*Original Research Article*

# Molecular Detection of Glucose-6-Phosphate Dehydrogenase Deficiency in Katsina State, Northern Nigeria


**ABSTRACT**

The Abstract should not exceed 300 word it should briefly described

**Aims:** To determine the prevalence of glucose-6-phosphate dehydrogenase deficiency and its variant (G6PD A$^-$) among children diagnosed with *Plasmodium falciparum* malaria in Katsina state, Nigeria.
**Study design:** Cross-Sectional Studies
**Place and duration of study:** General Hospitals Katsina, Dutsin-ma, Daura, Baure, Malumfashi and Funtua of Katsina state, Nigeria from June, 2020 to December, 2020.
**Methodology:** A total of 200 blood samples were collected from children diagnosed with *Plasmodium falciparum* Malaria attending the six selected hospitals after getting the ethical approval and informed consent. Their socio-demographic information and clinical presentations were also noted with the aid of questionnaire. G6PD deficiency was detected using G6PD qualitative test. Molecular characterization of African A$^-$ Variants was carried out using Polymerase Chain Reaction (PCR) and Sanger sequencing. Moreover, phylogenetic studies were carried out to analyze the relationship between the types of G6PD mutations found in Nigeria and to those found in other countries.
**Results:** The G6PD qualitative test result have shown that 35(17.5%) samples of children with *Plasmodium falciparum* malaria were G6PD deficient and this shows a significant association ($P<0.05$) between G6PD and malaria. The PCR and sequence analysis of the 35 G6PD deficient samples indicate the presence of G202A mutations in only 7(20.0%) of the samples. However, the BLAST analysis of the nucleotide sequences has shown 98.73% - 100% homology with other sequences of G6PD from the National Centre for Biotechnology Information (NCBI) database. The bioinformatics analysis revealed G6PD mutations which indicate a Guanine to Adenine mutations at amino acid number 68 substitution of valine to methionine.
**Conclusion:** This study has shown a high prevalence of G6PD deficiency among children diagnosed with *Plasmodium falciparum* malaria in Katsina State, North-western Nigeria. Polymerase Chain Reaction, NCBI blast, Phylogenetic and Bioinformatics analysis of the deficient samples shows that G202A mutation in relation to the deficient children was not statistically significant ($p>0.05$), hence does not appear to have a role in G6PD deficiency among children in the selected area of Katsina state, Nigeria though our findings were limited by the small sample size.



*Keywords: BLAST, G6PD, G202A mutation, Children, Plasmodium falciparum, Polymerase Chain Reaction, and NCBI*


## 1. INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) is the first enzyme in the pentose phosphate pathway and the main intracellular source of reduced nicotidamine adenine nucleotide phosphate (NADPH), involved in diverse physiological processes such as antioxidant defense, (for instance in the erythrocyte) endothelial growth modulation, erythropoyesis, vascularization and phagocitosis [1]. Although several enzymes can recycle the cofactors, G6PD has been identified as the only NADPH-producing enzyme that is activated during oxidative stress [2]. G6PD deficiency is X-linked and predisposes to hemolysis and to a lesser extent to methemoglobinemia in those persons in use of a substance with oxidative properties [3, 4].

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common hereditary hemolytic disorders in human, affecting around 400 million people worldwide [5]. Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency has been shown to protect against malaria infection which affect

million people worldwide with an estimate of 627 000 malaria deaths in 2020 of which 95% in the African region and 80% were children under 5 years of age. Malaria is the 3rd leading cause of death for children under five years worldwide, after pneumonisa and diarrheal disease [6].

The geographical distribution of malaria is remarkably similar to the world distribution of deficient G6PD variants [7]. It is postulated that the high frequency of G6PD deficiency has arisen because G6PD deficient variants confer some protection or resistance against malaria caused by Plasmodium falciparum and Plasmodium vivax [8]. Significant selective advantage against severe malaria has been reported in deficient individuals and heterozygous female carriers of deficient alleles.

