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CURRENT STATUS OF HEMOGLOBINOPATHY RESEARCH AMONG NILGIRI TRIBES – A MINI REVIEW

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ABSTRACT:
The Nilgiris district, home to 7.2 lakh people, has a diverse population of 27,032 tribal members, including six historical indigenous groups such as Todas, Kotas, Irulas, Kurumbas, Paniyas, Kaatunaiyakans, and Badagas (an aboriginal group). They reside in Kotagiri, Ooty, Gudalore, and Pandalore taluks. Hemoglobinopathy addresses the structure and function of hemoglobin at the genetic level. It involves thalassemia, G6PD deficiency, and sickle cell disease. In Nilgiris, people are more affected by a genetic disease called hemoglobinopathy. The most frequent causes are hemoglobin gene mutations, iron deficiency, and trait carriers because of consanguineous marriage. The aim of this review is to assess the status of hemoglobinopathy research among Nilgiris tribes at present. We used scientific databases like PubMed, Google Scholar, ScienceDirect and reviewed articles from the previous ten years. It has been found that sickle cell disease prevalence is highest in Irular, Panniya, Kurumba tribes, particularly in 0–14 and 25–49 age groups, with Irulasof 50.6%having the highest rate per 100,000 people. Gudallore Valley indigenous people are at high risk of premature death. ß-thalassemia cases have been reported in the Irula, Kurumba, and Paniya tribes, with a prevalence rate of 8%. The Nilgiris tribes have a genetic variant, G6PD Nilgiris, with a 10.0% occurrence rate. A rare variant called HBSD-Punjab SCT was found among the larger ethnic group called the Badagacommunity. The limited available data on this core domain necessitates further research to reduce its occurrence among these tribes and prevent its recurrence over time.

KEYWORDS: Tribes, Beta-Thalassemia, G6PD, Hemoglobinopathy, SCD

1. INTRODUCTION

People who live in rural areas, often in forests, and who adhere to a particular culture are referred to as tribes. [1] Tribes are one of the primary contributors to India's diverse culture, so their development is essential for the country's development [2]. Tribes are an important part of our civilization, but they differ from the general populace in that they are less adaptable" [3]. According to the Indian census, 4.1% of tribes reside in Tamil Nadu's Nilgiris district. The Department of Forests in Tamil Nadu [4]. There are about six different tribes living in various regions of the Nilgiris district. They are Todas (pastoralists who live on the upper plateau), the Kotas (artists), the Irulas, Kurumbas, and Paniyars (agriculturalists and hunter-gatherers), the Kaatunaiyakans (who emigrated from Kerala), and the larger ethnic group called the Badaga community, which is not considered a tribe but has lived in Nilgiris since the 16th century [5,6]. These five Adivasi communities are among the 75 Particularly Vulnerable Tribal Communities that the Indian government has identified. They are remote, hilly communities that are incredibly underprivileged and resource-poor [7]. Due to poor nutrition and genetic factors, hemoglobinopathy diseases have been found to be spreading among the tribes since 1972 [8].

The Gudalore district is home to about 50% of the tribal population, with the remaining 50% dispersed among the other three taluks.[2] The tribes are dispersed throughout the Nilgiris region. Gudalore and Pandalur have 50% of the world's tribes, while Kotagiri taluk has 25%, Udhagamandalam has 15%, and Conoor has 9%. The 6.51 lakh scheduled tribal people in Tamil Nadu are divided among 36 tribes, including six agrarian tribal groups in the Nilgiri district [4]. The Gudalur and Pandalur taluks of the Nilgiris in Tamil Nadu are home to 20,000 members of the Paniya, Bettakurumba, Mullakurumba, Katunayakan, and Irula tribal communities (Adivasi). [9]

Hemoglobinopathies, which are caused by quantitative hemoglobin (Hb) deficiencies (thalassemias) and Hb structural variants, are common in malaria-endemic areas such as the Mediterranean, Asia, and Sub-Saharan Africa.[10] Based on these categories, hemoglobinopathy can be of three types: SCD, thalassemia, and G6PD. [11] Depending on the specific mutation(s) present, these diseases can cause anemia, decreased RBC life span/hemolysis, and other systemic pathologies.[12] Hemoglobin variants occur due to abnormalities in the hemoglobin protein, which affect its production.[13] It is a monogenic disease that is found to be recurring due to consanguineous marriage among tribes.[14] Most tribes are found to be carriers of this disease.[15,16]

