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# 14. Burden of Glucose-6-Phosphate Dehydrogenase Deficiency- A Lesser-Known Asymptomatic Genetic Disorder: A Pilot Study from Bodoland Territorial Region (BTR), Assam

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***Abstract:***

*Glucose-6-Phosphate Dehydrogenase (G6PD) functions as a catalyst in the pentose phosphate pathway, converting glucose-6-phosphate into 6-phosphogluconate and reducing NADP+ to NADPH. In malaria endemic areas, this X-linked enzyme deficiency is common. G6PD deficiency renders the cell susceptible to oxidative damage. This deficiency is generally asymptomatic; however, it poses a life-threatening condition when exposed to oxidative triggers including antimarial drug, Primaquine. People with G6PD deficiency have a considerable selective benefit against severe malaria. According to a World Health Organization (WHO) report, 7.5% of world population constitute as G6PD deficiency carriers and 2.9% as deficient. G6PD deficiency affects 0–10% of the population in India, with tribal people having a higher frequency than other populations.*

*There have been very few studies conducted on this disorder in the Northeastern part of the country. Northeast India houses adiverse ethnic communities of Mongoloid, Proto-Australoid and Aryan stock. Thus, the present study was designed to understand the G6PD status among one of the North-east India's tribal populations, the Proto-Australoids (tea tribe) from malaria endemic Himalayan zone of Indo-Bhutan trans-border districts of Assam. We used the STANDARD G6PD Analyzer (SD-Biosensor) to conduct G6PD screening programs randomly on 1750 individuals. We found 6.74% of the total study*

*population as deficient; all were asymptomatic. Our results were in concurrent to India's overall prevalence of G6PD deficiency. Thus, considering the overall prevalence from this study, we may conclude that G6PD status should be investigated prior to anti-malarial treatment.*

***Keywords:***

*Glucose-6-Phosphate Dehydrogenase, Malaria, Northeast India, Mongoloid, Proto-Australoid, Aryan.*

## 14.1 Introduction:

Pentose phosphate pathway serves as the only source of nicotinamide adenine dinucleotide phosphate (NADPH), required for the maintenance of reduced glutathione (GSH), which provides protection to red blood cells (RBCs) against oxidative damage.

Glucose-6-Phosphate Dehydrogenase (G6PD) enzyme catalyzes the first and the rate-limiting step of this pathway, in which glucose-6-phosphate is converted to 6-phosphogluconate, resulting in reduction of $NADP^+$ to NADPH. Deficiency of G6PD enzyme renders the cell susceptible to oxidative damage. This X-linked enzyme disorder is estimated to affect over 400 million people globally (Nkhoma *et al*., 2009). Subsequently after its discovery in the 1950s, G6PD deficiency is now the most frequent human enzymopathy. This deficiency poses a life-threatening condition when exposed to oxidative stress (Efferth *et al*., 2005). G6PD deficient individuals and heterozygous female carriers have a considerable selective benefit against severe malaria (Goheen *et al*., 2017).

The X-chromosome's long arm is the location of the *g6pd* gene which has 13 exons and 12 introns, covering more than 18.5kb of the genomic region (Rattazi, 1968). G6PD is functionally active only in their dimer or tetramer form, subject to conditions such as pH of the cellular environment (Cohen & Rosenmeyer, 1969). Each G6PD monomer is made up of 515 amino acids that form two domains, a catalytic dinucleotide-binding domain for $NADP^+$/NADPH and a β+α domain serving as a further binding site for structural $NADP^+$. This additional $NADP^+$ binding site is responsible for structural stabilization of the enzyme (Kotaka *et al*., 2005).

The substrate binding site for Glucose-6-phosphate (G6P) is placed in between these two domains. Mutations occurring in these functional regions of the enzyme disrupt the activity and stability of the enzyme (Cunningham *et al*., 2017), resulting in severe or mild deficiency i.e., classes I to III as per World Health Organization (WHO).

Geographically, the worldwide prevalence of G6PD enzymopathy is correlated with areas where populations have a history of being exposed to endemic malaria. With regards to ethnicity, G6PD deficiency is more common in people of African, Mediterranean, or Asian descent, likely owing to its suggested protective effect against malaria. According to a WHO report, 7.5% of world population constitutes as G6PD deficiency carriers and 2.9% as deficient (WHO, 1989).

India has a population varying greatly with regards to castes, ethnicity and linguistic groups. Also, geographically and environmentally India has a great variation, which contributes to population diversity. In India, investigations on G6PD enzymopathy have been started after it was firstly reported by Baxi *et al*. in 1961.

