

Review Article

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency among tribal populations of India - Country scenario

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It is believed that the tribal people, who constitute 8.6 per cent of the total population (2011 census of India), are the original inhabitants of India. Glucose-6-phosphate-dehydrogenase (G6PD) deficiency is an X-linked genetic defect, affecting around 400 million people worldwide and is characterized by considerable biochemical and molecular heterogeneity. Deficiency of this enzyme is highly polymorphic in those areas where malaria is/has been endemic. G6PD deficiency was reported from India more than 50 years ago. The prevalence varies from 2.3 to 27.0 per cent with an overall prevalence of 7.7 per cent in different tribal groups. Since the tribal populations live in remote areas where malaria is/has been endemic, irrational use of antimalarial drugs could result in an increased number of cases with drug induced haemolysis. Therefore, before giving antimalarial therapy, routine screening for G6PD deficiency should be undertaken in those tribal communities where its prevalence is high.

Key words Deficiency - G6PD - malaria- tribes - variant

Introduction

Glucose is the main source of energy for the red cell, which is metabolized by two major routes; the glycolytic pathway and the hexose monophosphate (HMP) shunt. Glucose-6-phosphate-dehydrogenase (G6PD) is an X-linked enzyme that catalyses the first step in the HMP pathway of glucose metabolism and it produces NADPH, which is required for the maintenance of reduced glutathione (GSH). GSH is essential for protecting red cells from oxidative damage¹. Hence, this enzyme is important in red cell metabolism and its deficiency renders the red cell extremely vulnerable to any kind of oxidative stress. The major clinical manifestations of this disorder are

drug induced haemolytic anaemia and/or neonatal jaundice and a small proportion of G6PD deficient individuals have chronic non-spherocytic haemolytic anaemia (Class I G6PD deficiency)².

G6PD deficiency is an example of balanced polymorphism, in which high rate of mortality caused by this disorder is offset by the protection that it offers against *Plasmodium falciparum* malaria³. Alleles of the *G6PD* gene that encode a deficient enzyme attain high frequencies in areas where malaria is or has been endemic⁴. It is believed that this disorder is selected due to malarial endemicity in many regions of the country. A correlation was found between high prevalence of

malaria due to *P. falciparum* and incidence of G6PD deficiency⁵.

G6PD deficiency is very common among humans, affecting around 400 million people worldwide and is characterized by considerable biochemical and molecular heterogeneity⁶. A higher incidence of G6PD deficiency is seen in tropical and subtropical zones of the world. Molecular analysis has revealed that each population has a characteristic profile of deficient variants. The G6PD A⁻ variant is mainly found in African populations while G6PD Mediterranean variant is predominant throughout the Mediterranean region, Middle East and India².

Tribes of India

The most remarkable feature of the Indian population structure is the clear division of its population into strictly defined endogamous castes, tribes and religious groups. India has the largest concentration of the tribal population in the world. It is generally believed that the tribal people, who constitute 8.6 per cent of the total population (2011 census of India)⁷, are the original inhabitants of India and are generally called “*Adivasis*”. The tribals can be classified according to their ethnic origin, language, race, socio-economy and cultural pattern. The total number of tribal groups is estimated to be 461 who speak about 750 dialects that belong to one of the four language groups, Austro-Asiatic, Indo-Europeans, Dravidian and Tibeto-Burman^{8,9}. The tribals are found in all the States except in Punjab, Haryana, and Jammu & Kashmir.

Majority of the tribal people live below the poverty line. They generally reside in isolated hilly and forest areas and are not accessible at most of the times during the year. There is a consensus agreement that the health status of tribal populations is very poor and is even worse among the primitive tribes because of their isolation as a consequence of their residing in remote areas and thus being largely unaffected by the developmental processes going on in the country.

Geographical distribution of G6PD deficiency among the tribes

Data reported herein have been collected from various field surveys by different workers. Considerable differences were seen in the methods adopted for field surveys and also the mode of collection of blood samples for screening for G6PD deficiency. Frequencies of the Gd⁻ (G6PD deficient) gene are recorded as have been reported in various

studies, however, studies where the sample size was small have not been considered.

A total of 72 tribal groups from 56 districts of 16 States and two Union Territories of India were studied. The Figure shows the districts wise distribution of G6PD deficiency among the tribal groups in different States of India. The prevalence of G6PD deficiency varied from 2.3 to 27.0 per cent with an overall prevalence of 7.7 per cent. The frequencies of the Gd⁻ gene in different States of India showed a heterogeneous picture. Comparatively a higher frequency (>10%) of the Gd⁻ gene is observed among the tribal groups of Nagaland, Chhattisgarh, West Bengal, Dadra & Nagar Haveli and Gujarat. On the other hand, uniformly low frequencies (<5%) of Gd⁻ gene have been reported in Tripura followed by Himachal Pradesh, Uttarakhand, Andhra Pradesh and Madhya Pradesh. Gene frequency data of G6PD deficiency in various regions are summarized below:

