



# Increased Prevalence of Thalassemia in Young People in Korea: Impact of Increasing Immigration

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**Background:** Thalassemia is highly prevalent in Southeast Asia but is rare in Korea; however, Southeast Asian immigrant population is recently rising in Korea. We investigated the prevalence of thalassemia in Korea in the context of increasing immigration.

**Methods:** This prospective, observational, multicenter study was conducted between September 2015 and August 2017. A total of 669 subjects <30 years living in Korea were grouped into the multiethnic (N=314) and Korean (N=355) groups. Hb electrophoresis and complete blood count (CBC) were performed. If low mean corpuscular volume with high red blood cell distribution width coefficient of variation or a high fetal Hb (HbF) or Hb alpha 2 (HbA<sub>2</sub>) level was observed, genetic testing of the  $\alpha$ - and  $\beta$ -globin genes was performed. In addition, the number of potential thalassemia carriers in Korea was estimated by multiplying the prevalence of thalassemia in a specific ethnicity by the number of immigrants of that ethnicity.

**Results:** Twenty-six multiethnic and 10 Korean subjects showed abnormal results for Hb electrophoresis and CBC. Eighteen multiethnic subjects and four Korean subjects were tested for  $\alpha$ -globin and  $\beta$ -globin gene mutations. Within the multiethnic group, five subjects (1.5%) were  $\alpha$ -thalassemia carriers, and six (1.9%) were  $\beta$ -thalassemia minor. The SEA deletion in *HBA1* and *HBA2*, and c. 126\_129delCTTT (*p*.Phe42Leufs\*19) mutation of *HBB* were the dominant inherited mutations.

**Conclusions:** The prevalence of thalassemia in young people in Korea is increasing due to the increasing number of Southeast Asian immigrants.

**Key Words:** Prevalence, Thalassemia, Genetic testing, Korea, Immigrants

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## INTRODUCTION

Thalassemia is a genetic disorder with mutations in the  $\alpha$ -globin (chromosome 16) or the  $\beta$ -globin (chromosome 11) gene, and results in a lack of the affected globin chain but accumulation of

the unaffected one, which creates globin chain imbalance. Consequently, ineffective erythropoiesis, damage to erythroid membranes, and obstruction of the spleen can occur, accelerating hemolytic anemia or disorders of hematopoiesis [1, 2].

Thalassemia is a serious health problem worldwide, especially

in the Mediterranean region, Southeast Asia, and Southern China [1, 3, 4]. In 2008, approximately 20% of the world population carried  $\alpha^+$  thalassemia, and 5.2% of the population carried a significant variant of the Hb disorder, including  $\beta$ -thalassemia and  $\alpha^0$ -thalassemia [1]. Annually, 23,000 cases of  $\beta$ -thalassemia major are diagnosed in newborn infants, and there are 80 million carriers of  $\beta$ -thalassemia worldwide [2]. Approximately 56,000 infants are born annually with severe  $\alpha$ - or  $\beta$ -thalassemia, more than half of whom require regular transfusion. Approximately 5,500 annual prenatal deaths are due to hydrops fetalis caused by  $\alpha$ -thalassemia major [5].

Because of population migration and transition in recent years, thalassemia patients and carriers are distributed worldwide. The prevalence of thalassemia in Korea was extremely low [6], but the number of immigrants in Korea is increasing. In 2017, there were a total of 2,180,498 immigrants (Chinese: 46.7%, Vietnamese: 7.8%, Thai: 7.0%, and Filipino: 2.7%) in Korea, constituting approximately 4% of the total population [7]. Since thalassemia is a highly prevalent inherited disorder in the Southeast Asian population, its prevalence may increase in Korea in the near future. Hence, epidemiological studies evaluating the prevalence of thalassemia in Korea are necessary, especially since

no such studies have been conducted to date.

We investigated the prevalence of thalassemia in Korea in the context of increasing immigration. Our findings could inform guidelines on the diagnosis and management of thalassemia in Korea to improve public health services.

