Thalassemia and hemoglobinopathies in an ethnic minority group in Central Vietnam: implications to health burden and relationship between two ethnic minority groups

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Abstract Thalassemia is a genetic condition that can result in long and expensive treatments, and severe thalassemia may lead to death if left untreated. Couples contributing two genes for thalassemia place their children at particular risk for severe thalassemia. Gene frequency of thalassemia varies in Vietnam, but presents remarkably high levels among some ethnic minority groups. Limited information about thalassemia frequency makes prevention and control of thalassemia difficult. This study aimed to determine gene frequency of certain types of thalassemia among 390 women of reproductive age of the Ta-Oi ethnic minority. Hemoglobin and DNA analyses were carried out to diagnose thalassemia and hemoglobinopathies. Of the total participants, 56.1% (95% CI = 51.1–61.1) carried thalassemia genes. A remarkably high frequency of hemoglobin Constant Spring (Hb CS) of 23.8% (95% CI = 19.7–28.4) was noted. The frequency of α^+ -thalassemia (–3.7 kb deletion) was 26.4% (95% CI = 22.1–31.1), while hemoglobin E (Hb E) and hemoglobin Paksé (Hb Ps) were identified at frequencies of 14.6 (95%

CI = 11.2–18.5) and 2.6% (95% CI = 1.4–5.0), respectively. Further analysis of α -globin gene haplotype revealed the same Hb CS haplotype (+ – M + + –) as of the Co-Tu minority, a neighboring minority of the Ta-Oi, indicating that these two minorities may share the same ancestors. This information will be helpful for further studies in population genetics, as well as the development prevention and control program in the region.

Keywords Thalassemia · Hemoglobinopathies · Hemoglobin Constant Spring · α -Globin gene haplotype · Ethnic minority · Vietnam

Introduction

Thalassemia is an inherited disorder of hemoglobin (Hb) synthesis that results in reduced or absent globin chain production. All individuals may carry the gene without manifesting symptoms (Weatherall and Clegg 2001a). Couples in which both male and female have the thalassemia gene are at particularly high risk for having children with severe thalassemia disease. Premarital and antenatal screening programs could be highly effective in minimizing the risk by forewarning future parents; prenatal screening could be used to identify risks in pregnant women. Various interventions could be designed for high-risk populations once they are identified.

In Southeast Asia, thalassemia and hemoglobinopathies are common, with the prevalence range of 10–30% for all forms of α -thalassemia (α -thal), 3–9% for β -thalassemia (β -thal), and 1–53% for hemoglobin E (Hb E) (Weatherall and Clegg 2001b). Other α -thalassemic Hb variants commonly found in this region include hemoglobin Constant Spring (Hb CS) and hemoglobin Paksé (Hb Ps). The prevalence of these two forms has been well established in northeast Thailand and in Vientiane, the capital city of Laos, with a prevalence of

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approximately 5–10% for Hb CS, and approximately 1–2% for Hb Ps (Fucharoen et al. 2004; Sanchaisuriya et al. 2006; Savongsy et al. 2008; Panomai et al. 2010; Tritipsombut et al. 2012). Interactions of these thalassemia genes could result in many complex thalassemia syndromes with varying severities.

Vietnam is situated in the Southeast Asia region bordered by China, Laos, and Cambodia. The population of Vietnam comprises 54 ethnic groups in which 87% are the Kinh, and the remaining are ethnic minority groups residing mostly in mountainous areas throughout the country (World Health Organization 2011). A review of published literature resulted in a few community-based studies on the distribution of thalassemia in Vietnam. A large cohort survey in the southern part of Vietnam demonstrated varying carrier rates of thalassemia among the Vietnamese population including minority groups, i.e., 13–45% for all forms of α -thal, 0–10% for β -thal, and 0–58% for Hb E (O'Riordan et al. 2010). A study conducted in Thua Thien Hue Province, Central Vietnam reported that the prevalence of thalassemia among the ethnic minorities was higher than that among the Vietnamese majority group, the Kinh (Nguyen et al. 2013). A remarkably high frequency of Hb CS of 25% was reported for the first time among the Co-Tu minority (Nguyen et al. 2014), and this poses a query concerning the situation of thalassemia among other minorities residing in the neighboring mountainous areas.

In this study, we extended a survey on thalassemia and hemoglobinopathies among women of reproductive age of the Ta-Oi, an indigenous ethnic minority in Central Vietnam. Results from this research may provide evidence for building an appropriate prevention program for thalassemia as well as for a further study on population genetics within the region.

