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Abstract

We conducted a survey for glucose-6-phosphate dehydrogenase (G6PD) deficiency using blood samples from male outpatients of a local hospital in southern Vietnam. Most of the samples were from the Kinh (88.9%), the largest ethnic group in Vietnam, with a small number (11.1%) coming from the K'Ho, Chauma, Nung, and Tay minorities. We detected 25 G6PD-deficient cases among 1,104 samples (2.3%), and read the open reading frame of G6PD. A novel mutation (352T>C) predicting an aminoacid change of 118Tyr>His was found in a 1-year-old Kinh boy. His G6PD activity was estimated to be less than 10% residual activity, although he did not show chronic hemolytic anemia. Thus, we categorized this variant as Class II and named it G6PD Bao Loc. In the Kinh population, G6PD Viangchan (871G>A, 1311C>T, intron 11 nt93T>C), one of the most common variants in continental Southeast Asian populations, was the highest (6/19), followed by variants originating from the Chinese such as G6PD Canton (1376G>T) (5/19), G6PD Kaiping (1388G>A) (3/19), G6PD Gaohe (95A>G) (1/19), and G6PD Quing Yuan (392G>T) (1/19). In addition, G6PD Union (1360C>T) (2/19), which originated from the Oceania, was also detected. These findings suggest that the Kinh people are derived from various ancestries from continental Southeast Asia, China, and Oceania. In contrast, all of the 5 deficient cases in the K'Ho population were G6PD Viangchan, suggesting that they were very close to Southeast Asian populations such as the Khmer in Cambodia and the Lao in Laos. It is interesting that G6PD Mahidol (487G>A), another common variant in continental Southeast Asian populations in Myanmar, Thailand, and Malaysia, has not been detected from the Vietnamese.

KEYWORDS: Bao Loc, glucose-6-phosphate dehydrogenase defi ciency, Kinh, malaria, Vietnam

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Original Article

Seven Different Glucose-6-phosphate Dehydrogenase Variants Including a New Variant Distributed in Lam Dong Province in Southern Vietnam

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We conducted a survey for glucose-6-phosphate dehydrogenase (G6PD) deficiency using blood samples from male outpatients of a local hospital in southern Vietnam. Most of the samples were from the Kinh (88.9%), the largest ethnic group in Vietnam, with a small number (11.1%) coming from the K'Ho, Chauma, Nung, and Tay minorities. We detected 25 G6PD-deficient cases among 1,104 samples (2.3%), and read the open reading frame of *G6PD*. A novel mutation (352T > C) predicting an amino-acid change of 118Tyr > His was found in a 1-year-old Kinh boy. His G6PD activity was estimated to be less than 10% residual activity, although he did not show chronic hemolytic anemia. Thus, we categorized this variant as Class II and named it G6PD Bao Loc. In the Kinh population, G6PD Viangchan (871G > A, 1311C > T, intron 11 nt93T > C), one of the most common variants in continental Southeast Asian populations, was the highest (6/19), followed by variants originating from the Chinese such as G6PD Canton (1376G > T) (5/19), G6PD Kaiping (1388G > A) (3/19), G6PD Gaohe (95A > G) (1/19), and G6PD Quing Yuan (392G > T) (1/19). In addition, G6PD Union (1360C > T) (2/19), which originated from the Oceania, was also detected. These findings suggest that the Kinh people are derived from various ancestries from continental Southeast Asia, China, and Oceania. In contrast, all of the 5 deficient cases in the K'Ho population were G6PD Viangchan, suggesting that they were very close to Southeast Asian populations such as the Khmer in Cambodia and the Lao in Laos. It is interesting that G6PD Mahidol (487G > A), another common variant in continental Southeast Asian populations in Myanmar, Thailand, and Malaysia, has not been detected from the Vietnamese.

Key words: Bao Loc, glucose-6-phosphate dehydrogenase deficiency, Kinh, malaria, Vietnam

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We have introduced rapid diagnosis methods for malaria and the G6PD deficiency test in malaria endemic areas. With these methods, patients are notified of the results of the blood examination within

30 min and are able to receive anti-malaria medicine, including primaquine [1]. Primaquine can kill gametocytes, the sexual stage of malaria parasites, which are the cause of malaria transmission to mosquitoes. However, once G6PD-deficient persons take primaquine, a hemolysis attack can follow. Without G6PD, erythrocytes cannot prepare a sufficient amount of reduced pyridine nucleotide and reduced glutathione, and cannot prevent oxidant attack by primaquine. Thus, primaquine should not be administered to malaria patients before confirming their G6PD condition.

