



A Family With a Hemoglobin E Variant Including a Thai Immigrant Woman in Korea

Jaehoon Jahng, M.D.¹ and Kui Hyun Yoon, M.D.^{2,3}

Departments of Gastroenterology¹ and Laboratory Medicine², Wonkwang University Sanbon Hospital, Gunpo; Institute of Wonkwang Medical Center³, Iksan, Korea

Dear Editor,

A 33-yr-old Thai woman visited Wonkwang University Sanbon Hospital, Korea, with chief complaints of fatigue and dizziness. Peripheral blood smear examination revealed microcytic hypochromic anemia with target cells (Fig. 1). Routine laboratory analysis results were within normal limits (bilirubin, haptoglobin, reticulocyte, lactate dehydrogenase, iron, total iron binding capacity, ferritin, Coombs' test) except for mild anemia and abnormal Hb electrophoresis (Table 1). Hepatosplenomegaly was absent. Hb electrophoresis was performed on an alkaline agarose gel using a Hydrasis 2 (Sebia, Lisses, France), which revealed markedly increased Hb A₂ and Hb F fractions with a severely decreased Hb A₁ fraction. Hb E, Hb C, and Hb O migrated at the Hb A₂ position during alkaline Hb electrophoresis. To rule out hemoglobinopathy, *Homo sapiens* Hb β (*HBB*) (NM_000518.4) gene sequencing was performed. Genomic DNA was extracted from peripheral blood by using a QIAamp DNA mini kit (QIAGEN, Hilden, Germany). Two primer sets were utilized that included all exons, splice sites, and adjacent intron regions of the *HBB* gene. DNA was amplified by using a DNA Engine Tetrad 2 Peltier Thermal Cycler (BIO-RAD, Hercules, CA, USA) and sequenced by using an ABI PRISM 3730XL analyzer (Applied Biosystems, Foster City, CA, USA). Sequencing

data were analyzed by using Variant Reporter Software Version 1.1 (Applied Biosystems). The proband's sequencing data revealed a homozygous c.79G>A; p.Glu27Lys (Hb E) variant. A family study revealed Hb E heterozygosity in the proband's two children (Fig. 1).

Hemoglobinopathies include all genetic Hb diseases, and are divided into the thalassemia and structural Hb variant groups, which contain many subtypes and combined types. The prevalence of hemoglobinopathies depends on geographic location and ethnicity. Around 7% of the world's population comprises hemoglobinopathy gene carriers. Hb E is the most prevalent variant in Southeast Asia (Thailand, Myanmar, Cambodia, Laos, Vietnam), where its prevalence is 30-60% [1-4]. This common structural Hb variant results from the substitution of glutamic acid with lysine at codon 26 of the β globin chain. Hb E disorders may be heterozygous (AE), homozygous (EE), or compound heterozygous (e.g., Hb E with another Hb variant or thalassemia). Hb E is usually associated with a normal Hb concentration or mild anemia, but may also be associated with microcytosis, which may be confused with iron deficiency anemia until laboratory studies are completed. Although Hb E alone does not cause any significant clinical problems, its interactions with other hemoglobinopathies produce a wide range of clinical syndromes. Co-in-

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Corresponding author: Kui Hyun Yoon

Department of Laboratory Medicine, Wonkwang University Sanbon Hospital,
321 Sanbonro, Gunpo 15865, Korea
Tel: +82-31-390-2658, Fax: +82-31-391-2085
E-mail: wooju67@paran.com