Since then, various studies on the prevalence of G6PD deficiency in different groups of population of mainland India have been conducted. In India, the prevalence of G6PD deficiency varies from 0-10% among different population groups (Tripathy & Reddy, 2007). India being a malaria endemic country, the treatment course requires primaquine drugs which are generally conducted without routine G6PD screening. This makes patients vulnerable to prescription of potentially hemolytic drugs, especially putting G6PD deficient individuals at risk of serious complications.

The Northeastern region of India is highly endemic to malaria, contributing a very high proportion of malaria cases of India annually (Dev & Manguin, 2021). This region is occupied by diverse ethnic communities of Mongoloid, Proto-Australoid and Aryan stock, and a limited number of studies are available on this disorder.

An overall deficiency of 5.4% was observed from malaria-endemic regions of Northeast India (Bharti *et al*., 2020). Another hospital-based study from Northeast India has observed 33.75% of *Plasmodium vivax* malaria patients had G6PD deficiency (Rajkhowa *et al*., 2020). Thus, the present study was aimed to explore the status of G6PD among one of the tribal populations of Northeast India, the Proto-Australoids popularly called as "tea tribe" from the malaria-endemic Indo-Bhutan border areas of Assam.

## 14.2 Materials and Method:

The Institutional Ethics Committee, Bodoland University, Kokrajhar, Assam has granted the ethical approval for the study vide Ref. No: -IEC/BU/ICMR/2019-2 of dated 10/05/2019. We conducted screening programmes for G6PD status randomly among the tea-tribe population of four districts of Bodoland Territorial Region (BTR), Assam forming the Indo-Bhutan border region.

The STANDARD G6PD Analyzer (SD Biosensors) was used for detection of the G6PD status. Briefly, the process involves mixing of 10µl of whole blood to the extraction buffer; then, 10µl of the mixture was collected and applied to the test device. The device measures hemoglobin (Hb) level in g/dL and G6PD levels in U/g of Hb. Statistical analysis of the data was done by SPSS 26.0.

## 14.3 Results:

A total of 6.74% of the participants were detected as G6PD deficient out of 1750 individuals that were screened with the STANDARD G6PD Analyzer. All the deficient individuals were asymptomatic. Among the deficient people, 41.5% (49) were found to be severely deficient while 58.5% (69) were found as intermediate (Figure 14.1).