Malaria has also been implicated in the spreading of deficient variants in malaria endemic areas. A number of different G6PD deficient variants have reached polymorphic frequencies and each has a characteristic distribution in parts of the world where malaria is currently or was previously endemic. The mutations result in protein variants with different levels of enzyme activity that are associated with a wide range of biochemical and clinical phenotypes [8]. Approximately 140 mutations affecting the gene coding sequence have been reported [9, 10], most of which are single-base substitutions leading to amino acid replacements.

## 2. MATERIAL AND METHODS

### 2.1 Subjects

This study was a cross-sectional investigation, in which subjects aged **≤** 5 years that are unrelated admitted or presented with *Plasmodium falciparum* malaria to the selected hospitals from June, 2020 to December, 2020 were investigated for G6PD deficiency. Only one child was included from each family. This study was conducted in a total of 200 subjects. Of these, 119 (59.0%) were males and 81 (40.50%) females. Moreover, 120 (60.00%) subjects come from the rural areas of the study population while 80 (40.00%) were from the urban areas. Majority of the children in study population were within the range of 0-12months 62 (31.00%) and decreases as the months increases i.e. 13-24, 25-36, 37-48 and 49-60months with the following numbers and percentages 49 (24.50%), 34 (17.00%), 30 (15.00%), and 25 (12.50%) respectively.

Screening for G6PD deficiency was done qualitatively and venous blood samples (2.0mls) were withdrawn from each child of the study population at the selected hospital by the laboratory technician and ethical guidelines was followed. The samples were collected in EDTA tubes and transported immediately in ice-cooler box to the Laboratory Department of General Hospital Dutsin-ma for G6PD screening. The positive deficient samples were kept in a solar refrigerator before sampling is completed after which they were taken to Centre for Biotechnology Research, Bayero University Kano for molecular analysis.

### 2.2 Qualitative Assays for G6PD

For qualitative determination, the activity of G6PD enzyme was measured using commercially available G6PD screening test (Biorapid Diagnostics Nig. Ltd.) according to manufacturer's instructions using fresh blood samples as enzyme activity reduces on refrigeration. G6PD present in red blood cell hemolysate acts on glucose-6-phosphate and reduces $NADP^+$ which in the presence of Premium Motor Spirit (PMS) reduces the blue coloured 2, 6-dichlophenol indophenol into a colourless form leaving behind the original cherry red colour of the hemolysate. The rate of decolourisation is proportional to the enzyme activity.

### 2.3 Molecular Studies

DNA was extracted from G6PD-deficient blood using Nucleic Acid Extraction Kit II (Geneaid International) according to the manufacturer's instructions. Purified DNA was solubilized in a TE buffer (10 mM Tris–HCL, 1 mM EDTA, pH 8.0) and stored at -20 °C. The PCR reaction was carried out for detection of African mutation using one pair of oligonucleotides as follows: Forward primer 5′ TACAGTCGTGCCCTGCCCT 3' and reverse primer 5′ CCGAAGCTGGCCATGCTGG 3'. The PCR reaction to amplify G202A was initiated by denaturation at 94 °C for 5 min followed by 30 cycles of

denaturation at 94 °C for 30 seconds, annealing at 61 °C for 30 seconds, and extension at 72 °C for 45 s and final extension at 72 °C for 5 min. Amplification was done using one unit of *Taq* DNA polymerase per µL in a final volume of 23 µL.

The DNA sequencing of the amplified PCR products of G202A gene were performed by the Dideoxy/Chain Termination method at Inqaba Biotec West Africa LTD. This method was developed by Frederic Sanger and Alan Coulson in 1977. The automated cycle sequencing based on Sanger's principle, CEQ$^{TM}$ 200XL DNA Analysis System by BECKMAN COULTER Company, was used to sequence the PCR products.