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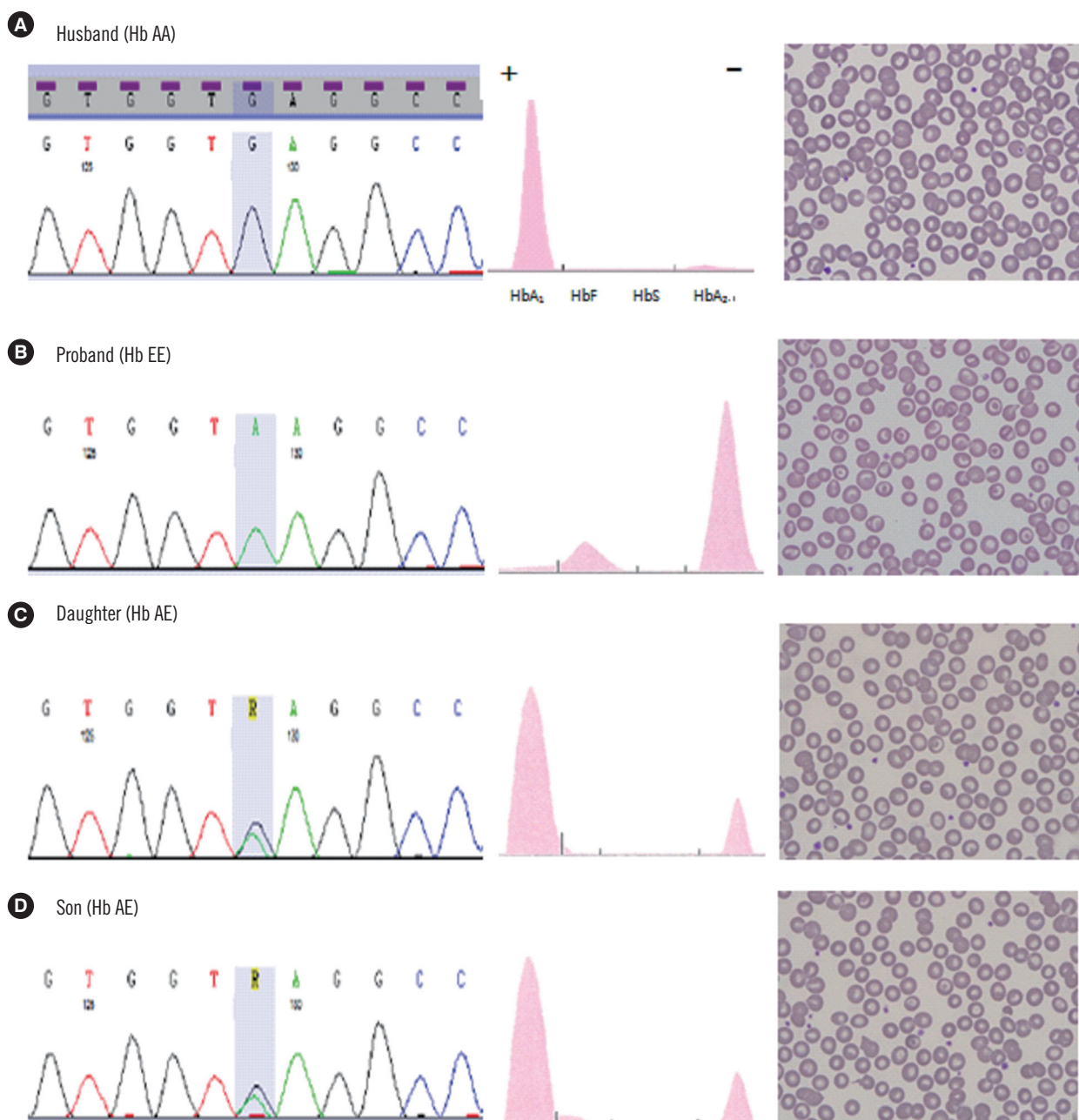


Fig. 1. Sanger sequencing of the *HBB* gene, alkaline Hb electrophoresis (see Table 1) and peripheral blood smear (Wright stain, $\times 1,000$) in the Hb E family. (A) Normal findings. (B) Homozygous Hb E (c.79G>A; p.Glu27Lys) variant, increased Hb F and Hb A₂ fractions, and many target cells. (C) Heterozygous Hb E, increased Hb A₂ and some target cells. (D) Heterozygous Hb E, increased Hb F and Hb A₂, and some target cells.

heritance of Hb E and β -thalassemia, Hb E/ β -thalassemia, results in a heterogeneous disease with a phenotype ranging from mild anemia to severe β -thalassemia. To our knowledge, Hb E has not been previously reported in Korea [5, 6]. However, international marriages with Southeast Asians and immigrants importantly contribute to the prevalence of hemoglobinopathy in Korea. This study indicates that clinicians should consider the

possibility of hemoglobinopathy in microcytic anemia.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

Table 1. Laboratory results of the proband's family

Test (reference range) Age/sex	Husband (44/M)	Proband (33/F)	Daughter (8/F)	Son (5/M)
Complete blood count				
Hb (M: 13-17 g/dL) (F: 12-16 g/dL)	14.8	11.4	12.7	12.3
MCV (M: 81-97.7 fL) (F: 79-96.7 fL)	100.0	64.1	74.6	73.5
MCH (M: 27-33 pg) (F: 26-32 pg)	33.5	21.9	25.0	24.3
MCHC (M: 32-36 g/dL) (F: 31-35 g/dL)	33.5	34.1	33.6	33.1
Red cell distribution width (11.5-14.5%)	12.5	14.3	13.6	14.3
Reticulocyte (0.2-2.0%)	1.25	1.99	1.16	1.06
Hb electrophoresis				
Hb A ₁ (≥96%)	97.4	3.2	84.3	80.7
Hb F (<2%)	0.0	16.6	0.8	3.6
Hb S (0%)	0.0	0.0	0.0	0.0
Hb A ₂ (≤3.5%)	2.6	80.2	14.9	15.7
Iron (M: 80-199 µg/dL) (F: 70-179 µg/dL)	189.49	201.32	116.97	138.11
TIBC (M: 210-461 µg/dL) (F: 220-471 µg/dL)	351.49	316.32	372.97	368.11
Ferritin (M: 18.2-341.2 ng/mL) (F: 4.0-232.3 ng/mL)	189.2	208.06	20.47	13.25
Haptoglobin (30-200 mg/dL)	111	56	55	61
Total bilirubin (0.22-1.4 mg/dL)	0.84	1.07	0.83	0.63
Lactate dehydrogenase (263-450 U/L)	365	272	537	502
Direct antiglobulin test	Negative	Negative	Negative	Negative
Indirect antiglobulin test	Negative	Negative	Negative	Negative

Abbreviations: MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TIBC, total iron binding capacity.

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