken from the blood bank as well as the laboratory at the Near East University Hospital (NEUH), in light of the fact that it was approved by the NEU scientific advisory board.

This experiment was carried out in the medical genetics' laboratory of Near East University. In accordance with the predetermined procedures, DNA was extracted from each of the samples, and PCR analysis was conducted to generate the necessary data.

3.6. Sampling Techniques and Sample Collection

100 Nigerians were selected randomly and 2.5-milliliter tubes including ethylenediaminetetraacetic acid (EDTA)were used to take venous peripheral blood

from individuals. Genomic DNA was isolated from whole blood by using a Hibrigen DNA extraction test kit (Hibrigen Biotechnology LTD, Gebze, Turkey).

3.7. Data Analysis Plan

3.7.1. PCR Amplification and Genotyping

Allele specific primers for HbS mutation (*HBB* 20A>T (p. Glu6Val)) were design using SNAP gene software. Real Time Polymerase Chain Reaction (RT-PCR) was conducted using 2xTaqMan Master Mix (Hibrigen Biotechnology LTD, Gebze, Turkey). The concentrations of each PCR reaction are given below in table 3.2.

Table: 3.2.

PCR Mix

Components	1 X
Taqman Master mixed	12.5µl
Forward Primer	0.5µM
Reversed Primer	0.5µM
Probe	0.25µM
dH_20	1.0 µl
DNA	2.5 µl

3.7.2. PCR Profile

After the initial denaturation at 96 °C for three minutes, the reaction mixture was subjected to 30 cycles of 96 °C for 20 seconds 60°C for 30 seconds, and 65^0C for one minute and 30 seconds. Selected fluorescent dyes are FAM channel to detect mutations in the sample. the Himedia Insta Q96 plus Real Time PCR machine was used to amplify the desired region of the gene (India). The Himedia has a sample capacity of 96 wela ls, a Volume Thermal Block Sample, number of channels is 5.

3.7.3. DNA PCR Amplification

All tubes were properly closed, labeled, and centrifuged for a short period; they were all placed in a thermocycler PCR programmable amplification machine which ran for 35 cycles, as seen in table 3.3.

Table 3.3.

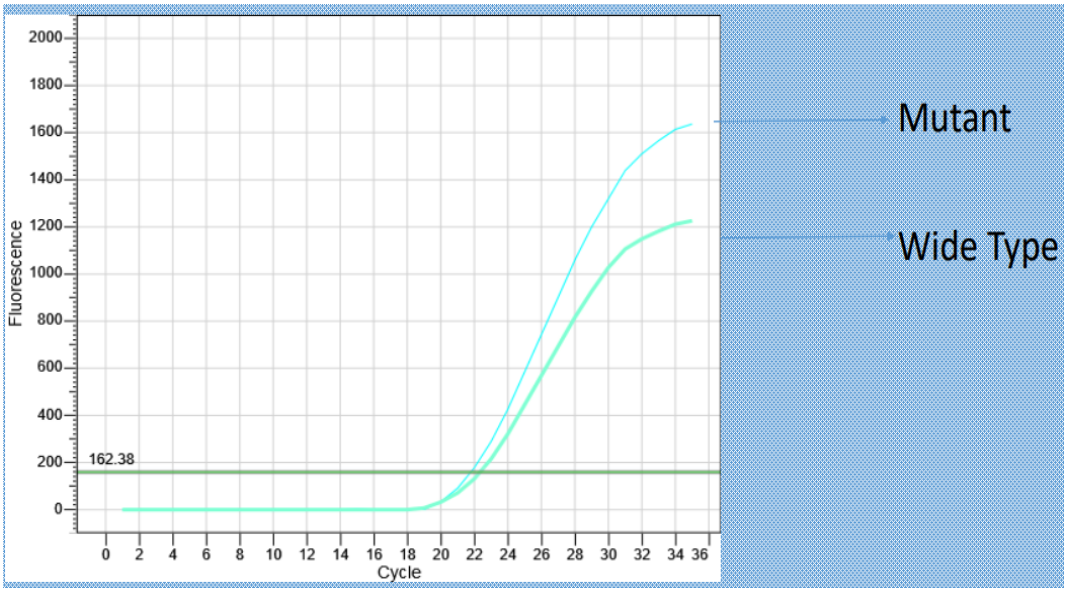
DNA PCR Amplification cycles.