### 2.4 Statistical Analysis

The data generated from this study were analysed by descriptive statistics (mean, standard deviation, percentage), Pearson correlation by 2 tailed-tests of significance, and comparing means by paired samples t-test using IBM Statistical Package for Social Sciences (SPSS) 16.0 software. Differences between normal and G6PD-deficient subjects were considered significant at $p<0.05$.

## 3. RESULTS AND DISCUSSION

### 3.1 Prevalence of G6PD Deficiency

This study considered one of the few reports which have been done in Katsina state, northern Nigeria, to evaluate the frequency of African variant of G6PD mutations. The prevalence of G6PD deficiency among the total subjects was 17.5% (35 out of 200). Males were 11.5% (23 out of 119) compared to 6.0% (12 out of 81) for females. In addition, the difference in prevalence of G6PD deficiency between male and female were statistically not significant (*P*>0.05). The number of G6PD deficient subjects based on age encountered in this study showed no significant differences (P>0.05) among the age group. However, children within the age-group of 0-12 months have the highest deficiency, 14 (22.6%) while those between the age of 49-60 months shows the least deficiency 03 (12.0%). Moreover, the prevalence of G6PD deficiency did not differ between the sampling area, (P>0.05). The prevalence was 34.30%, 34.30% and 31.40% for Katsina Central, Katsina North and Katsina South respectively.

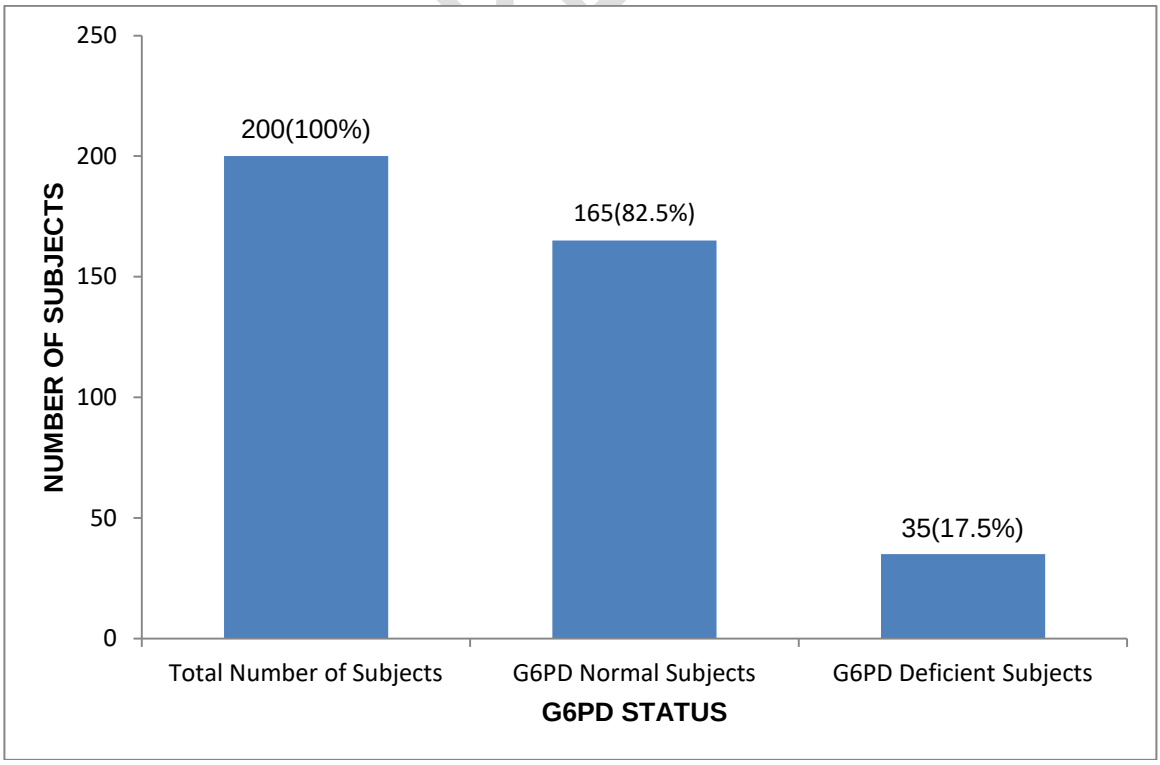

Figure 1. Prevalence of G6PD deficiency among children diagnosed with Plasmodium falciparum malaria