## METHODS

### Subjects

This was a prospective and observational multicenter study. Between September 2015 and August 2017, we recruited a total of 669 healthy subjects and patients <30 years from seven Korean hospitals: Pusan National University Hospital, Busan; Busan National University Yangsan Hospital, Yangsan; Chonnam National University Medical School, Gwangju; Chonbuk National University Hospital, Junju; Dong-A University Hospital, Busan; Kosin University Gospel Hospital, Busan, and Busan St. Mary Hospital, Busan. Subjects or their parents identified their ethnicity. Subjects were divided into the multiethnic (either or both parents of foreign ethnicity; N=314) or Korean group (both parents of Korean ethnicity; N=355). In the multiethnic group, 80.8% (N=254) had one or more parents who came from Asia. We ex-

**Table 1.** Characteristics of the study subjects

		Multiethnic group (N=314)	Korean group (N=355)	
Age (yr)	Median (range)	13 (0–30)	14 (0–30)	
Sex	Female	147	154	
	Male	167	201	
Hematologic test [median (range)]	Hemoglobin (mmol/L)	8.19 (3.85–11.98)	8.07 (3.29–10.74)	
	MCV (fl)	84.9 (57.2–128.2)	85.3 (65.3–119.3)	
	RDW-CV (proportion of 1.0)	0.132 (0.112–0.243)	0.128 (0.114–0.236)	
Hemoglobin electrophoresis [median (range)]	HbA (%)	97.1 (8.9–98.6)	96.2 (46.8–97.9)	
	HbA <sub>2</sub> (%)	2.6 (0–6.1)	2.7 (0.2–3.9)	
	HbF (%)	0 (0–91.1)	0 (0.0–52.2)	
Ethnicity of parents	Southeast Asian	Vietnamese	95	0
		Thai	11	0
		Filipino	13	0
		Cambodian	22	0
		Other	11	0
	Northeast Asian	Chinese	37	0
		Other	11	0
	South Asian, Central Asian, Southwest Asian		54	0
European, American, African, Oceanian		61	0	

Abbreviations: HbF, fetal Hb; HbA<sub>2</sub>, Hb alpha 2; HbA, adult hemoglobin; MCV, mean corpuscular volume; RDW-CV, red blood cell distribution width coefficient of variation.

cluded subjects with ambiguous parental ethnicity, incomplete laboratory test results, or parents known to have hematological malignancies. Subjects' characteristics are described in Table 1. There were no differences in parameters between the two groups.

The study protocol was approved by the Institutional Review Board of Pusan National University Hospital (H-1509-001-033). The board decided this study was exempted from the requirement for informed patient or guardian consent when residual serum samples were obtained from subjects during routine testing. The subjects who underwent the genetic testing or their guardians provided written informed consent.

### Hematologic testing

Peripheral blood was collected into EDTA-containing tubes, and complete blood count (CBC) was tested simultaneously using an automated cell counter (Sysmex XN-3000; Sysmex, Kobe, Japan). Hb, mean corpuscular volume (MCV), and red blood cell (RBC) distribution width coefficient of variation (RDW-CV) were recorded. An MCV <70 fL and an RDW-CV >14% were classified as abnormal findings. The tests were performed at the recruiting hospital for each subject.

### Hb Electrophoresis (EP)

Hb EP was performed on the hemolysate of packed RBCs from blood samples obtained as described above at one core laboratory in Pusan National University Hospital. A complete Hb profile was obtained by capillary zone electrophoresis using CAPILLARYS 2 (Sebia, Lisses, France), as per the manufacturer's instructions. Hemolysis was performed by mixing 18  $\mu$ L of whole blood with 90  $\mu$ L of alkaline hemolyzing solution (pH 9.4), and the sample was injected by aspiration at the anodic end of the capillary. Hb was separated according to mass:charge ratio under a constant voltage for eight minutes. Hb was detected at 415 nm, resulting in interpretable electropherograms. Electrophoresis quality was tested using the Hb alpha 2 (HbA<sub>2</sub>) and AFSC commercial control materials (catalog number: PN 4,779) (Sebia). HbA<sub>2</sub> >3.5% was considered abnormal. In subjects older than two years, fetal Hb (HbF) >1.2% was considered abnormal, while in those younger than two years, an age-appropriate reference HbF range was used [8].