Genetic screening, genetic counseling, and awareness programs must be implemented to reduce its occurrence among tribes in future generations.[17,18]The main aim of this review is to update the current status of hemoglobinopathy research among the Nilgiris tribes. By reviewing the recent literature, we found that there is limited data available for hemoglobinopathy studies among the Niligiri tribes. The aboriginal Badaga group, which is the larger population in Nilgiris, has not yet undergone adequate hemoglobinopathy research. Therefore, implementing more research on hemoglobinopathy among the Nilgiris tribes is desperately needed. Table 1 lists a summary of the hemoglobinopathies seen among the Nilgiris tribes.

2. METHODS:

2.1 Search and Inclusion Criteria

This study is designed to review all available literature on hemoglobinopathy. A thorough search of the literature was performed on diseases such as SCD, beta-thalassemia, G6PD deficiency through case-control reports, cohort studies, and review articles published in reputed journals in English in various journals related to hemoglobinopathy disease. We referred to papers in PubMed, Google Scholar, and ScienceDirect for potentially relevant articles published in English. We have also referred to a paper in the Nature journal. The following keywords and/or their combinations were used for search purposes: SCT, SCD, hemoglobinopathy, G6PD, Nilgiris tribes, Tribes. Ethical committee approval is not required for this review paper, as it is solely based on a literature search from various sources.

2.2 Hemoglobinopathy Study

Hemoglobins, ferrous proteins in erythrocytes, transport oxygen within the human organism. They are heterotetramers with two types: adult (HbA) consists of two α and two β-chains (α2β2), and fetal (HbF) consists of two α and two γ chains (α2γ2), each carrying an iron heme group. [19] Hemoglobinopathies, which are linked to the structure and function of the disease on a genetic level, are referred to as hemoglobinopathies.[20] The clinically significant hemoglobinopathies include α- and β-thalassemia,sickle cell disease (SCD), HbE disease, and HbC disease.[21]HbS, HbE, and HbC are the three main varieties of abnormal hemoglobin.[22] Hemoglobinopathies are of two categories according to the pathophysiological mechanisms: (i) those caused by a hereditary structural modification in one of the globin chains leading to abnormal physical properties of the Hb, for example, SCA (qualitative changes), and (ii) hereditary deficiency in the production of one or more Hb chains leading to ineffective erythropoiesis, a variable degree of anemia, and hemolysis, for example, thalassemia (quantitative changes).[23]

2.3 Qualitative Changes

2.3.1 Sickle cell anemia

The most common genetic disorder with a significant risk of death is SCA. Sickle-shaped hemoglobin (HbS), which predominates in SCA, polymerizes under anoxic conditions to produce abnormally shaped cells that are susceptible to endothelial adhesion, vascular occlusion, and hemolysis, leading to a variety of acute and chronic complications.[24] Sickle-shaped cells frequently tangle, blocking the blood vessels and posing a serious threat to one's health.[18] A prime example of a balanced polymorphism is the rs334 A-T single-nucleotide polymorphism in HBB, which led to the causative mutation. The mortality rate is higher in homozygotes who have the homozygous allele. [25]

SCD is the term for HbS in a heterozygous, homozygous, or compound heterozygous form that results in red blood cell sickling.[26] Over 1,000 structural Hb variations in the HbVar database, mainly from single amino-acid changes in the HBB gene, are documented. HbE illness and sickle Hb (HbS) are significant enough for population screening.[27] Hemoglobin S (HbS) homozygosity is a characteristic of sickle cell anemia (SCA), which is considered the most common and severe kind of the disease.[28] Mutations in the beta-globin chain HBB gene cause sickle cell disease.[29]The creation of HbS is caused by a point mutation in the sixth codon of the β (beta) globin gene (HBB) from GAG to GTG. This mutation substitutes valine for glutamic acid. Because of the hydrophobic interaction between phenylalanine (at position 88 in the globin chain) and valine (at position 85 in the globin chain), HbS forms lengthy polymers when the oxygen tension is low.[30] People with sickle cell anemia (SCA) have less flexible red blood cells (RBCs) because polymers can alter rheological and biochemical properties, which can hinder blood flow and result in vaso-occlusion (VO). [31] Acute chest syndrome, anemia, and sepsis were the three leading causes of death for SCD patients.[32] Patients are typically given hydroxyurea to treat the painful SCD crisis. Both HbF% and MCV are trustworthy markers for determining SCD.[33, 34] Advanced treatment involves CRISPR Cas 9 gene editing for SCA [35]. Use of an adenine base editor can convert HBBS to HBBG, which minimizes DNA breaks [36], and administration of LentiGlobin decreases hemolysis and resolves vaso-occlusion.[37]