### 3.2 Prevalence of G6PD Mutations

The distribution of G202A mutations in Katsina state was obtained from a total of 35 G6PD deficient subjects. Polymerase chain reaction of the 35 deficient samples indicates the presence of G202A mutation in only five samples, upon sequencing (forward and reverse) of the five deficient samples two samples failed quality control but the remaining three samples shows high percentage identities, small gaps and low e-values, hence the sequences are homologous. Nucleotide blast of sample 7 forward sequence shows 98.73% identity and the reverse sequence shows 100% identity while the nucleotides blast of sample 10 and 12 both forward and reverse sequences shows 100% identity.

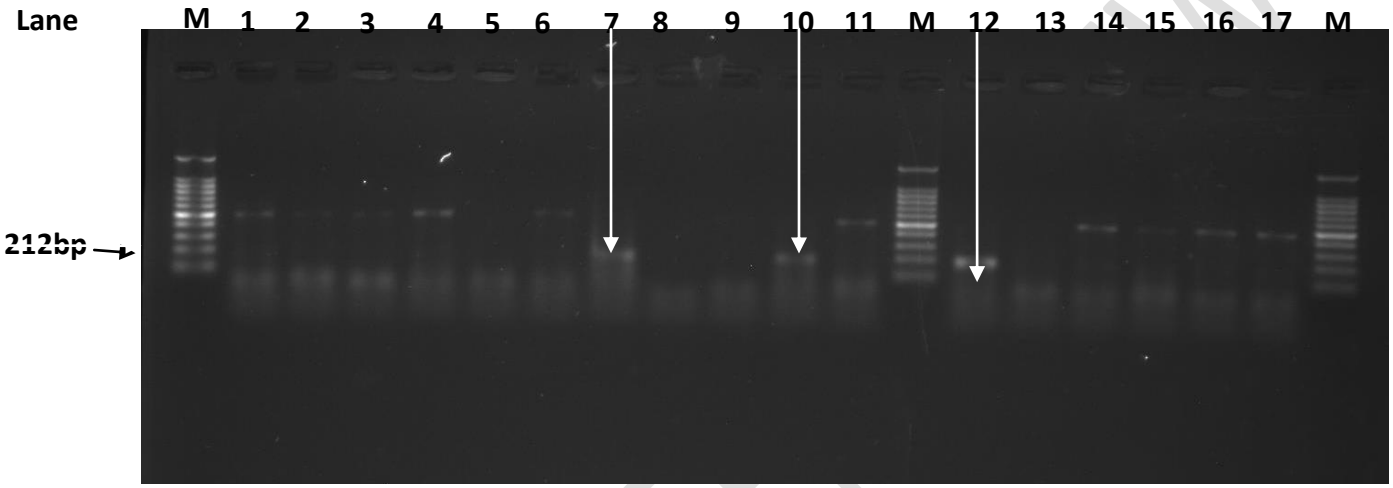


Fig. 2. Gel picture of the PCR products showing the 3 positive samples for African variant mutation (G202A) in lane 7, 10, 12; Lane M: Molecular marker and Lane 1, 2, 3, 4, 5, 6, 8, 9, 11, 13, 14, 15, 16, 17 shows negative samples for G202A mutation. The horizontal arrow shows the position of the base pairs in the molecular marker.