### Genetic testing

Thalassemia was confirmed by genetic testing in subject with low MCV, high RDW-CV, or high HbF and HbA<sub>2</sub> levels. Genetic testing was not performed if consent was not obtained or if the amount of sample was insufficient.

Genomic DNA was prepared from whole blood using the Quick-Gene DNA whole blood kit S (Kurabo Industries, Osaka, Japan). The DNA samples were stored at -80°C until genetic testing. For  $\beta$ -thalassemia, *HBB* whole gene sequencing was performed. For  $\alpha$ -thalassemia, *HBA1* and *HBA2*-specific PCR and sequence analysis, multiple ligation-dependent probe amplification (MLPA), and gap-PCR for deletion analysis were performed. All subjects were tested using MLPA. When MLPA result was  $-\alpha 3.7$ ,  $-\alpha 4.2$ , --SEA (South-East Asian) type deletion of *HBA1* and *HBA2* genes, gap-PCR was performed. When the MLPA result was negative, sequence analysis was performed.

MLPA was performed using the P140 HBA -C1 Kit (MRC, Holland, Amsterdam, The Netherlands). Amplified products were analyzed using an ABI 3100 analyzer (Applied Biosystems, Foster City, CA, USA) with GeneMarker software version 1.5.1 (Soft-Genetics, State College, PA, USA). Peak heights were normalized, and a deletion or duplication was identified when the normalized peak ratio value was null or two for male subjects.

Sequencing was performed on an ABI 3730 analyzer (Applied Biosystems) using a BigDye Terminator version 3.1 Cycle Sequencing Kit (Thermo Fisher Scientific, Rochester, NY, USA). The sequences were analyzed using SeqScape version 2.5 (Applied Biosystems) and Mutation Surveyor version 3.25 (SoftGenetics). We designed the primer sets using *HBA1* (National Center for Biotechnology Information (NCBI) RefSeq: NC\_000016.8, NM\_000558.3), *HBA2* (NC\_000016.8, NM\_000517.3), and *HBB* (NC\_000011.8, NM\_000518.4) DNA sequences. The mutations have been reported according to HbVar: a Database of Human Hemoglobin Variants and Thalassemias [9]. Tests were performed at one core laboratory in Seoul National University Hospital.

### Estimation of potential thalassemia carriers in Korea

The number of potential thalassemia carriers in Korea was estimated by multiplying the prevalence of thalassemia in a specific ethnicity by the number of immigrants of that ethnicity. Potential carriers were analyzed for more than 100,100 immigrants categorized by ethnicity. Information on the number of immigrants was extracted from demographic statistics published by the Ministry of Justice [7], and the prevalence of thalassemia in Chinese [4], Vietnamese [10], Thai [11], and American [5] populations was obtained from the literature.