Materials and methods

Study population

A cross-sectional study was conducted in Thua Thien Hue Province, Central Vietnam, during August to October 2015. The population of Thua Thien Hue Province includes the ethnic majority, the Kinh, and three main minority groups, i.e., Co-Tu, Ta-Oi, and Bru-Vankieu. While the Co-Tu minorities reside in the west mountainous region of Phu Loc and Nam Dong districts, the Ta-Oi minorities live mainly in the A Luoi mountainous district, where the data were collected (Fig. 1). This area is located in the Annamite Mountains which cover most of the district. Height of the mountains ranges from 500 to 1774 m. The district is located at approximate 572 m above sea level. Based on data from the Thua Thien Hue Center of Health Education and Communication, the occurrence of malaria in this region reduced dramatically during 1991–2005 from 15.8 to

0.74/100,000 populations (Hau Van Nam, personal communication).

According to the results of the 2009 Vietnam population and housing census, the total number of Ta-Oi people in Vietnam is 29,558, accounting for 4% of the Thua Thien Hue population. Ta-Oi people live predominantly in eight communes, with 5003 women of reproductive age in 2014. A sample size formula for proportion estimation in the known population was used to estimate the number of participants required. Applying a reported proportion of thalassemia of 52.7% (Nguyen et al. 2014) with 95% confidence interval (CI) at 5% marginal error, a minimum sample size was 356. A proportional to size random sampling from the district census roster was used to recruit women of reproductive age (15–49 years) for the study.

Prior to data collection, the project was announced to the Ta-Oi minority via the commune loudspeaker. Research orientation was held at the village meetinghouse. At that meeting, the research team introduced the purpose of the research, procedures, anticipated outcomes, benefits and risks of participation, and the rights of the participants. An invitation letter was also sent to 385 women who were selected by a random sampling technique. On the day of sample collection, all 385 women, and an additional five women who were interested in our project, came to participate. In total, 390 women of reproductive age participated. Women willing to participate were asked to sign an informed consent that had been approved by the university review boards. Anthropometric measurement and medical history were taken and recorded by the health workers at Commune Health Centers. Technicians from the District Health Hospital collected 2-ml venous blood into EDTA tube from all participants. Blood samples were stored at 2–6 °C before sending to Hue Central Hospital within 6 hours to determine hematological parameters. Remaining blood samples were kept on ice and transported to the Centre for Research and Development of Medical Diagnosis Laboratories (CMDL), Khon Kaen University, Thailand for further investigations. The study was approved by the Ethics Committee in Biomedical Research of Hue University of Medicine and Pharmacy, Vietnam and the Ethics Committee of Khon Kaen University, Thailand.

Hematological determinations

Complete blood count (CBC) including red blood cell (RBC) indices was measured using an automated blood cell counter (Sysmex KX-21, Sysmex Co, Kobe, Japan). Hb separation was performed by cellulose acetate electrophoresis (CAE) at alkaline pH (Helena Laboratories, TX, USA). Samples with normal Hb type (A_2A) and abnormal values of mean corpuscular volume (MCV <80 fl) and/or mean corpuscular hemoglobin (MCH <27 pg) were subject to further investigation by capillary zone electrophoresis (Capillarys II; Sebia, Lisse, France). β -Thal was diagnosed in cases with Hb A_2 >4% and MCV <80 fl (Yamsri et al. 2010, 2011). In order to

Fig. 1 Map of Thua Thien Hue Province demonstrating A Luoi District, a catchment area where the study was conducted. Star marks indicate eight communes where the Ta-Oi people live

provide information about cause of anemia to participants, all anemic cases (defined by Hb <12 g/dl) were also investigated further for serum ferritin using the Access Chemiluminescent Immunoassay Test Kit (Beckman Coulter Inc., CA, USA).

DNA analysis

Previously described gap-PCR and allele specific PCR (ASPCR) were used to identify six forms of α -thal mutations common in Southeast Asia, including SEA (NG_000006.1: g.26264_45564del19301) and THAI (NG_000006.1: g.10664_44164del33501) deletions causing α^0 -thal, -3.7 (NG_000006.1: g.34164_37967del3804) and -4.2 kb (exact deletion breakpoints are not available) deletions causing α^+ -thal, Hb CS (HBA2:c.427T>C), and Hb Ps (HBA2:

c.429A > T) (Sanchaisuriya et al. 2002; Fucharoen et al. 2003; Boonsa et al. 2004; Sae-ung et al. 2006). Based on our experience of using these methods in routine practice, the false negative rate was less than 0.1%.