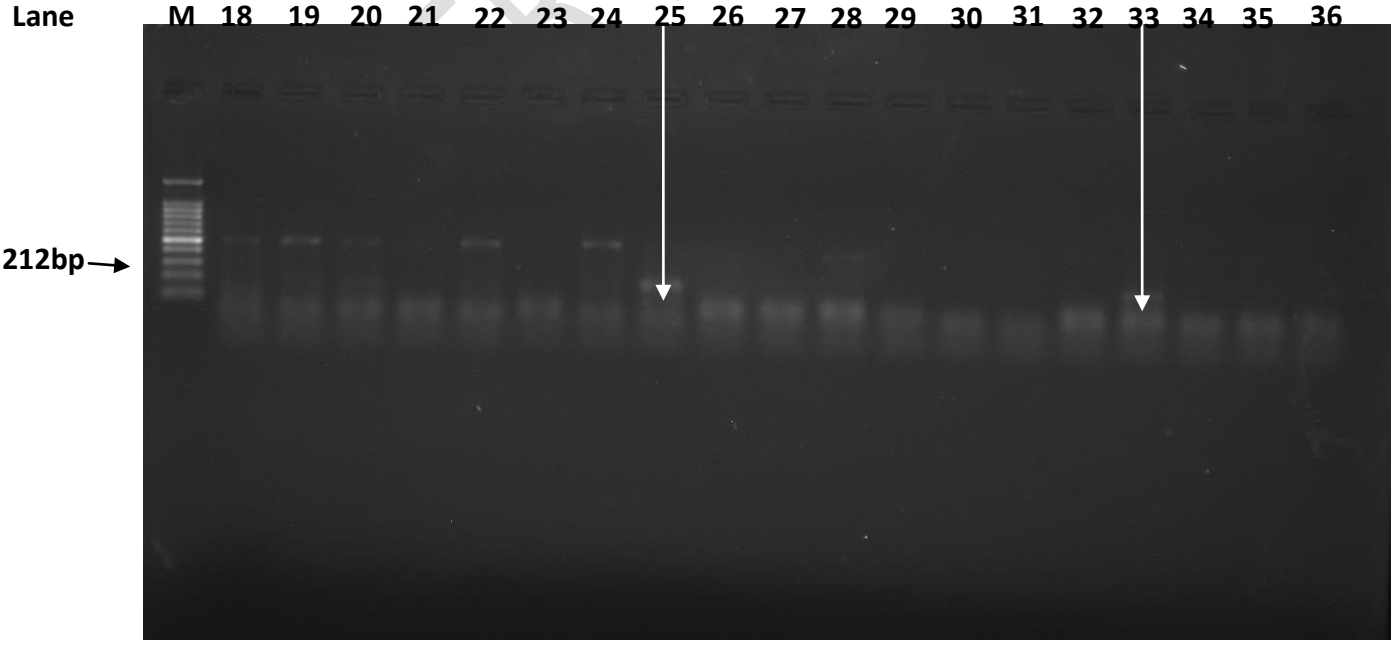

Fig. 3. Gel picture of the PCR products showing the 2 positive samples for African variant mutation (G202A) in lane 25, 33; Lane M: Molecular marker and Lane 18, 19, 20, 21, 22, 23, 24, 26, 27, 28, 29, 30, 31, 32, 34, 35 shows negative samples for G202A mutation and Lane 36: free nuclease water (Negative control). The horizontal arrow shows the position of the base pairs in the molecular marker.