State	Temperature	Time
Denaturation	95 °C	1minute
Annealing	57 °C	30 sec
Extension	72	1 minute

Selected fluorescent dyes are FAM channels, to detect mutations **i**n the sampl**e** we used the Himedia Insta Q96 plus Real-Time PCR machine (India). The Himedia has a sample capacity of 96 wells, Volume Thermal Block Sample, number of channels is 5. Below Figure 3.2 shows the threshold value for the PCR amplification curve.

Figure 3.2

PCR Amplification Curve for the Mutant and Wide Type Alleles



3.7.4. Measurement of DNA Concentrations

The quantification of DNA concentration was performed utilizing a NanoDrop ND200 Spectrophotometer (Thermo Scientific, Waltham, Massachusetts, United States) at wavelengths of 260/280 nm. The DNA isolation process was carried out employing the reagents provided by Hibrigen Biotechnology LTD, located in Gebze, Turkey. For primer design, the SNAP gene Software was employed, and the oligomers were ordered from INEOS Oligomer based in the United States. The Marcogen primer (Marcogen, United States) was utilized in the experimental procedures.

Table 3.4.

Primer Sequences

Oligo name	Base Pair 5' 3'
HbS-M	GCAGTAACGGCAGACTTCTCCT
BbS-WT	GCAGTAACGGCAGACTTCTCCA
HbS-P	FAM-GGAGCAGGGAGGGCAGGAGCCAGG-BHQ1
HBB-MC_F	TGCCAGAAGAGCCAAGGACA
HbS_M	GCAGTAACGGCAGACTTCTCCT

3.7.5. Method

The Block Heater (HB-1 (WEALTEC Corp.U.S.A), HERAEUS PICO 17 Centrifuge (Thermo Electron Corporation), Columbia, Vortex machine (VELP SCIENTIFICA), Europe, Himedia Insta Q96 plus Real Time A PCR machine (India), was used during the study.

i. Computers

Complete PC computer system with software packages Microsoft Office, XP

CHAPTER IV:

Results

4.1. Introduction

This chapter presents the findings based on the collected data.

In this particular study, the distribution of sickle cell traits among Nigerian students has been investigated in Northern Cyprus. The findings obtained from this study regarding the distribution of the observed results are incongruent with Hardy-Weinberg's law. This inconsistency remains statistically significant at a significance level of less than 0.5.

The prevalence of Nigerians in the studied population was determined to be 1 in 45 individuals. This finding aligns with previous research, emphasizing the need for preventive measures in Northern Cyprus and increased awareness among Nigerian students in Cyprus. The study included a total of 100 Nigerian students, with a mean age of 19.9±4.71. Among the participants, 50% were male, with a mean age of 29.4±4.53, while the female participants had a mean age of 30.5±4.91. Statistical analysis revealed a non-significant P-value of 0.458 and an F-value of 0.560. PCR amplification was conducted following the methodology described in Chapter II of the materials and methods section. Table 3.1 provides an overview of the study population and presents the genotype results for each individual. The results indicate that 51% of the individuals had normal hemoglobin (HbAA), 47% were heterozygous carriers of the trait (HbAS), and only 1% of the study group exhibited the disease (SS). Furthermore, less than 1% (0.75%) of the study population was identified with (A), while 0.25% were affected with (S).

Table 4.1.