In the past, there have been many malaria endemic areas in Vietnam. Although the numbers of malaria cases and malaria endemic areas are decreasing, malaria is still a serious disease in Vietnam. It is therefore of value to introduce rapid diagnosis methods for malaria and G6PD deficiency in rural areas in Vietnam. We started the technical transfer to a general hospital in Bao Loc in 2001, and we have succeeded in transferring these methods. Local staffs can now carry out malaria diagnosis and G6PD deficiency tests by themselves in the hospital laboratory. In addition, we could obtain blood samples of malaria patients and G6PD-deficient persons with informed consent. We further conducted analysis of some genes of malaria parasites [2] and of *G6PD* of deficient persons. We here present the first report describing the genomic analysis of *G6PD* in Vietnamese.

Materials and Methods

This study was approved by the local government of Lam Dong Province, Vietnam, and the Ethical Committee of Jichi Medical University, Japan. To test G6PD activity, we adopted Fujii's method [3]. This method is useful for testing hundreds of blood samples per day, although it is difficult to distinguish full activity from 50% residual activity in female samples [4]. We therefore concentrated only on males in the study.

Between 1997 and 2003 at Bao Loc General Hospital in Lam Dong Province, located 100 km from the border of Cambodia, blood samples (2 ml) were collected from malaria patients to investigate glucose metabolism [5] and genomic variations of *Plasmodium falciparum* [2]. Beginning in 2001, informed consent was obtained from each blood donor, allowing investigation of not only malaria DNA but also other hereditary abnormalities in each patient's own genes. In 2003, we began to expand the study population to outpatients who consulted the hospital for common diseases because the number of malaria patients was reduced. Blood samples (0.5 ml) were collected only from outpatients consenting to the test of G6PD activity followed by *G6PD* analyses.

Blood samples were stored at −20°C until the G6PD activity test. When more than 100 samples were collected, we conducted the G6PD activity test using Fujii's method [3]. When we found G6PD-deficient samples, we extracted genomic DNA from 0.1 ml of whole blood with a DNA purification kit (Amersham Pharmacia Biotech, Buckinghamshire, UK). Since genomic *G6PD* consists of 13 exons, we prepared primers for these exons [6] as shown in Table 1, amplified each exon by PCR, and read the

Table 1 Origonucleotide primers for PCR

Exon	Name, Sequence and Location of SENSE primers		Name, Sequence and Location of ANTISENSE primers		Product length (bp)
2	1a	5'-AGACCCCAGAGGAACTCTCAAGAAA (Intron 1)	2b	5'-TGCAACAATTAGTTGGAAAAGCTGA (Intron 2)	294
3 & 4	B1a	5'-TGTCCCCAGCCACTTCT (Intron 2)	B2	5'-CCGAAGCTGGCCATGCTGGG (Intron 4)	358
5	B3	5'-ACACACGGACTCAAAGAGAG (Intron 4)	B2a	5'-TGGTGGGAGCACTGCCTG (Intron 5)	343
6	B5	5'-AGCTCTGATCCTCACTCCCC (Intron 5)	8b	5'-GGCCAGGTGAGGCTCCTGAGTA (Intron 6)	285
7	7a	5'-ACATGTGGCCCCTGCACCACA (Intron 6)	B6	5'-GTGACTGCTCTGCCACCCTG (Intron 7)	242
8	9a	5'-TTGGGGTCCCCATGCCCTTG (Intron 7)	B8	5'-TGCCTCGTCACAGATGGGCC (Intron 8)	231
9	B9a	5'-ACCCAAGGAGCCCATTC (Intron 8)	R2	5'-ACACAGGGCATGCCCAGTTCTG (Intron 9)	276
10	E	5'-CTGAGAGAGCTGGTGCT (Intron 9)	B10	5'-CACCATGTGGAGTCCCCCGG (Intron 10)	342
11&12	B11	5'-ACTCCACATGGTGGCAGGCAG (Intron 10)	B12	5'-ATGAGGTAGCTCCACCCTCA (Intron 12)	397
13	RB12	5'-TGAGGGTGGAGCTACCTCAT (Intron 12)	18a	5'-CGGGGGTGGAGGTGGGTGCCCA (Intron 13)	164

DNA sequence (ABI PRISM 310; Applied Biosystems, Foster City, CA, USA). Both strands of each exon were sequenced. To indicate the mutation point, the nucleotide number of the cDNA sequence was used. We also read some introns of *G6PD* because silent mutations had been found on introns of genomic *G6PD*; *e.g.* nt175C > T on intron 7, nt163C > T on intron 8 [7] and nt93T > C on intron 11 [8].