To determine genetic background of Hb CS, haplotype analysis was performed using PCR-restriction fragment length polymorphism (PCR-RFLP). Six polymorphic restriction sites on the α -globin gene cluster, namely XbaI, SacI, BglI, AccI, RsaI, and α -PstI, were investigated (Jomoui et al. 2015). This analysis was done in cases diagnosed as homozygous Hb CS.

Data analysis

Statistical analysis was performed using Microsoft Office Excel 2013 and Stata software version 12 (Stata Corp, TX,

USA). Frequency of thalassemia and hemoglobinopathies was presented as percentage and 95% CI. Mean and standard deviation (SD) were calculated to describe hematological parameters. Either Student *t* test or Mann-Whitney *U* test was used to determine the difference in hematological parameters between two independent groups. *P* value <0.05 was considered a statistically significant difference.

Results

Table 1 presents the thalassemia genotypes and the corresponding hematologic features among the 390 participants. Thalassemia carriers totaled 56.1% (95% CI = 51.1–61.1%), with 17 genotypes. The prevalence of all forms of α^+ -thal was 26.4% (95% CI = 22.1–31.1%), comprising 17.2% heterozygotes and 1.5% homozygotes, and the rest were compound heterozygote for either α^+ -thal/Hb CS or α^+ -thal/Hb Ps, or coinherited with Hb E. A total of 93 (23.8%; 95% CI = 19.7–28.4%) were found to carry the Hb CS gene, of which 62 (15.9%) were heterozygous Hb CS. The homozygous state for Hb CS was found in five cases (1.3%), in which one of them also carried the Hb E gene. Compound heterozygous state and its concomitance with Hb E were also

observed. Fifty-seven (14.6%; 95% CI = 11.2–18.5%) individuals carried Hb E gene, including 52 (13.3%) heterozygotes and five (1.3%) homozygotes. All homozygous states were in agreement with Hardy-Weinberg proportions (chi-square test, *P* > 0.05). Hb Ps was also identified in 11 participants (2.8%; 95% CI = 1.4–5.0%). No α^0 -thal and β -thal were detected in this ethnic population. The only α -deletional mutation found in this investigation was –3.7 kb deletion. Neither the persistence of high-fetal Hb (so-called hereditary persistence of fetal hemoglobin; HPFH) nor $\delta\beta$ -thal was observed as none of the cases showed Hb F bands or peaks on electrophoresis.

Comparing hematological parameters between thalassemic and non-thalassemic participants revealed that while MCV and MCH values of all thalassemia genotypes were significantly lower than those of non-thalassemia, the number of RBC and the RBC distribution width (RDW) were significantly higher. Though Hb levels of all genotypes were also lower than those of non-thalassemia, these values were above the threshold used to define anemia. Of the total participants, anemia was identified in 38 cases (9.7%). Most of them (35/39) were identified as thalassemia carriers with different genotypes. Severe anemia due to iron deficiency was found in only one participant (data not shown).

Table 1 Thalassemia genotypes and corresponding hematologic features among 390 Ta-Oi women of reproductive age; values are presented as mean $\pm$ 1 standard deviation or raw data where appropriate