Western India: Comparatively large data have accumulated in western India comprising of Rajasthan, Gujarat, Dadra & Nagar Haveli and Maharashtra¹⁰⁻¹⁵. A total of 22 tribal groups were studied and the prevalence varied from 1.4 to 31.4 per cent. It is apparent that considerable heterogeneity in G6PD deficiency exists in this region. Among the tribal groups studied, a very high frequency of G6PD deficiency was observed in the *Gamits* (31.4%), *Dhankas* (20.4%), *Warlis* (19.6%), *Dhodias* (17.8%), *Bhils* (16.3%) and *Garasiyas* (15.2%). *Bhils* from Nasik district of Maharashtra have a very low frequency (1.4%). A complete absence of Gd⁻ gene was observed among the *Mahadev Kolis* from Ahmednagar district of Maharashtra.

Central India: Central India comprises Madhya Pradesh and Chattisgarh State, and *Gonds* and *Bhils* are the major tribal groups. Among *Gonds*, the prevalence of G6PD deficiency varies from 13.0 to 21.3 per cent^{10,16,17} while in the *Bhils* the prevalence varies from 3.4 to 6.7 per cent^{10,17}. A high frequency of G6PD deficiency is observed in *Kawars* (21.5%) and *Oraons* (13.4%)¹⁷.

Southern India: In 1964, Meera Khan reported a high incidence of G6PD deficiency in the *Koya Dora* tribal groups of Andhra Pradesh¹⁸. Subsequent studies¹⁰ in other tribal groups of Andhra Pradesh exhibited frequencies of 0 to 6.1 per cent. In Tamil Nadu, tribal groups of Nilgiri hills were studied and the prevalence varied from 0 to 10.6 per cent^{10,15}. In Kerala, only *Kadar* tribal group has been studied and none of the individuals showed the presence of G6PD deficiency¹⁰.

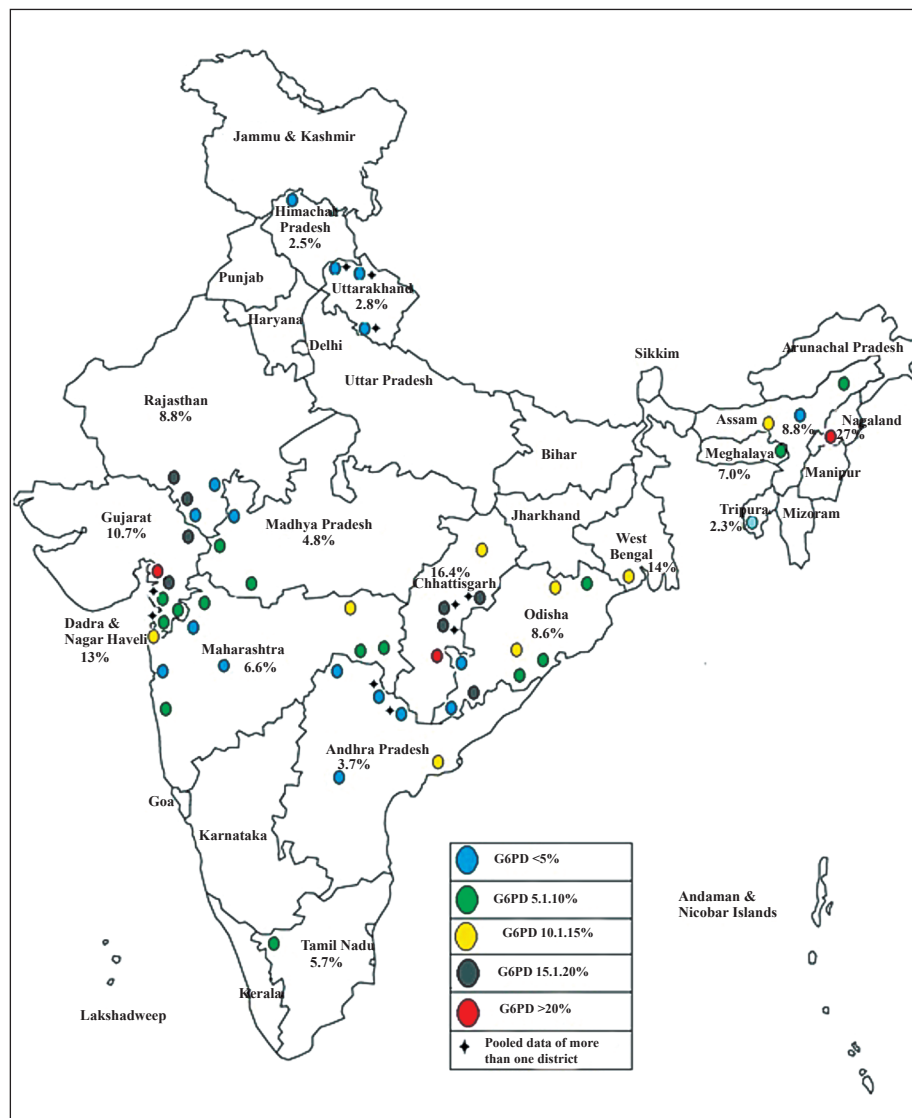


Fig. District-wise distribution of G6PD deficiency among the tribal groups in different States of India.