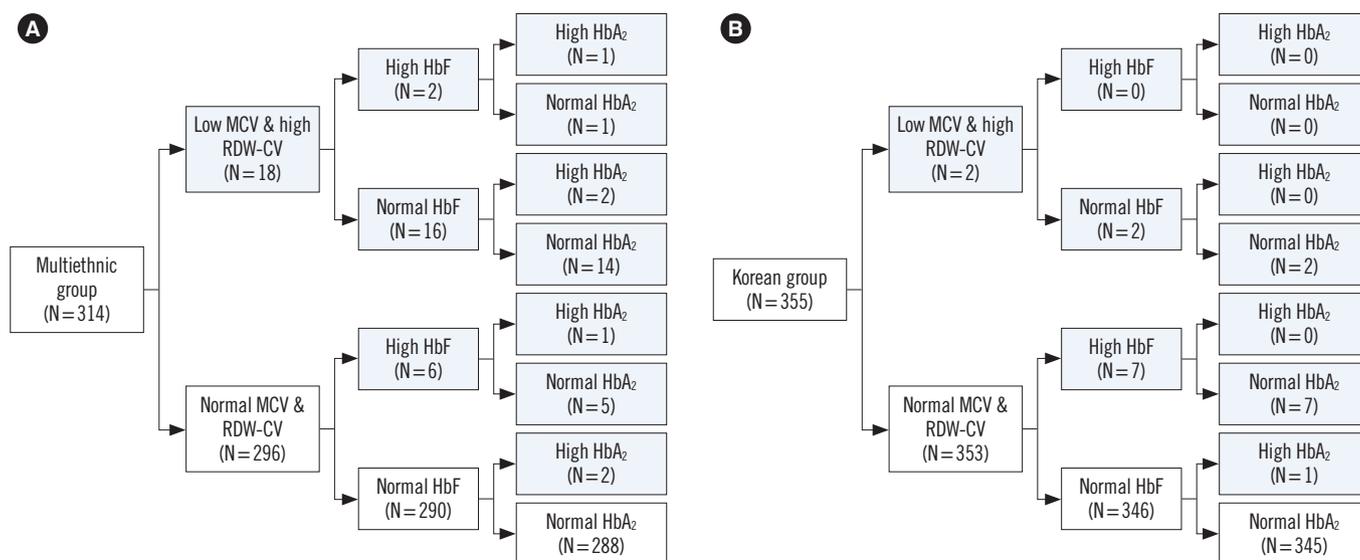
## RESULTS

In 26 subjects (8.3%) from the multiethnic group and 10 (2.8%)

from the Korean group, Hb EP and/or RBC indices showed abnormal findings (Fig. 1). In the multiethnic group, 18 subjects (5.7%) showed low MCV (range: 57.2–69.9 fL) and high RDW-CV (range: 14.0–24.3%), eight subjects (2.5%) showed high HbF (range: 1.6–7.4%), and six (1.9%) showed high HbA<sub>2</sub> (range: 3.7–6.1%). In the multiethnic group, two subjects (0.6%) showed high HbF and HbA<sub>2</sub>, three subjects (1.0%) showed high HbA<sub>2</sub> and low MCV, and one subject (0.3%) showed high HbF and HbA<sub>2</sub> and low MCV. In the Korean group, two subjects (0.6%)

showed low MCV (range: 50.4–65.3 fL) and high RDW-CV (range: 21.6–23.1%), seven subjects (2.0%) showed high HbF (range: 1.3–4.8%), and one subject (0.3%) showed high HbA<sub>2</sub> (3.9%). No Korean subject showed two or more abnormal findings.

We performed  $\alpha$ - and  $\beta$ -globin gene testing in 18 multiethnic subjects and four Korean subjects. Five  $\alpha$ -thalassemia carriers (1.5%) were identified, and six subjects (1.9%) were diagnosed as having  $\beta$ -thalassemia minor, all from the multiethnic group. Table 2 shows the subjects' hematological findings and geno-



**Fig. 1.** Hb electrophoresis and RBC indices of the multiethnic group (A) and Korean group (B). Abnormal results are indicated in gray. Abbreviations: HbF, fetal Hb; HbA<sub>2</sub>, Hb alpha 2; HbA, adult hemoglobin; RBC, red blood cell; MCV, mean corpuscular volume; RDW-CV, RBC distribution width coefficient of variation.

**Table 2.** Hematological findings and results of DNA analysis of  $\alpha$ -thalassemia trait and  $\beta$ -thalassemia minor subjects in the study (N=11)