Type of thalassemia	N (%)	RBC ($\times 10^{12}/l$)	Hb (g/dl)	MCV (fl)	MCH (pg)	MCHC (g/dl)	RDW (%)
α -Thalassemia							
• Heterozygous α^+ -thal	67 (17.2)	4.93 $\pm$ 0.38*	13.4 $\pm$ 0.9*	83.7 $\pm$ 4.4*	27.2 $\pm$ 1.6*	32.5 $\pm$ 0.8*	14.6 $\pm$ 0.7*
• Heterozygous Hb CS	62 (15.9)	4.81 $\pm$ 0.45*	12.9 $\pm$ 1.3*	83.0 $\pm$ 4.4*	26.9 $\pm$ 1.9*	32.5 $\pm$ 1.4*	14.9 $\pm$ 1.2*
• Heterozygous Hb Ps	8 (2.05)	4.92 $\pm$ 0.14	13.4 $\pm$ 0.7	82.9 $\pm$ 4.6	27.3 $\pm$ 1.5	33.0 $\pm$ 1.0	14.5 $\pm$ 0.4
• Homozygous α^+ -thal	6 (1.54)	5.35 $\pm$ 0.44	13.1 $\pm$ 1.1	76.4 $\pm$ 5.8	24.5 $\pm$ 2.0	32.1 $\pm$ 1.3	15.1 $\pm$ 0.6
• Homozygous Hb CS	4 (1.03)	4.91 $\pm$ 0.14	12.0 $\pm$ 0.3	78.1 $\pm$ 2.8	24.4 $\pm$ 1.2	31.3 $\pm$ 2.1	16.5 $\pm$ 0.9
• Compound heterozygous α^+ -thal/Hb CS	12 (3.1)	5.11 $\pm$ 0.47	12.4 $\pm$ 1.4	77.9 $\pm$ 4.0	24.4 $\pm$ 1.6	31.3 $\pm$ 1.0	15.5 $\pm$ 0.8
• Compound heterozygous α^+ -thal/Hb Ps	3 (0.77)	5.08 $\pm$ 0.37	13.4 $\pm$ 0.9	83.0 $\pm$ 7.7	26.5 $\pm$ 3.7	31.9 $\pm$ 2.1	14.6 $\pm$ 1.2
β -thalassemic Hb variant							
• Heterozygous Hb E	30 (7.7)	5.09 $\pm$ 0.43*	13.1 $\pm$ 0.9*	77.2 $\pm$ 3.2*	25.8 $\pm$ 1.0*	33.4 $\pm$ 0.9	14.8 $\pm$ 0.4*
• Homozygous Hb E	1 (0.26)	6.22	12.0	57.0	19.3	33.8	16.5
Coinheritance of Hb E with α -thalassemia							
• Heterozygous Hb E with α^+ -thal	9 (2.3)	4.78 $\pm$ 0.56	12.0 $\pm$ 0.9	81.9 $\pm$ 5.2	27.5 $\pm$ 1.8	33.6 $\pm$ 0.9	14.6 $\pm$ 0.6
• Heterozygous Hb E with heterozygous Hb CS	8 (2.05)	4.52 $\pm$ 0.31	11.9 $\pm$ 0.8	81.9 $\pm$ 2.4	26.7 $\pm$ 1.8	32.6 $\pm$ 1.8	14.6 $\pm$ 0.9
• Heterozygous Hb E with α^+ -thal/Hb CS	3 (0.77)	5.03 $\pm$ 0.42	12.0 $\pm$ 0.6	74.6 $\pm$ 1.4	23.5 $\pm$ 0.5	31.5 $\pm$ 0.7	14.9 $\pm$ 0.3
• Heterozygous Hb E with homozygous α^+ -thal	1 (0.26)	5.83	13.4	72.1	23.0	31.9	16.2
• Heterozygous Hb E with homozygous Hb CS	1 (0.26)	4.67	10.7	76.3	22.9	30.1	16.5
• Homozygous Hb E with heterozygous α^+ -thal	1 (0.26)	5.83	13.0	65.4	22.3	34.0	17.5
• Homozygous Hb E with heterozygous Hb CS	2 (0.51)	5.28, 5.21	10.5, 11.2	61.0, 63.7	19.9, 21.5	32.5, 33.7	17.1, 18.2
• Homozygous Hb E with α^+ -thal/Hb CS	1 (0.26)	5.37	8.8	57.4	16.4	28.5	18.0
Non-thalassemia	171 (43.7)	4.65 $\pm$ 0.4	13.8 $\pm$ 1.1	89.0 $\pm$ 4.8	29.8 $\pm$ 1.9	33.5 $\pm$ 1.0	14.3 $\pm$ 0.7

*Significantly differed from non-thalassemia

As a further validation of the hypothesis that Hb CS is more prevalent in certain ethnic minorities, the gene frequency of each thalassemia was calculated and compared with that reported in Co-Tu minorities, which are neighboring minorities of the Ta-Oi. As shown in Table 2, allele frequency of Hb CS obtained in this study did not differ from the Co-Tu. Gene frequencies of Hb E and Hb Ps were also comparable. α^0 -Thal was not found in either group. However, gene frequency of α^+ -thal among the Ta-Oi was significantly higher than that of the Co-Tu. Further haplotype analysis of α -globin gene among the five participants with homozygous Hb CS revealed a single haplotype (+ − M + + −). Hematologic features and results of haplotype analysis of these five cases are shown in Table 3.