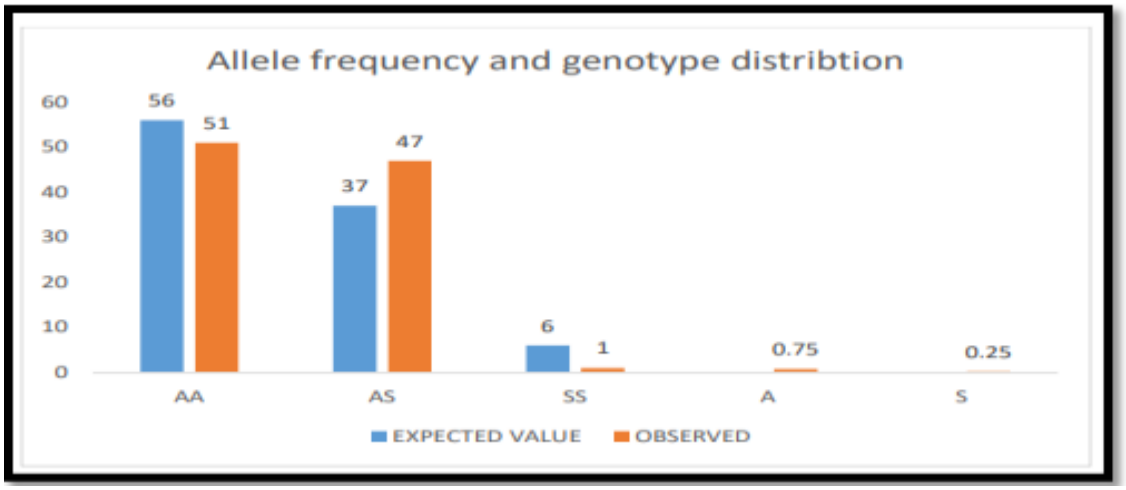
Distribution of Alleles and genotypes

Genotype	Expected	Observed
AA	56.0	51.0
AS	37.0	47.0
SS	6.0	1.0
A		0.75
S		0.25
Chi-Squared		7.466
P-Value		0.02
Yate's Chi-Square Value		6.318
Yate' s P-Value		0.04

Figure 4.1.

Allele frequency and genotype distribution

The present investigation focuses on assessing the frequencies of alleles and examining the distribution of genotypes within the studied population.



As seen in Figure 4.1, the expected value of individuals with normal hemoglobin (*AA*) was 56. The observed value is 51 (51%) has normal haemoglobin cell, the observed value is lower than expected. The value for *AS* is higher than expected, 47 (47%) was observed rather than 37 which means more individuals possess the traits than expected. The carrier individuals are higher than expected. One (1%) of the study group is observed as having the disease, while the expected was six (6%). In addition, while the observed values for A and SS are 0.75% and 0.25% respectively.

The mean age of the study group is 19.9±4.71, the male was 29.4±4.53 and female were 30.5±4.91 respectively, with a P-value of 0.450 and F-value of 0.560. As seen in table 3.2.

CHAPTER V:

Discussion

This chapter presents a discussion of these findings in comparison to the studies in the literature.

Sickle cell disease (SCD) is the second most prevalent autosomal recessive inherited genetic disease and the first *HB* variant to be known, affecting millions of people of their background, education, race etc (Ohaeri & Shokundi, 2001). This hereditary condition is widely acknowledged as one of the most frequently encountered genetic disorders, particularly prevalent in the African region, where it manifests with escalated mortality rates among children aged 1 to 5 (Weatherall, 2006). Furthermore, it exhibits a substantial presence in developed nations, impacting a significant proportion of the global population. Sickle Cell Disease (SCD) arises due to a mutation in the beta-globin gene, whereby a substitution occurs, replacing a single hydrophobic glutamic acid with a hydrophilic valine amino acid at position 6. This genetic alteration triggers the polymerization of hemoglobin molecules upon deoxygenation, resulting in the structural distortion of red blood cells (RBCs) and their premature demise through processes such as hemolysis and vaso-occlusion. Consequently, SCD manifests as a progressive acute and chronic disorder that affects all cells, tissues, organs, and virtually all systems within the human body (Weatherall, 1997; Serjeant, 2013).

In sub-Saharan Africa, where healthcare assets are limited and the awareness of community and healthcare providers is low, sickle cell anemia plays a significant role in the morbidity and mortality of children (Inusa et al., (2020). Most infants die of serious problems before turning five if they are not diagnosed earlier and preventive measures are not started (Uyoga et al., (2019). In Africa, data obtained from long-term, extensive sickle cell screening programs is still lacking; despite being one of the most prevalent diseases there, SCD receives insufficient attention (Mukherjee et al., (2021). Insufficient financial resources allocated to combat sickle cell disease (SCD) constitute a significant contributory factor to its economic burden (Oron et al., 2020). Within the healthcare landscape of numerous regions, there exists a scarcity of preventive, early detection, and treatment services specifically tailored for individuals affected by this disorder (Geethakumari et al., 2021). In Nigeria, for instance, the limited number of dedicated treatment centers for SCD results in a situation were the

majority of general practitioners encounter only a small fraction of patients with this condition. As a consequence, maintaining up-to-date knowledge and proficiency in the management of SCD can pose challenges (Adewoyin, 2015).