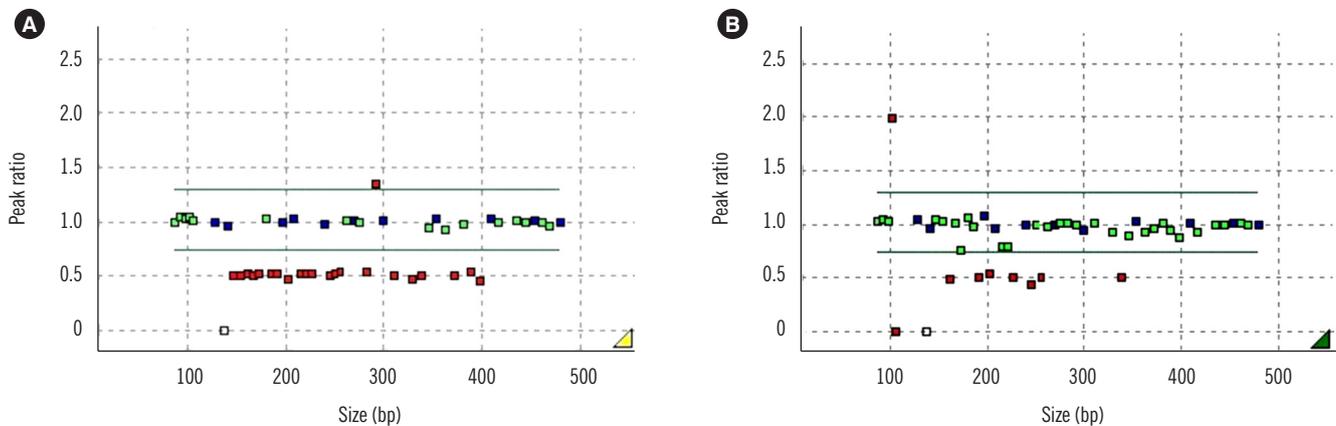
No. case	Dignosis	Mutation	HbA (%)	HbF (%)	HbA <sub>2</sub> (%)	Hb (mmol/L)	MCV (fL)	RDW-CV (Proportion of 1.0)	Father's Ethnicity	Mother's Ethnicity
1	$\alpha$ thalassemia trait	SEA deletion, heterozygote	97.3	0.3	2.4	7.07	62.8	0.164	Korean	Thai
2	$\alpha$ thalassemia trait	SEA deletion, heterozygote	96.8	1.1	2.1	6.7	64.5	0.154	Korean	Thai
3	$\alpha$ thalassemia trait	deletions of ~3.7 kb, heterozygote ( $\alpha\alpha$ - $\alpha$ 3.7)	73.2	0	3.7	7.45	74.4	0.141	Korean	Thai
4	$\alpha$ thalassemia trait	SEA deletion, heterozygote	97.9	0	2.1	7.01	65.4	0.142	Korean	Vietnamese
5	$\alpha$ thalassemia trait	SEA deletion, heterozygote	95.9	1.7	2.4	6.95	57.2	0.164	Korean	Chinese
6	$\beta$ thalassemia minor	c.-81A>G, (promoter), heterozygote	87.4	7.4	5.2	7.39	71.2	0.161	Singaporean	Singaporean
7	$\beta$ thalassemia minor	c.126_129delCTTT, p.Phe42Leufs*19, heterozygote	49.2	48.8	2.0	6.58	69.4	0.214	Korean	Thai
8	$\beta$ thalassemia minor	c.126_129delCTTT, p.Phe4fs, heterozygote	91.1	2.8	6.1	6.21	58.1	0.169	Korean	Vietnamese
9	$\beta$ thalassemia minor	c.126_129delCTTT, p.Phe4fs, heterozygote	95.1	0.2	4.7	6.45	69.7	0.160	Vietnamese	Vietnamese
10	$\beta$ thalassemia minor	c.126_129delCTTT, p.Phe42fs, heterozygote	93.3	1.1	5.6	6.39	85.6	0.168	Korean	Vietnamese
11	$\beta$ thalassemia minor	c.92+1G>T, (IVS1+1), heterozygote	93.5	1	5.5	8.13	59.5	0.184	Vietnamese	Vietnamese

Abbreviations: HbF, fetal Hb; HbA<sub>2</sub>, Hb alpha 2; HbA, adult hemoglobin; MCV, mean corpuscular volume; RDW-CV, red blood cell distribution width coefficient of variation; IVS1; first intervening sequence; SEA, South East Asian.

types. The SEA deletion in the *HBA1* and *HBA2* genes, and c.126\_129delCTTT (p.Phe42fs) mutation of *HBB* were the dominant inherited mutations (Figs. 2, 3). All six subjects with high HbA<sub>2</sub> in the multiethnic group were diagnosed as having thalassemia: one subject with  $\alpha$ -thalassemia and five subjects with  $\beta$ -thalassemia minor. Among the 11 subjects with low MCV and high RDW-CV, in the multiethnic and Korean groups, four were