2.4 Quantitative changes

2.4.1 Thalassemia

Thalassemia is caused by a reduction in the production of either the alpha or beta chains of hemoglobin (Hb). Since thalassemia is an inherited condition, it must have at least one parent to be a carrier. It results from a genetic mutation or the removal of specific, important gene segments.[38] It can take one of two general forms: (i) the α-type, which develops when there is insufficient α-globin synthesis, or (ii) the β-type, which develops when there is insufficient β-globin production. If insufficient amounts are produced, the concentration of globin chains will increase, and if insufficient amounts are synthesized, the production of globin chains will increase (resulting in thalassemia).[39] The preferred method of treatment for the most severe forms of thalassemia is stem-cell transplantation.[40] Advanced techniques for screening and diagnosis can be done by using next-generation sequencing or hemoglobinopathies.[41,42]

2.4.1.1 Alpha-Thalassemia

Alpha-thalassemia has two clinically significant forms: hemoglobin Bart hydrops fetalis (Hb Bart) syndrome and hemoglobin H disease, caused by the deletion or inactivation of four alpha-globin genes.[43] Hb Bart syndrome is a

severe form of hemoglobinemia characterized by prenatal edema, heart failure, and severe anemia. It can cause death in neonatal periods and can be diagnosed during routine hematologic analysis. Symptoms include spleen enlargement, jaundice, and bone changes.[44]HbH disease, a phenotypic spectrum affecting individuals, can develop in early life but may not be present until adulthood or diagnosed during routine hematologic analysis. It can cause spleen enlargement, jaundice, gallstones, and hemolysis.[45] Treatments such as intrauterine transfusions (IUT) and hematopoetic stem cell transplantation could be performed.[46]

2.4.1.2 Beta-Thalassemia

Hemoglobin production is decreased in people with beta-thalassemia. The low hemoglobin level causes depletion of oxygen in various bodily regions.[47] Anemia, or low red blood cell counts, is a condition that affects people and can lead to pale complexions, weakness, exhaustion, and more significant issues.[48] Individuals who have beta-thalassemia are more likely to get abnormal blood clots.[49] Based on the severity of the disease, it is classified as beta-thalassemia major or beta-thalassemia intermedia. Thalassemia major, a life-threatening anemia, typically manifests in children within the first two years of life, causing weight loss, jaundice, enlarged spleen, liver, and heart, and delayed puberty. Chronic blood transfusions may lead to iron buildup, causing liver, heart, and hormone issues. Thalassemia intermedia, a milder form of thalassemia, typically manifests in early childhood or later life, causing mild to moderate anemia, slow growth, and bone abnormalities.[50] The HBB gene mutation affects beta-globin chain production. Beta-zero thalassemia is the absence of beta-globin, while beta-plus thalassemia has reduced amounts. Both types can lead to thalassemia major and intermedia. The lack of beta-globin results in a shortage of mature red blood cells, leading to anemia and other health issues.[51] Hematopoietic stem cell transplantation, gene therapy, and lupatercept treatment are currently used as treatment options.[52] In patients with transfusion-dependent beta-thalassemia, the Lupatercept group demonstrated a considerably larger reduction in transfusion burden than the placebo group, and there were fewer adverse events that resulted in therapy termination.[53] Additionally, iron chelation therapy is also used for beta-thalassemia patients.[54]

2.4.2 G6PD deficiency

Glucose-6-phosphate dehydrogenase (G6PD) is an X-linked genetic anomaly that results in insufficient levels of G6PD in the blood.[55,56] G6PD deficiency always coexists with SCD and beta-thalassemia.[57] G6PD deficiency could cause severe hemolysis, even though hemoglobinopathy is curable.[58] Hemolytic anemia is a common medical issue caused by a defect in the enzyme glucose-6-phosphate dehydrogenase, causing premature red blood cell breakdown.[59] This condition can lead to paleness, jaundice, dark urine, fatigue, shortness of breath, and a rapid heart rate. It is often triggered by infections, drugs. It also causes mild-to-severe jaundice in newborns.[60] The G6PD assay is used to measure its deficiency.[61] Treatment involves a blood transfusion and gene editing.[62]