Results

From 1997 to 2003, we collected 362 blood samples from malaria patients. We added 742 blood samples from outpatients in 2003 and 2004.

Among the samples, 88.9% (981/1104) were from the Kinh. The K'Ho (10.3%, 114/1104), Chauma (0.5%, 5/1104), Nung (0.3%, 3/1104), and Tay (0.1%, 1/1104) were minorities. The incident rates of G6PD deficiency in the Kinh and the K'Ho were 1.9% and 4.4%, respectively (Table 2). Among malaria patients, 12 samples showed G6PD deficiency (3.3%, 12/362). Among samples from outpatients with common diseases, 13 samples showed G6PD deficiency (1.8%, 13/742). There was no significant difference between these 2 incidence rates. Together with those 2 groups, the incidence rate of G6PD deficiency was 2.3% (25/1104) in Lam Dong Province, Vietnam (Table 2).

We analyzed the *G6PD* genes of G6PD-deficient persons. Table 3 shows the frequency of G6PD mutations in 25 samples. G6PD Viangchan (871G > A, 1311C > T and intron 11 nt93T > C) was the most frequent mutation, but 6 other mutations were also detected. In particular, we found a novel G6PD mutation with a single nucleotide change at 352T > C (Fig. 1). Amino-acid change was predicted as 118

Table 2 The incidence of glucose-6-phosphate dehydrogenase (G6PD) deficiency in 5 ethnic groups in Lam Dong Province, Vietnam

	Ethnic group					
	Kinh	K'Ho	Chauma	Nung	Tay	Total
No. of sample	981	114	5	3	1	1,104
No. of deficiency	19	5	0	1	0	25
Incidence (%)	1.9%	4.4%				2.3%

Table 3 Glucose-6-phosphate dehydrogenase (G6PD) variants in 3 ethnic groups in Lam Dong Province, Vietnam

Nucleotide change	Amino acid change	Name of variant	Ethnic group			
			Kinh	K'Ho	Nung	Total
95A > G	32H > R	Gaohe	1	0	1	2
352T > C	118Y > H	Bao Loc*	1	0	0	1
392G > T	131G > V	Quing Yuan	1	0	0	1
871G > A	291V > M	Viangchan**	6	5	0	11
1360C > T	454R > C	Union***	2	0	0	2
1376G > T	459R > L	Canton	5	0	0	5
1388G > A	463R > H	Kaiping	3	0	0	3
Total			19	5	1	25

* New variant being reported in the present study.
** In each case, 2 more nucleotide changes, a nonsense mutation of 1311C > T on exon 11 and a mutation of nt93T > C on intron 11, were confirmed. Note: There is a variant named G6PD Jammu, which has a change of 871G > A, but 1311C on exon 11 and nt93T on intron 11 are the wild type [33].
*** In each case, one more nucleotide, 99A in the exon 2, was confirmed. Note: There is a variant named G6PD Honiara, which has double mutations of 99A > G and 1360C > T [29].

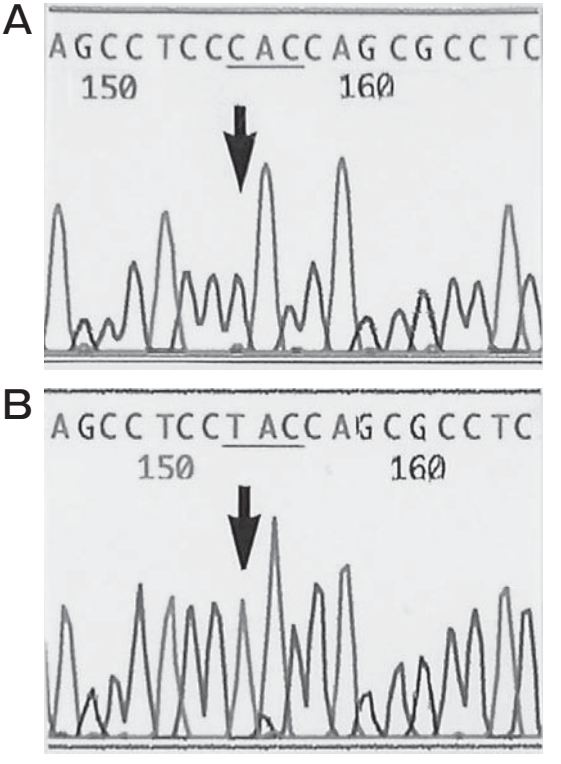

Fig. 1 **A**, A part of the DNA sequence on exon 5 of a male with glucose-6-phosphate dehydrogenase (G6PD) Bao Loc, hemizygote; **B**, A part of the DNA sequence on exon 5 of a normal control. Arrows show 352T > C and 352T.