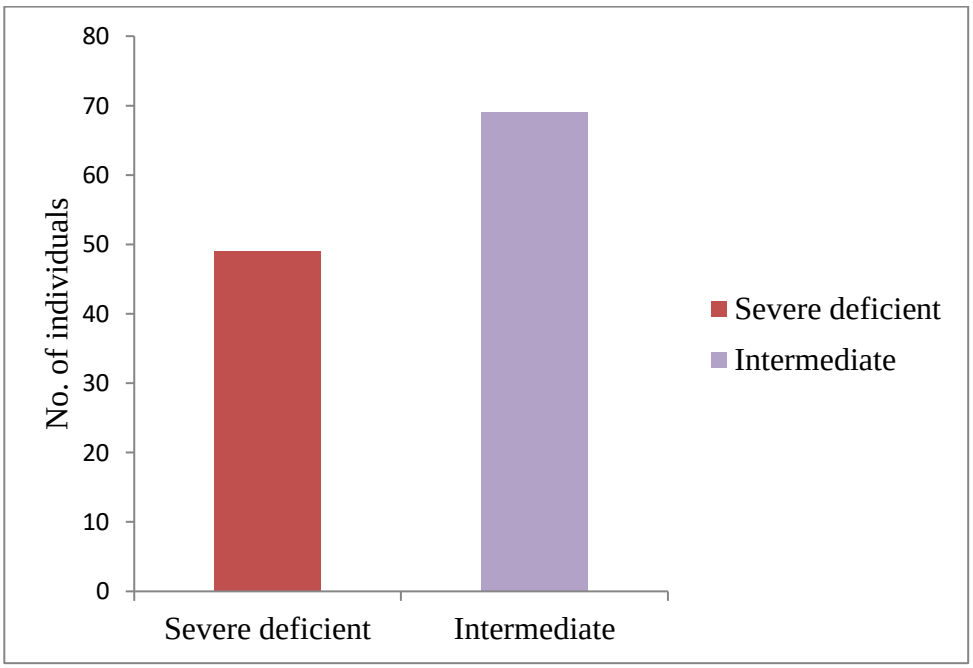


**Figure 14.1: Status of G6PD among the participants.**

**14.4 Discussion:**

According to latest studies, G6PD deficiency is prevalent in 8.5% of India's population (Kumar *et al*., 2016). Limited studies on G6PD deficiency have been conducted from North-Eastern states of India. According to a recent study, the prevalence of people with G6PD deficiency in the region was 5.4% (Bharti *et al*., 2020). Two different studies from Odisha reported that the prevalence of deficiency varied from 0.3 to 30.7% (Balgir, 2010; Mukherjee *et al*., 2015). Several reports on G6PD deficiency have been published in various caste groups/tribes across India as a whole. These include the Parsee, Muslim, Brahmin, Jat, Rajputs, Vataliya Prajapati, Nagas, Kharia, Bhuyan, Danguria Tharu, Kabui and so on. The scheduled tribes have a greater rate of G6PD deficiency than other ethnic groups, ranging from 0 to 10% among the entire Indian population (Tripathy & Reddy, 2007).

Geographically speaking, the prevalence of the G6PD deficient allele is relatively higher in the North and West Indian zones compared to the South Indian zones, with the exception of the states of Andhra Pradesh and Tamil Nadu (Rai & Kumar, 2012). While the majority of the population has a prevalence of 0–10% G6PD deficiency, there may be higher frequency in some communities. The Vataliya Prajapati population from Western part of India showed a prevalence of 27.5% (Gupte *et al*., 2005) and 27.1% among Angami Nagas of Northeast India (Seth & Seth, 1971). In the present study, the Proto-Australoid population's G6PD deficiency was found to be 6.74%, which corresponds to the reported range in Indian population groups. Since limited studies are available from the Northeastern region of India, and the region being malaria endemic, there is absolute necessity to explore the G6PD status prior to anti-malarial treatment.

Populations having their origin from tropical and subtropical regions of the world were the ones most likely to have G6PD deficiency. Geographically, the condition is distributed similarly to *falciparum* malaria, suggesting that the malaria parasite played a role in the selection of the G6PD deficiency (Bhasin, 2006).

It has been determined that this deficiency extends from the Mediterranean region to Southwest Asia, India, and Southeast Asia. There are several areas in Asia and the Middle East where the frequency of the deficiency is as high as 62% in Kurdish Jews and 31% in Northern Vietnam, according to several epidemiological studies (Steensma *et al*., 2001; Verle *et al*., 2000). The prevalence of the deficiency varies globally among different ethnic groups. In Greece, the deficiency varies between 20 to 30%, Saudi Arabia has a 6% deficiency, and South China has a 5.5% deficiency (Gandapur *et al*., 2002). In Africa, Southwest Nigeria (28.1%), Congo (22.5% in Brazzaville), Mali (15.7% in Bamako), Uganda (13.0%) and Gabon (9.0–15.5%) are the countries with the highest documented rates of G6PD deficiency (May *et al*., 2000; Bouanga*et al*., 1998; Duflo *et al*., 1979; Davis *et al*., 2006; Migot-Nabias*et al*., 2000).

In Asian countries, numerous reports are available on this enzymopathy from Indonesia, Thailand, Malaysia, Taiwan, Bangladesh, Pakistan, China and Myanmar. The frequency of G6PD deficiency varies widely across Southeast Asia, depending on geography and ethnicity.

For instance, in Myanmar, the incidence of the deficiency is nonexistent in the Akha while living close to the Shan, which has the highest prevalence (10.8%) and being present in the Burma (7.3%) (Iwai *et al*., 2001). Syria (30%) and Saudi Arabia (39.8%) in the Mediterranean region and Southwest Asia, respectively, have the greatest rates of G6PD deficiency (Usanga & Ameen, 2000; Alabdulaali *et al*., 2010), while China (5.5%), Bangladesh (3.33-20%), Myanmar (10.8%), and Vietnam (2.3%) in Southeast Asia have lower rates (Chan & Todd, 1972; Akhter *et al*., 2009; Matsuoka *et al*., 2007).

## 14.5 Conclusion:

In malaria endemic regions like Northeast India, the key to effective care and control is early detection of G6PD deficiency and its prevention. Through preventative genetics, the affected people and their families can benefit from genetic counseling, prenatal diagnosis, and public awareness. Given that the disorder is generally asymptomatic, it is emphasized that additional research is necessary to assess the clinical and prognostic aspects of the G6PD enzyme deficiency among other populations in this area as well. This will provide some clear insights into this genetic health issue. In areas where malaria is prevalent, the availability of population-specific data may aid in the early detection of the enzymopathy and prevent upcoming hemolytic crises.

## Limitation:

The current investigation was carried out among the tea tribes of BTR, Assam. Other communities in the region were excluded from the study. Thus, the result does not represent the G6PD deficiency prevalence of the region taken as a whole.

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**Conflict of interest:** The authors of this work declare that they have no financial or other conflicts of interest.

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