Discussion

Within the field of mother and child care, consideration of genetic diseases should no longer be the domain of a few experts in high-income countries, but should be considered by health authorities to be a public health problem also in the rest of the world. Due to global migration, thalassemia and hemoglobinopathies are now spreading throughout the world and have become a serious burden for healthcare systems (Williams and Weatherall 2012). Not only the patients suffer from health problems but also their families suffer mentally and economically from a requirement of long-term medical care. Therefore, a number of countries have initiated prevention programs aiming at decreasing the incidence of severe thalassemia diseases. Such a program does not exist in several low-middle income countries including Vietnam. Collection of local information on epidemiology and health burdens is one of the prerequisites for implementation of effective prevention measures.

The burden of thalassemia disease varies depending on ethnicity. It has been documented in Vietnam that the prevalence of thalassemia and hemoglobinopathies is particularly high among minority groups (O'Riordan et al. 2010; Nguyen et al. 2013, 2014). The Ta-Oi minorities live mainly in mountainous areas of A Luoi District of Thua Thien Hue and Huong Hoa District in Quang Tri Province (Dang et al. 2000). As predicted, various thalassemia genotypes were identified among the Ta-Oi. The most common forms of thalassemia included α^+ -thal (−3.7 kb deletion), Hb CS, and Hb E. Interaction of these three forms led to the finding of several complex genotypes including compound heterozygous states for α^+ -thal/Hb CS and coinheritance of Hb E with various forms of α -thal. Nevertheless, none of them resulted in severe clinical manifestations based on hematologic features presented in Table 1. It should be noted that by using the criteria of Hb <12 g/dl (World Health Organization 2008), most participants had no anemia. However, microcytosis was observed among those with heterozygous Hb E as well as those with homozygous states for α^+ -thal and Hb CS. A marked reduction in MCV and MCH with mild anemia was observed in all forms of Hb E homozygotes. These hematologic changes were consistent with our previous studies (Sanchaisuriya et al. 2003, 2006; Fucharoen et al. 2004, 2006; Savongsy et al. 2008; Wongprachum et al. 2016). Based on hematological parameters reported here, anemia seems not to be a major health burden in this minority group.

It is of great importance to mention that severe thalassemia syndromes including homozygous α^0 -thal, homozygous β -thal, and β -thal-Hb E diseases may not cause public health problems for this community because α^0 -thal and β -thal were not found. Instead, we found the remarkably high frequency of Hb CS of 0.125 with the overall prevalence around 24%, of which 1.3% (5/390) were Hb CS homozygotes. These five cases were apparently healthy with normal BMI. Neither jaundice nor splenomegaly was observed. Their hematologic

Table 2 Allele frequency of thalassemia among 390 Ta-Oi women of reproductive age, in comparison to that of the Co-Tu minority

Thalassemia type	Ta-Oi minority (total allele = 780)		Co-Tu minority (total allele = 596) ^a		P value
	No. of alleles	Gene frequency (95% CI)	No. of alleles	Gene frequency (95% CI)	
Hb CS	98	0.126 (0.103–0.151)	85	0.143 (0.116–0.173)	0.361
α^+ -Thal ^b	110	0.141 (0.117–0.167)	34	0.057 (0.040–0.079)	<0.001
Hb E	62	0.079 (0.061–0.101)	43	0.072 (0.053–0.096)	0.609
Hb Ps	11	0.014 (0.007–0.025)	1	0.0017 (0.000–0.009)	N/A
β -Thal	None	None	2	0.0034 (0.000–0.012)	N/A
α^0 -Thal	None	None	None	None	–

^a Data from Nguyen et al. (2014)

^b −3.7 kb deletion

N/A not applicable due to small samples

Table 3 Hematologic features and results of haplotype analysis of the five participants with homozygous Hb CS

No.	Age (years)	BMI (kg/m ²)	Thal genotype	Hematological parameters						α -Globin gene haplotype					
				RBC ($\times 10^{12}/l$)	Hb (g/dl)	MCV (fl)	MCH (pg)	MCHC (g/dl)	RDW (%)	Xba I	Bgl I	S/M/L	Acc I	Rsa I	α Pst I
1.	30	18.8	Homo. Hb CS	4.86	12	81.7	24.7	30.2	16.5	+	–	M	+	+	–
2.	33	21.0	Homo. Hb CS	5.11	11.6	78.8	22.7	28.9	17.4	+	–	M	+	+	–
3.	25	22.2	Homo. Hb CS	4.90	12.2	75.6	24.9	32.9	15.3	+	–	M	+	+	–
4.	32	23.7	Homo. Hb CS	4.78	12.1	76.1	25.3	33.2	16.6	+	–	M	+	+	–
5.	20	24.9	Hb E trait with homo. Hb CS	4.67	10.7	76.3	22.9	30.1	16.5	+	–	M	+	+	–