Eastern India: In West Bengal, *Santals* from Midnapur district showed a high prevalence of G6PD deficiency¹⁰. In Odisha, the prevalence of G6PD deficiency varied from 1.3 to 17.4 per cent^{10,15,19,20}. A very high frequency has been observed in the *Parajas* (17.4%), *Juangas* (15.6%), *Kondhas* (12.5%), *Bhumizs* (12.2%) and *Kolhas* (10.7%)^{15,20} while the lowest frequency is found among the *Bondos* from Malkangiri district¹⁵.

North India: Data from North India were uniformly low and the prevalence varied from 1.2 to 4.4 per cent¹⁰.

North-East India: G6PD deficiency was present in all the tribal groups studied from North-East India. A very high frequency was observed in *Angami Nagas*

(27.0%) from Nagaland followed by *Rabhas* (15.8%) and *Mikirs* (15.6%) from Assam¹⁰.

Andaman & Nicobar Islands: A total of 29 Great Andamanese individuals, a primitive *Negrito* tribe of the Andaman and Nicobar Islands, India, with a total population of 37 were studied and one female was found to be G6PD deficient²¹.

Laboratory investigations

The diagnosis of red cell enzyme deficiency usually depends on the demonstration of decreased enzyme activity either through a quantitative assay or a screening test. There are several methods available for the diagnosis of G6PD deficiency. However, fluorescent spot test and dichlorophenol indophenol

(DPIP) decolourisation method were found to be useful and suitable for routine use. The fluorescent spot test is based on the fluorescence of NADPH which has been generated by G6PD while in the DPIP dye decolourisation method; presence of G6PD in red cells is detected by the decolourisation of the dye within a specified time. It has an advantage over fluorescent spot test in that the heterozygotes can be easily detected and a large number of samples can be processed together at the same time. It is the method of choice along with quantitation of enzyme while screening large population²². Quantitation of enzyme activity involves the measurement of reduction of NADP to NADPH spectrophotometrically in the presence of G6P and haemolysate.

Molecular pathology of G6PD deficiency

In India, the spectrum of mutations causing G6PD deficiency has not been well elucidated. However, earlier studies have revealed that the G6PD Mediterranean mutation (563C→T) is the most common deficient variant followed by G6PD Kerala-Kalyan (949G→A) and G6PD Odisha (131C→G)²². G6PD Mediterranean was found to have significantly lower red cell enzyme activity and more severe clinical manifestations than the other two²². Of the three common mutations, G6PD Odisha and G6PD Mediterranean were found to be the main mutational event causing G6PD deficiency among the tribal groups of Maharashtra, Odisha and Gujarat²³⁻²⁶ while G6PD Namoru (208 T→C) was exclusively found among the Dravidian speaking tribes of Nilgiri district, Tamil Nadu, which further supported the human migration from Africa to Australia along the coast of southern India²⁷. Besides these mutations, G6PD Chatam, G6PD Coimbra, G6PD Nilgiri, and G6PD Gond have also been reported in the Indian tribal populations^{25,28,29}.

Alleles of the *G6PD* gene that encode a deficient enzyme attain high frequencies in areas where malaria is or has been endemic. Decreased parasitaemia has been observed among the patients with G6PD deficiency and the malarial parasite also does not grow well in G6PD deficient red cells as compared to normal cells³⁰. In India, it is believed that this disorder is selected due to malarial endemicity in many regions of the country⁵. A wide variability in the prevalence of G6PD deficiency has been observed in the tribal population groups even within small geographical areas, as the design of these studies and the methodology used have not been uniform. At the same time, the clinical manifestations

of these deficient cases are not well documented. Based on the epidemiological studies, it has been estimated that more than four million male tribal individuals are G6PD deficient and, therefore, the irrational use of antimalarial drugs causes concern in the medical fraternity about the occurrence of haemolysis in these individuals. Most of the individuals are underdiagnosed due to lack of awareness and testing facilities.

Our earlier study suggested that the use of antimalarial drugs could result in an increase in the number of cases with drug induced haemolysis. Ciprofloxacin alone also caused haemolytic anaemia³¹. This is a burden on the National Health Programme and highlights the need to undertake systematic studies on G6PD deficiency in the Indian tribal population. There is a consensus agreement that the health status of tribal populations is very poor and is even worse among the primitive tribes because of their isolation as they reside in remote areas where malaria is or has been endemic. Therefore, it is recommended that the vulnerable tribal communities should be screened before administering the oxidative drugs. In the tribal areas, the medical officer of the primary health centres should be made aware of this fact so that the oxidant drugs are prescribed with caution.

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