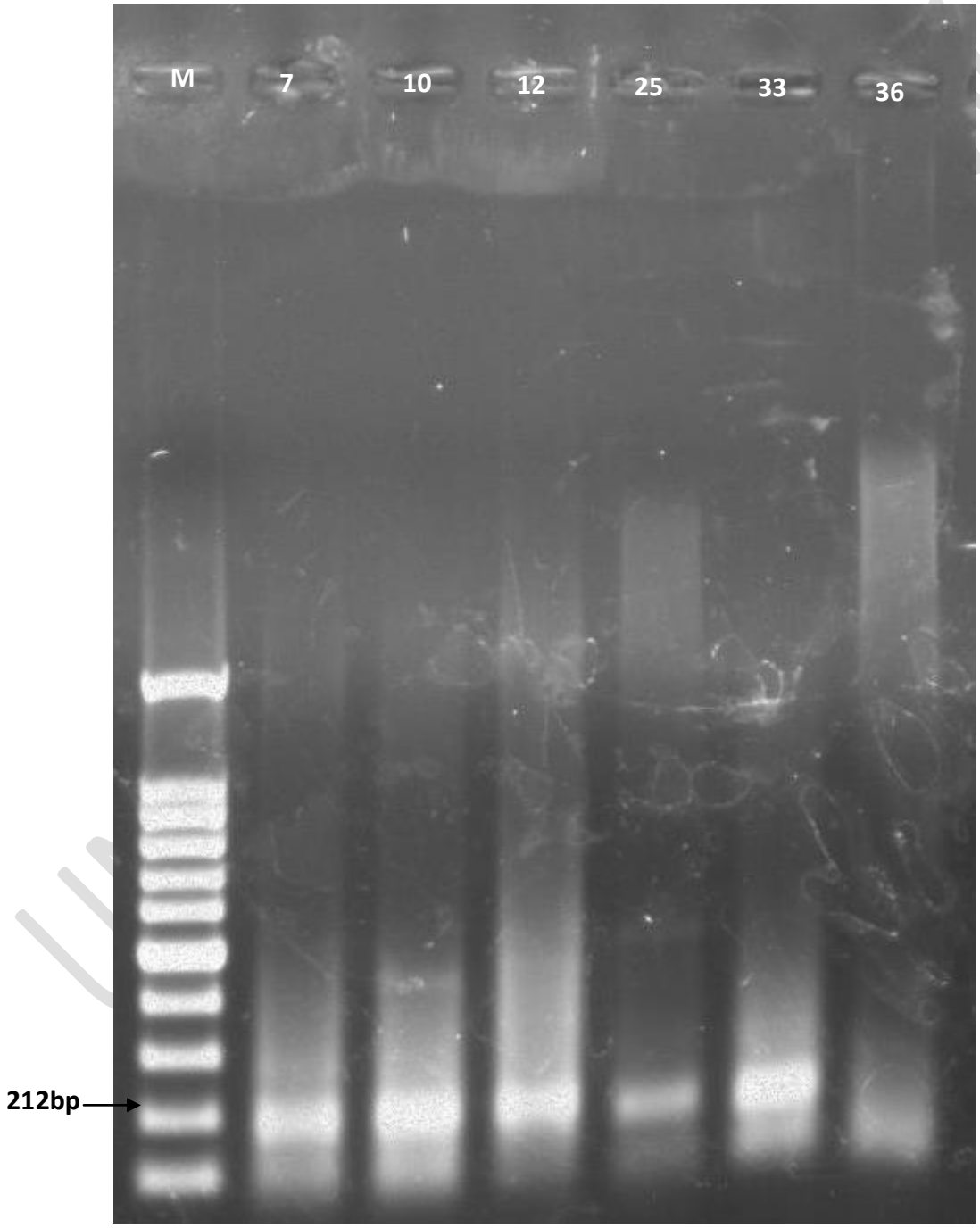

Fig. 4. Gel picture of the PCR products showing the 5 positive samples for African variant mutation (G202A) in lane 7, 10, 12, 25, 33; Lane M: Molecular marker and Lane 36: free nuclease water (Negative control). The horizontal arrow shows the position of the base pairs in the molecular marker.