Tyr > His. G6PD activity was estimated at less than 10% residual activity. There was no other mutation detected in his *G6PD*. The subject was 14 months old and had been brought to the hospital with an acute pharyngitis. The hemoglobin level was relatively low (9.3 g/dl), but he did not have chronic hemolytic anemia. Thus, we classified his condition as Class II, less than 10% residual activity without chronic hemolytic anemia, as defined by the WHO working group [9]. We named this new mutation G6PD Bao Loc (GenBank database accession number: DQ839546). All of the other six G6PD mutations found during this work have also been categorized as Class II.

Discussion

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most frequent hereditary disorders in the world. Since the G6PD gene is located on the X chromosome, G6PD activity is drastically reduced (less than 10% residual activity) in males with G6PD abnormality. In females, only homozygous persons show complete G6PD deficiency, and G6PD activities vary greatly in heterozygous persons. The G6PD gene consists of 13 exons. The size of the open reading frame is 1,545 base pairs [10]. Most G6PD deficiency is caused by a single nucleotide change, resulting in 1 amino-acid change. One hundred forty mutations causing G6PD deficiency have been reported thus far [11].

The distribution of G6PD mutations in Southeast Asian countries differs in each country. For exanmple, in Myanmar, more than 90% of G6PD-deficient cases are G6PD Mahidol (487G > A), and there are no cases of G6PD Viangchan (871G > A, 1311C > T, and intron 11 nt93T > C) [12]. In contrast with Myanmar, more than 90% of G6PD-deficient cases in Cambodia are G6PD Viangchan, and there are no cases of G6PD Mahidol [13, 14]. When we investigated G6PD deficiency in Indonesia, we found 7 different G6PD mutations even on a small island [15, 16]. Other groups have reported finding several G6PD variants in the Thai population [17], Malaysian population [18], and Chinese population [19]. In terms of G6PD-deficient people, Myanmarese and Cambodian people are derived from homogenous ancestries, but Indonesian, Thai, Malaysian, and Chinese people are from various ancestries.

In Vietnam, the frequency of G6PD deficiency is reported to be 1.4–4.1% [20]. Thus, it is likely that the incidence of G6PD deficiency was approximately 2.3% in our present study. However, if we compare the incidence rates in terms of malaria endemic areas, the rate (2.3%) is lower than those in other Southeast Asian countries. According to our previous observation, the rates of G6PD deficiency are 10.5% (45/430) in Myanmar, 3.9% (25/648) in Indonesia [21], and 8.1% (29/360) in Cambodia [14]. The incidence of G6PD deficiency and endemicity of malaria are thought to correlate with each other [22]. There is a hypothesis that G6PD-deficient red blood cells are more tolerant of malaria parasites of *Plasmodium falciparum* [23]. Places in Myanmar, Indonesia, and Cambodia where we examined G6PD activity are all malaria endemic areas. For instance, positive rates of malaria are 45.8% (298/650) in Myanmar, 43.4% (308/709) in Indonesia [21], and 24.9% (167/670) in Cambodia [14]. Compared to these high rates, those in our observation area in Lam Dong Province are not as high. We have found similar results in North Sumatra, Indonesia. The incidence of G6PD deficiency was 4.6% (21/458) in malaria endemic areas, but was 0.9% (1/110) in non-malaria endemic areas [24].

Vietnamese are composed of more than 50 ethnic groups. The Kinh is the largest ethnic group, accounting for approximately 90% of the Vietnamese population [25]. In the present study, the tendency was similar because 88.9% of the blood samples were from ethnic Kinh. Even in the same ethnic group, we found 7 different mutations in 19 persons with G6PD deficiency. G6PD Viangchan was the most frequent mutation in the Kinh population. As shown in Fig. 2, this variant is very common in Laos [26] and Cambodia [13, 14], and it may be from the Khmer, which is the largest ethnic group in Southeast Asian countries.