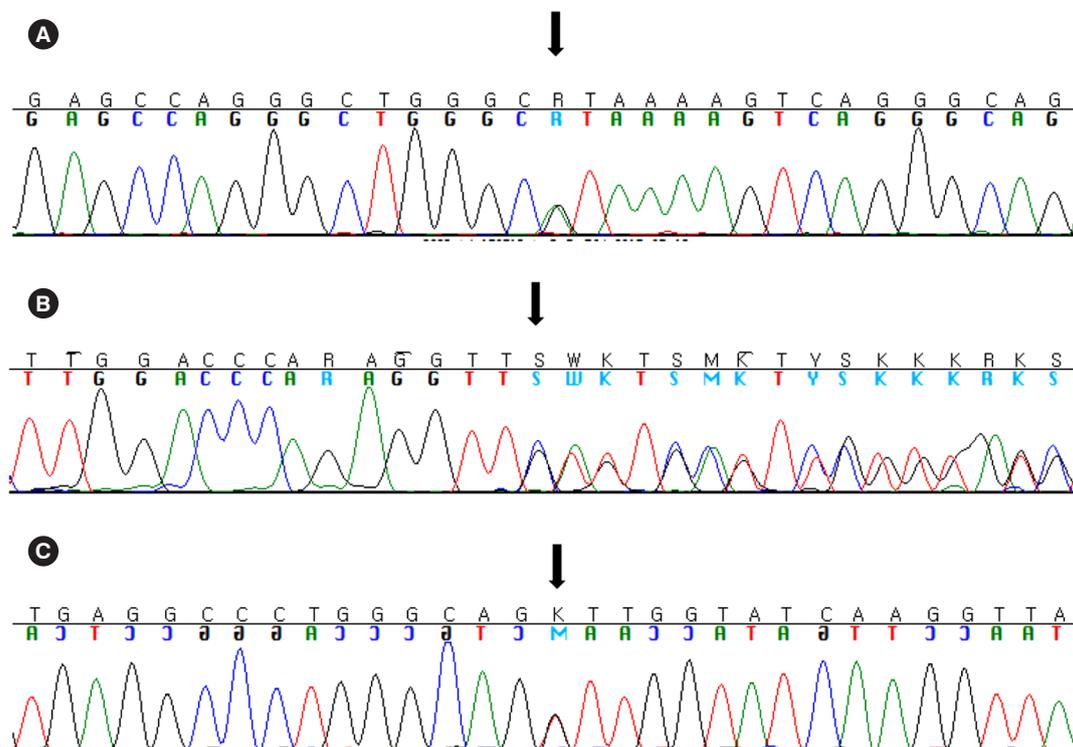
diagnosed as having the  $\alpha$ -thalassemia trait, and four were diagnosed as having  $\beta$ -thalassemia minor. Among six subjects in the multiethnic and Korean groups with only high HbF and who underwent genetic testing, none were diagnosed as having thalassemia.

Among 37 subjects with one or both parents from China, one subject (2.7%) was diagnosed as having  $\beta$ -thalassemia minor.



**Fig. 2.** Multiple ligation-dependent probe amplification results of the *HBA1* and *HBA2* genes. (A) SEA deletion, heterozygote, (B) Deletions of ~3.7 kb, heterozygote ( $\alpha\alpha$ - $\alpha$  3.7).

Abbreviations: SEA, South East Asian; bp, base pair.



**Fig. 3.** Direct sequencing results of the *HBB* gene. (A) c.-81A>G, (promoter), heterozygote, (case 6 in Table 3). (B) c.126\_129delCTTT, p.Phe42Leufs\*19, heterozygote, (case 7–10 in Table 3). (C) c.92+1G>T, (IVS1+1), heterozygote (case 11 in Table 3).