In this study we observed a prevalence of 17.5% (35/200) among the 200 *Plasmodium falciparum* positive children studied which is statistically significant. In epidemiological studies, it was shown that the prevalence of G6PD deficiency is related to malaria. Malaria is known as a parasitic disease that affects 300-500 million people all over the world [11, 12]. The finding from this study is consistent with previous reports in Nigeria and other parts of the world. In previous reports in Nigeria, the prevalence of G6PD deficiency ranged from 4% to 26%. However, a study by [13] in Sokoto, Nigeria among 118 children visiting the Emergency Paediatric unit of Usman Danfodiyo University Teaching Hospital for paediatric related care indicated G6PD deficiency of 14.4%. Also a study by [14] in Oshogbo, Nigeria among 200 blood donors and 86 jaundiced neonates indicated G6PD deficiencies of 19.5% and 47.7%, respectively. The study also indicates that a significant number of prevalence with G6PD deficiency was in the children within 1 year old (31.25%). The second highest are the children within 2 years old (25.00%) followed by those within 3 years old (18.75%) but those within 4 and 5 years old indicated the same prevalence (12.50%). This is statistically significant and is consistent with the work of [13] where a significant number of subjects with G6PD deficiency in their study were in the 2- to 3- and 4- to 5-year age-groups. However, this is different from a previous report [15] assessing the frequency of G6PD deficiency in Sardinian patients with nonarteritic anterior ischemic optic neuropathy, which indicated based on sex and G6PD deficiency interaction that sex does not have any modifier effect on G6PD deficiency. Also, another report [16] among children in Malaysia indicated that sex was not a significant predictor associated with actual G6PD enzyme levels.

Moreover, a high prevalence of G6PD deficiency was also observed in male children (11.5%) compared to female children (6.5%) and is statistically significant. G6PD deficiency is an X-linked recessive hereditary disease characterized by abnormally low levels of G6PD. The deficiency is X-linked since the X chromosome carries the gene for G6PD enzyme; therefore this deficiency mostly affects males. G6PD deficiency is inherited from females who carry one copy of the causative gene on one of their X chromosomes. Males who inherit the causative gene from the mother have G6PD deficiency, while females who receive the gene are carriers (carrier females generally do not show any characteristic symptoms). The deficiency is rare in females because the mutation would have to occur in both copies of the gene to cause the disorder, whereas in males only one abnormal copy of the gene is required for manifestation of the disease. This is consistent with previous reports that indicated that the sex of the patient is important and that males are at greater risk based on severity compared to females [17, 18].

A study by [19] among males resident of Jos, Nigeria showed prevalence of 20% G6PD deficiency. G6PD deficiency is beneficial as it is known that red blood cells that are deficient in G6PD are resistant to *Plasmodium falciparum* invasion since the parasite require the enzyme for its normal survival in the host cell. This deficiency offers a selective protection against *Plasmodium falciparum* malaria [20, 21].

The study also shows that there was no correlation statistically between G6PD deficiencies with either of the Senatorial zones i.e the sampling areas (Central, North and South senatorial zones). Therefore this shows that G6PD deficiency does not depend on the locality of the children within the state. Irrespective of the senatorial zone of origin a child may have the G6PD deficiency or not. The geographical distribution of G6PD deficiency suggests that some polymorphisms confer resistance to *Plasmodium falciparum* malaria [22]. This phenomenon has been investigated mainly for the African variant (G6PD A-), showing that it also confers protection against lethal falciparum malaria [23]. The higher prevalence of G6PD deficiency in malaria endemic countries is an indication that malaria infection has exerted a strong selective pressure in many human populations [20, 7]. In *Plasmodium falciparum* infection it has been demonstrated that shorter half-life and rapid clearance of red blood cells of G6PD deficient individuals make them less susceptible to malaria attacks from these parasites [24].

In UAE the prevalence of G6PD deficiency in national populations is significantly higher (7.4%) compared to the non-nationals (3.8%) ($p < 0.001$) [5]. This reflects high incidence of the disease in the region. Earlier studies on G6PD deficiency among UAE national males living in Al-Ain have reported frequencies of 9.1 to 11% [25, 26] which is slightly higher than the frequency of 7.4% seen in the recent study. The

frequency of G6PD deficiency in the UAE is less than that in Kuwait (19%), Bahrain (21%), and Oman (27%) [27, 28].