The substantial incidence of “sickle cell” disease (SCD) in sub-Saharan Africa has been attributed to these factors because of the "protective effect" and the higher chance of staying alive for those who are heterozygous for sickle cell (McGann et al., (2023). This selective pressure has maintained the sickle cell gene in human populations in malaria-endemic regions such as sub-Saharan Africa. The higher prevalence of sickle cell disease (SCD) in Africa can be attributed to the advantageous effects conferred by the sickle cell trait against the "Plasmodium falciparum" parasite, which causes malaria (Ebel et al., 2022; Fasano et al., 2022). In response to this significant health concern, prenatal screening for SCD has demonstrated effectiveness in reducing mortality rates, even in the absence of observable symptoms. Developed countries, such as the United States, Brazil, Italy, and Germany, have implemented both selective (targeting high-risk parents) and universal newborn screening programs for sickle cell disease (Panepinto, 2000; Lobitz, 2018). In contrast, screening initiatives in sub-Saharan Africa are typically limited in scale, experimental, or non-existent (Fanu et al., 2022). Consequently, the majority of children born with sickle cell disease in sub-Saharan Africa face slower progress in terms of healthcare advancements compared to their counterparts in high- and middle-income nations (Bell et al., 2010). The challenges pertaining to the assessment of the health implications of sickle cell disease in sub-Saharan Africa pose a hindrance to the mobilization of funds for combating the ailment. The majority of public statements concerning disease-related fatalities in this region are predicated upon an examination of published data (Nnodu et al., 2021). Enhancements in sickle cell disease management within various healthcare systems worldwide have led to an increase in life expectancy (Brousse et al., 2014). Given the elevated prevalence of sickle cell disease in Nigeria, it is imperative to establish comprehensive and robust legislation and regulations that will facilitate the development of context-specific and effective knowledge-based campaigns (Adigwe et al., 2022).

Since an individual who is a carrier (has one mutant allele) does not show the serious symptoms of sickle cell disease individuals who are homozygous (have two mutant alleles) show the symptoms of the disease. Heterozygous carriers with sickle cell allele generate both regular and aberrant hemoglobin (Roach, 2005). “Sickle cell trait”

(SCT) is related to those who are heterozygous or carriers of the mutation, whereas sickle cell disorder (SCD) relates to those who are homozygous or combined heterozygous for the mutation (Nwabuko et al., (2022).

There are approximately three hundred million SCT carriers around the world (Kehinde & Osundiji, 2020). The sickle cell trait gives an evolutionary survival advantage because it protects against severe malaria (Crossley et al., (2022). The sickle cell trait is most prevalent in Africa and among people of African heritage worldwide (Erhabor et al., 2019). Approximately 5% of the global population carries a significant genetic variation in the hemoglobin gene (Chaparro et al., 2019).

In conclusion, this study was limited by a small sample size, which affected the generalizability of the findings to the larger Nigerian student population in Northern Cyprus. A larger sample size would provide more robust and representative results.

This study on the ethnic distribution of Sickle cell trait in Nigerian students in Northern Cyprus is unique due to its specific geographic focus, emphasis on a particular ethnic group, international context, student population, and its implications for healthcare and support services. By exploring these factors, the study contributes to the understanding of sickle cell trait prevalence and its impact on the Nigerian student community in Northern Cyprus.

CHAPTER VI:

Conclusion and Recommendations

6.1. Conclusion

The study findings indicate a lack of adherence to Hardy-Weinberg's Equilibrium in terms of allele and genotype distribution. Specifically, the observed frequency of the Nigerian population is 1 in 45, aligning with the outcomes of prior research. Consequently, this emphasizes the necessity for preventive measures within Northern Cyprus and the importance of raising awareness among Nigerian students in Cyprus.

6.2. Recommendations

1. There is a need to develop and implement comprehensive educational and awareness campaigns to increase understanding of SCD and sickle cell traits in Nigeria. These can include public health campaigns, targeted community outreach, and educational programs in schools and health centers.

2. Policymakers should prioritize the development of culturally appropriate and effective health education materials to ensure that the public is well informed about the disease and its implications.