**Table 3.** Estimated number of potential thalassemia carriers in Korea

	Population in Korea (N)	Prevalence in their ethnicity (%)		Estimated potential carriers in Korea in 2017 (N)		Reference
		$\alpha$ -thalassemia	$\beta$ -thalassemia	$\alpha$ -thalassemia	$\beta$ -thalassemia	
Chinese (Korean Chinese excluded)*	338,345	7.88	2.21	26,662	7,477	Lai <i>et al.</i> [3]
Vietnamese	169,738	3.4	1.6	5,771	2,716	O'Riordan <i>et al.</i> [10]
Thai	153,259	6	0.9	9,196	1,379	Nuinoon <i>et al.</i> [11]
American	143,568	4.8	1.6	6,891	2,297	Modell <i>et al.</i> [5]
Total	804,910			48,520	13,869	

\*Chinese who migrated from Korea were excluded.

Among 94 subjects with one or both parents from Vietnam, one (1.1%) was diagnosed as having  $\alpha$ -thalassemia, and four (4.3%) were diagnosed as having  $\beta$ -thalassemia minor. Among 11 subjects with one or both parents from Thailand, three (27.2%) were diagnosed as having  $\alpha$ -thalassemia, and one (9.1%) was diagnosed as having  $\beta$ -thalassemia minor. Among nine subjects with one or both parents from America, none was diagnosed as having thalassemia. As shown in Table 3, the number of potential  $\alpha$ -thalassemia and  $\beta$ -thalassemia carriers among immigrants was estimated as 48,520 and 13,869, respectively.

## DISCUSSION

Through genetic testing in individuals with microcytic anemia and abnormal findings on Hb EP in Korea, we found that 1.9% and 1.5% of the multiethnic group were diagnosed as having  $\beta$ -thalassemia minor and  $\alpha$ -thalassemia trait, respectively. None from the Korean group was diagnosed as having thalassemia or being a carrier.

Thalassemia results in anemia of various forms, depending on the penetrance of the relevant genetic abnormality [12]. Silent carriers of  $\alpha$ -thalassemia are asymptomatic and show an  $\alpha\alpha/\alpha-$  genotype, with normal hematologic findings [13]. *SEA* deletion, the most prevalent mutation in our study, is a large deletion (19.3 kb) that is prevalent in Southeast Asia [1]. It involves the removal of the  $\theta 1$ ,  $\alpha 2$ , and  $\alpha 1$  genes [14]. The carrier frequency of  $\alpha(0)$ -thalassemia *SEA*-type deletion has been found to be 3–11% in Thailand depending on the region [15], 2.5–6.1% in China [1], and 13.9% in Japan [16]. In a study on the Korean population, *SEA* deletion was not reported [17], and only two cases have been reported in patients with South Asian mothers [6]. Since the number of potential thalassemia carriers among immigrants was estimated as 53,740, thalassemia may become a cause of anemia in Korea, unlike before.

Similar to other mutations in  $\alpha$ -thalassemia, carriers of the

$\alpha(0)$ -thalassemia *SEA* deletion do not show any clinical symptoms. Gene deletions leading to an  $\alpha\alpha/--$  (cis) (16) or  $\alpha/\alpha-$  (trans) genotype manifest as  $\alpha$ -thalassemia minor, characterized by microcytosis without anemia or infrequently with mild microcytic hypochromic anemia [13]. Compound heterozygosity for the  $\alpha$ -globin gene with an  $\alpha/--$  genotype results in HbH disease, characterized by microcytic anemia, hemolysis, and splenomegaly, while an  $\alpha\alpha^{T}/--$  genotype results in HbH disease with normocytic anemia, growth retardation, and splenomegaly. Gene deletions with a  $--/--$  genotype for the  $\alpha$ -globin gene lead to  $\alpha$ -thalassemia major hydrops fetalis, which is the most severe form of  $\alpha$ -thalassemia [13]. Further, approximately 75% of mothers homozygous for the  $\alpha(0)$ -thalassemia *SEA* deletion develop toxemia of pregnancy [18].