Moreover, the variation of G6PD deficiency within different geographical regions in Oman ranges between 8.7 and 29% [29]. In contrast, the prevalence of G6PD in the UAE population is relatively higher than that in the populations residing in some other Mediterranean countries such as Italy (1 to 2%) [30], Spain (1%) [31], Turkey (1.2%) [32]. The frequencies of G6PD deficiency which have been reported throughout the Eastern Mediterranean Region ranges from 3.6% in Jordan to 39.8% in Eastern Saudi Arabia [33].

In one comprehensive review in India, it shows that the wide variability of G6PD deficiency has been observed ranging from 0% - 30.7% among the different caste, ethnic, and linguistic groups of India. The area wise distribution revealed frequency of G6PD deficiency ranging between 0% - 30.70% in Eastern India to 0% - 27.9% in Western India. The prevalence of G6PD deficiency was found ranging from 0% - 23.21% in Northern India to 0% - 18% in Southern India. Whereas it was found ranging between 1.86% - 15.71% in North-eastern, India and 0% - 19.23% in Central India, the range in the island regions of India is reported to be even lower [34].

Molecularly, Polymerase chain reaction of the 35 deficient samples indicates the presence of G202A mutation in only five samples. Sequencing reaction of the five deficient samples, though two out of the five failed quality control, the remaining three samples shows high percentage identities, small gaps and low e-values, hence the sequences are homologous. There is no significant difference statistically in the presence of this mutation between the three samples. The nucleotide sequences obtained from the sequenced genes (both forward and reverse) are 99%, 100%, 100%,100%,100% and100% respectively.

This gene encodes glucose-6-phosphate dehydrogenase. This protein is a cytosolic enzyme encoded by a housekeeping X-linked gene whose main function is to produce NADPH, a key electron donor in the defense against oxidizing agents and in reductive biosynthetic reactions. G6PD is remarkable for its genetic diversity. Many variants of G6PD, mostly produced from missense mutations, have been described with wide ranging levels of enzyme activity and associated clinical symptoms. G6PD deficiency may cause neonatal jaundice, acute hemolysis, or severe chronic non-spherocytic hemolytic anemia. Two transcript variants encoding different isoforms have been found for this gene. This record has been curated by NCBI staff in collaboration with Sujatha Mohan. The reference sequence was derived from AC244090.3 and is a reference standard in the RefSeqGene project, January 17, 2014.

## 4. CONCLUSIONS

These conditions reach life-threatening scenarios for all G6PD deficiency patients with different genetic variants. The data on G6PD deficiency among children in Katsina state, northern Nigeria have been established. The clinical and biochemical effects, evidence-based data required for the management of G6PD deficiency among children are now known in the area.

Therefore, high percentages of G6PD deficiency prevalence in many malaria endemic countries account for considerable difficulties in effort to eradicate malaria [35]. Testing individuals for G6PD status in field conditions is currently unrealistic due to the costs involved and logistic aspects, and therefore, most countries opt not to administer primaquine in order to avoid drug related haemolysis. This highlights the need for comprehensive estimates of G6PD deficiency in malaria endemic regions and its clinical consequences.

This study has been done only in six selected hospitals of the state and with limited sample size. Hence does not reflect the whole picture of G6PD prevalence in Katsina state. It is highly recommended that a comprehensive study that includes all hospitals and medical centres in the state should be performed to better determine the accurate prevalence rate of G6PD African mutation among children (0- 5 years).

## Ethical Approval

The ethical approval for this study was obtained from Katsina State Ministry of Health Ethical Research Committee (MOH/ADM/SUB/1152/1/276) that grants ethical clearance for research that involves human subjects.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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