3. Access to genetic counseling services can help individuals and families make informed decisions about their reproductive health.

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Appendix A
Ethical Approvement Document

Appendix C
CV

CURRICULUM VITAE

1. PERSONAL INFORMATION

NAME, SURNAME: DATE of BIRTH and PLACE:	Dabbah Maima Gbassay 11.02.1987
CURRENT OCCUPATION: Teacher ADDRESS of CORRESPONDENCE: Faculty of Medicine, Near East University, Nicosia, Cyprus TELEPHONE: 05338738654 E-MAIL: 20215615@std.neu.edu.tr	

2. EDUCATION

YEAR	GRADE	UNIVERSITY	FIELD
2012	BSc.	Mothern Pattern college of Health Sciences, Liberia	Biology and Chemistry

3. ACADEMIC EXPERIENCE

PERIOD	TITLE	DEPARTMENT	UNIVERSITY
2009-2021	Full time teacher	Biology	Royal Learning Academy

4. FIELD OF INTERESTS

FIELDS OF INTERESTS	KEY WORDS
Medical biology, genetics, medicine, biology	Medical, Biology, genetics, medicine

5. SELECTED PUBLICATIONS OF THE LAST 5 YEARS

N/A

Appendix C
Similarity Report

THESIS

ORIGINALITY REPORT

14%	13%	7%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.hindawi.com Internet Source	2%
2	www.biomedres.us Internet Source	1%
3	www.ncbi.nlm.nih.gov Internet Source	1%
4	www.mdpi.com Internet Source	1%
5	dl.booktolearn.com Internet Source	1%
6	globalhealthmagz.com Internet Source	1%
7	en.wikipedia.org Internet Source	1%
8	www.pulsus.com Internet Source	1%
9	adc.bmj.com Internet Source	1%
10	docksci.com Internet Source	<1%
11	biomedres.us Internet Source	<1%
12	"Pediatric Hematology", Wiley, 2006 Publication	<1%
13	gen-project.sei-international.org Internet Source	<1%
14	"13th European Congress of Clinical Microbiology and Infectious Diseases", Clinical Microbiology and Infection, 2003 Publication	<1%
15	www.science.gov Internet Source	<1%
16	Cameron K. Tebbi. "Sickle Cell Disease, a Review", Hemato, 2022 Publication	<1%
17	silo.pub Internet Source	<1%
18	myschool.ng Internet Source	<1%
19	wrap.warwick.ac.uk Internet Source	<1%
20	www.substituenti.lx.ro Internet Source	<1%
21	spiral.imperial.ac.uk Internet Source	<1%
22	www.researchgate.net Internet Source	<1%
23	detailedpedia.com Internet Source	<1%
24	documents.mx Internet Source	<1%
25	Nyesa A. Enakaya, Aniah Jefferson, Danielle Chew-Martinez, Jason S. Matthews. "Design, Synthesis, and Evaluation of Allosteric Effectors for Hemoglobin", Accounts of	<1%

NEAR EAST UNIVERSITY
SCIENTIFIC RESEARCH ETHICS COMMITTEE

RESEARCH PROJECT EVALUATION REPORT

Meeting date :27.04.2023

Meeting Number :2023/113

Project number :1714

The project entitled **"The Ethnic Distribution of Sickle Cell Trait in Nigerians in Northern Cyprus"** (Project no: NEU/2023/113-1714) has been reviewed and approved by the Near East University Scientific Research Ethical Committee.

Prof. Dr. Şanda Çalı
Near East University
Head of Scientific Research Ethics Committee

Committee Member	*Decision*	*Meeting Attendance*
	Approved (✓) / Rejected (X)	*Attended (✓) / Not attended(X)*
Prof. Dr. Tamer Yılmaz	✓	✓
Prof. Dr. Şahan Saygı	✓	✓
Prof. Dr. İlker Etikan	✓	✓
Doç. Dr. Mehtap Tınazlı	✓	✓
Doç. Dr. Nilüfer Galip Çelik	X	X
Doç. Dr. Dilek Sarpkaya Güder	✓	✓
Doç. Dr. Gulifeiya Abuduxike	✓	✓
Doç. Dr. Burçin Şanlıdağ	✓	✓