BMI body mass index, Homo. Hb CS homozygous Hb CS

features were normal or mild microcytic anemia (Table 3). As for this study, a community-based survey conducted previously in the Co-Tu minority disclosed the markedly high frequency of Hb CS of 25%, and the apparently healthy individuals with Hb CS homozygotes were observed (Nguyen et al. 2014). Inconsistent with our findings, hospital-based studies reported clinical manifestations of hemolytic anemia among homozygous Hb CS patients (Schrier et al. 1997; Noguera et al. 2000; Viprakasit et al. 2004). Combining these contradictory findings together, it is likely that there might be some other factors responsible for the varying severities of the disease. Further in-depth research of this issue in the two populations is needed.

As the Ta-Oi, a neighboring minority of the Co-Tu, has a tradition of marrying into neighboring minorities (Schliesinger 2003), this might be the reason explaining the similarly high frequency of Hb CS in the study group. A previous study on α -globin gene haplotype associated with Hb CS among the Co-Tu discovered a single α -globin gene haplotype (+ – M + + –) (Jomoui et al. 2015). The same haplotype was also found among the five Ta-Oi subjects with homozygous Hb CS (a total of 10 Hb CS conferring chromosomes) (Table 3); the data indicate a single founder effect of Hb CS genes in these two minority groups. Interestingly, Jomoui et al. (2015) also demonstrated that this particular haplotype was found predominantly among Laotian Hb CS carriers. Considering the fact that both Co-Tu and Ta-Oi are residents in mountainous areas of Central Vietnam and Southeastern Laos (Gehrmann and Conver 2015), it might be possible that the relatively lower frequency of Hb CS found among the Kinh and Laotian populations may arise from these minorities.

Comparing gene frequencies of other thalassemia types, it was noticed that the frequency of α^+ -thal found among the Ta-Oi minorities was significantly higher than that of the Co-Tu (Table 2). Also, this α^+ -thal frequency differed from those reported in southern Vietnam, Laos, and Thailand (O'Riordan et al. 2010; Tritipsombut et al. 2012). Several reasons including the founder effect and population migration may explain the unequal distribution of gene frequencies among different populations, even within the same country. In addition, as explained in many reports, the existing high frequencies of thalassemia genes may reflect natural selection of these alleles that protect the population from severe malaria, as well as the longstanding practice of consanguineous marriage (Williams and Weatherall 2012).

This study has limitations such as that the spectrum and frequency of thalassemia reported here are limited to only certain types of thalassemia commonly found in this region. Atypical β -thal carriers (those with high-Hb A₂ level but normal hematologic features) may not be detected as only cases with low MCV <80 fl were selected for further investigation. However, such cases appear to be rare. Based on our data

collected independently from several communities (Fucharoen et al. 2004; Sanchaisuriya et al. 2006; Savongsy et al. 2008; Panomai et al. 2010; Tritipsombut et al. 2012; Wongprachum et al. 2016), only 0.09% (2/2329) of individuals with normal MCV had elevated Hb A₂. Nonetheless, our study provides evidence supporting the remarkably high Hb CS in ethnic minority groups in Central Vietnam. Given that thalassemia types found among this minority group are not of clinical significance, interaction of these thalassemia with α^0 -thal and/or β -thal could lead to the occurrence of several forms of thalassemia diseases, including severe Hb H-CS and Hb E- β -thalassemia diseases. This might occur at national or international level due to population migration. As Vietnam is an ethnically diverse country, up until now, epidemiological information on thalassemia is available for just a few minority groups. To develop an appropriate prevention program, more research is needed. Basic epidemiological information on thalassemia provided here will be helpful for further studies in population genetics, as well as the development of thalassemia prevention in the future.

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Compliance with ethical standards The study followed standard guidelines for human research ethics and has been approved by the Institution Review Boards of both Vietnam and Thailand. Written informed consent was received from all participants.

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Conflict of interest The authors declare that they have no conflict of interest.

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