Furthermore, G6PD Gaohe (95A > G), G6PD Quing Yuan (392G > T), G6PD Canton (1376G > T), and G6PD Kaiping (1388G > A) were also detected in the Kinh population, and their total frequency reached 52.6% (10/19). These variants are commonly found in Chinese [19]. It is well known that Vietnam has had a strong historical connection with China for 2,000 years. Until recently, marriages

between the Kinh and Chinese have not been rare. Thus, it is easily estimated that the G6PD variant of Chinese origins were introduced into the Kinh population and shared with G6PD Viangchan, reflecting another old ancestral source, for Southeast Asian populations.

G6PD Union is dominantly found in countries in the Pacific Ocean such as the Philippines [27], Papua New Guinea [28], Solomon Islands [29], and the Vanuatu archipelago [30]. Two cases of this variant were also detected among the Kinh. These results suggest that the Kinh ethnic group has several different ancestral sources, including the Khmer, Chinese, and people from the Pacific Ocean.

In contrast, all 5 cases detected in the K'Ho were G6PD Viangchan. In Laos [26] and Cambodia [13], more than 90% of G6PD-deficient cases are G6PD Viangchan, and this tendency is the same in the 2 minorities (the Tum Pun and the Cha Ray) in Cambodia [14]. In Vietnam and Cambodia, these minorities have remained isolated from each other and have not until recently intermarried with other tribes. Thus we suspect that G6PD Viangchan was introduced in Southeast Asian countries in an old era, more than 1,000 years ago, and the K'Ho, the Khmer, and the Lao were separated after this variant was introduced in their original tribe.

The Kinh people might obtain deferent genes by intermarrying with other populations from China and Oceania. It is interesting to note that there were no Kinh people showing G6PD Mahidol, which is another common G6PD variant distributed in continental Southeast Asian countries of Myanmar, Thailand, and Malaysia. This variant has not yet reached Cambodia, Laos, and Vietnam.

In the present study, we adopted Fujii's method, which makes it difficult to distinguish full activity from 50% residual activity in female samples. However, new rapid G6PD tests are currently being developed to detect samples with 50% residual activity [31, 32]. With these methods, we may detect heterozygous G6PD deficiency among female blood

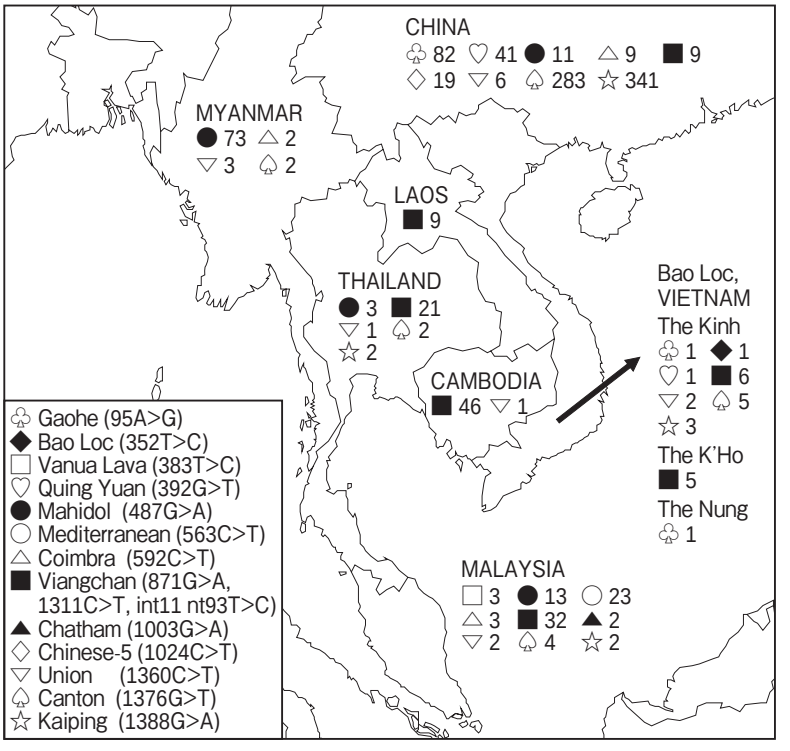

Fig. 2 Distribution and frequencies of glucose-6-phosphate dehydrogenase (G6PD) variants in Southeast Asian countries. Each number indicates the number of G6PD-deficient cases confirmed by sequence analysis. Data for Myanmar, Laos, and Cambodia are from our previous reports [12, 14, 26]. Data for Thailand [17], Malaysia [18], and China [19] are from other group's reports.

samples. In further studies, we should carry out genetic analysis of female cases of G6PD deficiency.

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