2.5 Research on Hemoglobinopathy in Nilgiri tribes

Studies showed that these tribes have a higher incidence of SCT, followed by beta-thalassemia carriers.[63] In India, there are more than 30 million people who carry the thalassemia gene. Each year, 10% of the thalassemia infants born worldwide are in India.[64] Studies on hemoglobinopathy among the Nilgiris tribes revealed that β-thalassemia, as well as the prevalence of glucose 6-phosphate dehydrogenase deficiency, were present. This is primarily because people in the Nilgiris marry each other in consanguineous unions.[65]

2.6 Research on SCD in Nilgiris tribe

Sickle cell anemia (SCA) is the most significant hemoglobinopathy in the world in terms of frequency and societal impact, according to the World Health Organization (WHO). Sickle cell anemia is very prevalent in Africa and India.[66] Only two of the approximately 29 primary health centers in the Nilgiris district provide care for SCD patients.3 Sickle-cell disease is prevalent in tropical and subtropical areas.[67]

A study reported that, in the western and eastern parts of the Nilgiris District, SCD was most frequently observed. Among the Nilgiris tribes, the main SCD concern related to the sickling of red blood cells has grown. Each tribe's genetic makeup influences how often this disease strikes.[4] Lehmann and Cutbush reported discovering Hb-S in the southern Indian Nilgiris tribes in 1952.[18] The sickle gene affects three socioeconomically disadvantaged ethnic groups in India: backward classes, scheduled castes, and scheduled tribes. STs are more affected due to lower socioeconomic status, remote areas, poverty, illiteracy, inherited disorders, and a higher S allele frequency in scheduled communities.[68] According to Archana et al., the rare South Indian hemoglobin variant HbSD-Punjab with Sickle Cell trait, which is double heterozygous with symptoms, was discovered during a hemoglobinopathy screening among the Badaga community.[69]

The sickle cell trait, which acts as a carrier for increased anemia among communities through consanguineous marriage, is a serious problem in SCD among tribes. A study in 2013 reported that the Irular,Panniya,and Kurumba tribes had the highest SCD prevalence rates. 205 of these individuals were found to be sickling homozygous (HbSS), whereas 1543 individuals displayed a heterozygous state (HBAS). SCD cases increased quickly in the age groups of 0–14 (25.8%), 15–24 (19.7%), and 25–49 (44.1%), with only 0.2% of cases occurring in those under 75.[1]Irula (95%) had the highest age-adjusted rate for both genders per 100,000 people, followed by Kurumba, Pannaiya, and Kattunaikan. Another study reported that Irulas had the highest incidence of sickle cell disease among tribes, with 1451 (50.6%) cases, and Kattunaicken had the lowest incidence, with 58 (2.0%) cases.[24] In 2018, Kumar et al. found that sickle cell disease affects people of all ages, but that it is more common in those under 15 and between the ages of 16 and 25.[18] According to Sheshadri et al., indigenous people of the Gudalur Valley are afflicted by the serious condition of SCD, which carries a high risk of premature death. 25% of deaths occurred between the ages of 6 and 18.[24] Recently, research done by Sheeba and Sarojini has developed a classification-based prediction model utilizing data mining techniques for SCA illness prediction.[70]

2.7 Research on β-Thalassemia in Nilgiris tribes

The prevalence of carriers ofβ-Thalassemia is about 3–4% in India. According to Kumar et al., some ethnic groups are substantially more prevalent than others, with a tribal group predominance of roughly 8%.[71] In 2013, Santhosam& Samuel have reported cases of the ß-thalassemia trait, which are primarily carriers, have been reported among the Irula tribes and in the Kurumba and Paniya tribes of the Nilgiris.[72] A study conducted by Labie et al. found high frequencies of the (-alpha) haplotype in the Nilgiris (0.89).[73]