The c.126\_129delCTTT (p. Phe42fs), the most common mutation of  $\beta$ -thalassemia in our study, is a frameshift mutation that results in a stop codon, terminating translation at the new codon 59. This is a common mutation in China and Southeast Asia, and affects 22–35.3% of the Vietnamese population [19, 20], 31.7–33.3% of the Chinese population [21, 22], 37.5% of the Thai population [23], 13.6% of the Japanese population [16], and 4.2% of the Korean population [24]. A  $\beta/\beta^0$  or  $\beta/\beta^+$  genotype of the  $\beta$ -globin gene manifests as  $\beta$ -thalassemia minor, leading to microcytosis and anemia. A  $\beta^0/\beta^+$  or a  $\beta^+/ \beta^+$  genotype is characteristic of  $\beta$ -thalassemia intermedia, leading to moderate anemia. Cooley's anemia ( $\beta$ -thalassemia major), the most severe form of  $\beta$ -thalassemia, results from a  $\beta^0/\beta^0$ ,  $\beta^0/\beta^+$ , or  $\beta^+/ \beta^0$  genotype [13]. It is often called transfusion-dependent thalassemia since patients require repeated blood transfusions throughout their life [12]. In our study, only subjects with  $\beta$ -thalassemia minor and  $\alpha$ -thalassemia carriers were identified, not subjects with  $\beta$ -thalassemia major or  $\alpha$ -thalassemia. The prevalence of thalassemia major is expected to increase over generations.

Thalassemia is diagnosed on the basis of hematologic findings of microcytic hypochromic anemia and Hb analysis that re-

veals increased amounts of HbF, HbA<sub>2</sub>, Hb Barts, and HbH. Identification of pathogenic variants in *HBA1*, *HBA2*, and *HBB* that result in deletion or inactivation of  $\alpha$ -globin and  $\beta$ -globin alleles confirms the diagnosis [25, 26]. However, silent carriers of  $\alpha$ -thalassemia and individuals with  $\alpha$ -thalassemia minor present with normal hematologic findings or with asymptomatic microcytosis. These conditions are difficult to detect, so we could detect only a few cases of these disorders. Consequently, we observed similar prevalence rates for  $\alpha$ -thalassemia and  $\beta$ -thalassemia, unlike in other studies. To assess the true prevalence rate of  $\alpha$ -thalassemia carriers, mass screening without hematologic screening is needed. No subject with only high HbF was diagnosed as having thalassemia, and all subjects with high HbA<sub>2</sub> were diagnosed as having thalassemia.

Therapies, including allogeneic hematopoietic stem cell transplantation and gene therapy, and pharmacological agents have been developed and tested on patients [26-30]; however, blood transfusion remains the mainstay of symptomatic management [31, 32]. Lifelong supportive blood transfusion could lead to iron overload in patients. Thus, close monitoring of serum ferritin levels and iron monitoring by magnetic resonance imaging to prevent iron overload-related organ complications are important [33, 34]. In Korea, there are no special guidelines for blood transfusion in cases of inherited hemolytic anemia, including thalassemia. Thus, it is important to establish guidelines for blood transfusion and monitoring of iron overload [35].

Children born to parents who are both thalassemia carriers inherit the disease in an autosomal recessive manner and have an increased risk of manifesting thalassemia. Parents and siblings of diagnosed individuals should be screened for carrier status or other mutations, and they should be provided perinatal screening and genetic counseling [13, 36, 37]. When awareness of thalassemia increases in Korea, timely diagnosis and treatment can be provided.

The prevalence of  $\alpha$ -thalassemia was lower than expected. This is probably because we screened blood samples of subjects according to hematologic findings from CBC and Hb EP, and we did not screen for disease carriers. Additional research screening for carriers of  $\alpha$ -thalassemia is required.

In summary, we found that 3.4% of the multiethnic group was diagnosed as thalassemia carriers, but none with thalassemia major or severe symptoms. The prevalence of thalassemia may be increasing in young people in Korea because of the increase in the number of immigrants, and the prevalence of thalassemia major is expected to increase over generations. The immigrant population needs to be comprehensively screened as a matter

of public health policy to ensure timely diagnosis and treatment of thalassemia. Furthermore, it is imperative that in patients with microcytic hypochromic anemia, which does not respond to iron therapy, a differential diagnosis of thalassemia is evaluated by Hb EP and genetic testing in all Korean patients.

## Authors' Disclosures of Potential Conflicts of Interest

The authors have no conflicts of interest to declare.

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