2.8 Research on G6PD deficiency in Nilgiris tribes

It affects about 400 million people worldwide. In areas where malaria is or has been endemic, there are wide variations in the severity of this enzyme's deficiency. More than 50 years ago, India was the first nation to report a G6PD deficiency.[74] The prevalence varies among different tribal groups, with an average of 7.7 percent and a range of 2.3 to 27.0 percent. Due to the tribal populations' isolation from areas where malaria is or has been prevalent, the indiscriminate use of antimalarial drugs runs the risk of increasing the incidence of drug-induced hemolysis.[75] A study conducted by Depika Mohanty and Kishalaya Das reported that the Nilgiri tribes had a prevalence range of 0 to 10.6%.[76] According to a study, a 15-year-old Italian boy has the G6PD Nilgiris (c.593G>A, p.Arg198His) genetic variant of the Nilgiris tribal groups.[77] Using exon-by-exon DNA sequencing, G6PD Nilgiris (10.0%) was discovered in the Nilgiris.[78]

3. EXCLUSION CRITERIA

In this article, we have excluded the studies for the following reasons: In this review, we concentrated on hemoglobinopathy studies that have been done on Nilgiris tribes since the last ten years until the current year. We have analyzed the potentially relevant literature based on that; hence, we neglected the papers of hemoglobinopathy research done in other populations.

4. CONCLUSION

Irular, Panniya, and Kurumba tribes have the greatest rates of sickle cell disease prevalence, with Irula having 50.6% rate especially in the 0–14 and 25–49 age categories.Indigenous inhabitants in the Gudallore Valley face a significant danger of dying early. The broader ethnic population known as the Badaga community was found to have an uncommon variation known as HBSD-Punjab SCT. There have been reports of ß-thalassemia patients with a prevalence rate of 8% in the Irula, Kurumba, and Paniya tribes. The G6PD Nilgiris genetic variation, which has a 10.0% incidence rate, is specific to the Nilgiris tribe**.**This review gives an update on hemoglobinopathy disease research among the Nilgiris tribes. We conclude that tribes in Nilgiris District are more prone to this genetic disease. We also found that a rare trait of SCD was identified among the aboriginal group called the Badaga population who are not considered as tribes and more research is needed for this community. Therefore, increasing research and survey in this field would pave the way for researchers to develop valid treatment options for hemoglobinopathies and could decrease its prevalence among Nilgiris tribes.

5. Need for Future Interventions

Tribes are at high risk for hemoglobinopathy diseases, particularly in the Nilgiris tribes due to genetic and hereditary factors. Early detection and referral mechanisms are needed, along with improved primary healthcare systems and community mobilization. Human-centered intervention strategies such as intervention of nutritious food, screening, genetic counselling, genetic testing, and evidence-based therapies can improve quality of life for SCD patients, particularly in tribal communities.

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Conflicts of interest

There are no conflicts of interest.

Table 1: Hemoglobinopathy hereditary disease among Nilgiris Tribe

Genetic Disease	Tribes	References
SCD	Toda, Kota, Irula, Kurumba, Katunayakan's, Paniya	[1]
a) Risk rate of SCD in Tribes	Irula- 50.6%	[3,24]
	Pannaiya- 63.7%	
	Kurmbas- 17.8%	
	Todas- 0%	

	Kattunaiyakans-8.3%	
b) Mortality	Higher in paniyas of Nilgiri tribe. Males have higher death. 1. 6-29 age – 70% death 2. 19-29 age- 45.4% death 3. 6-18 age- 24.6% death	[24]
Treatment	Hydroxyurea	[79]
Future intereventions	Need for Health care interventions, proper screening, Genetic Counselling, Prenatal care	[80]
Diagnosis	Solubility test, Genetic screening, Peripheral Blood smear, Sickling test, automated HPLC	[39,81]
2) ß-Thalassemia	Kurumba, Irula, Panniya	[82]
Diagnosis	Paper or Cellulose acetate electrophoresis, HPLC, NESTROFT test, DPIP test	
Risk rate	0.5-0.3%	[77]
G6PD Deficiency	Almost all tribes in Nilgiris	[55]
a) Risk rate	0-10%	
b) Diagnosis	Enzymatic assay, DPIP dye decolorizer method, fluorescent spot test.	[55]
HBSD-Punjab SCT	A rare trait found among Badaga community- Non tribe	[69]
Diagnosis	Beta-globin distal promoter motif screening	

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