Thalassemia and Abnormal hemoglobins in Thailand

รองศาสตราจารย์ ดร.สุพรรณ ฟู่เจริญ

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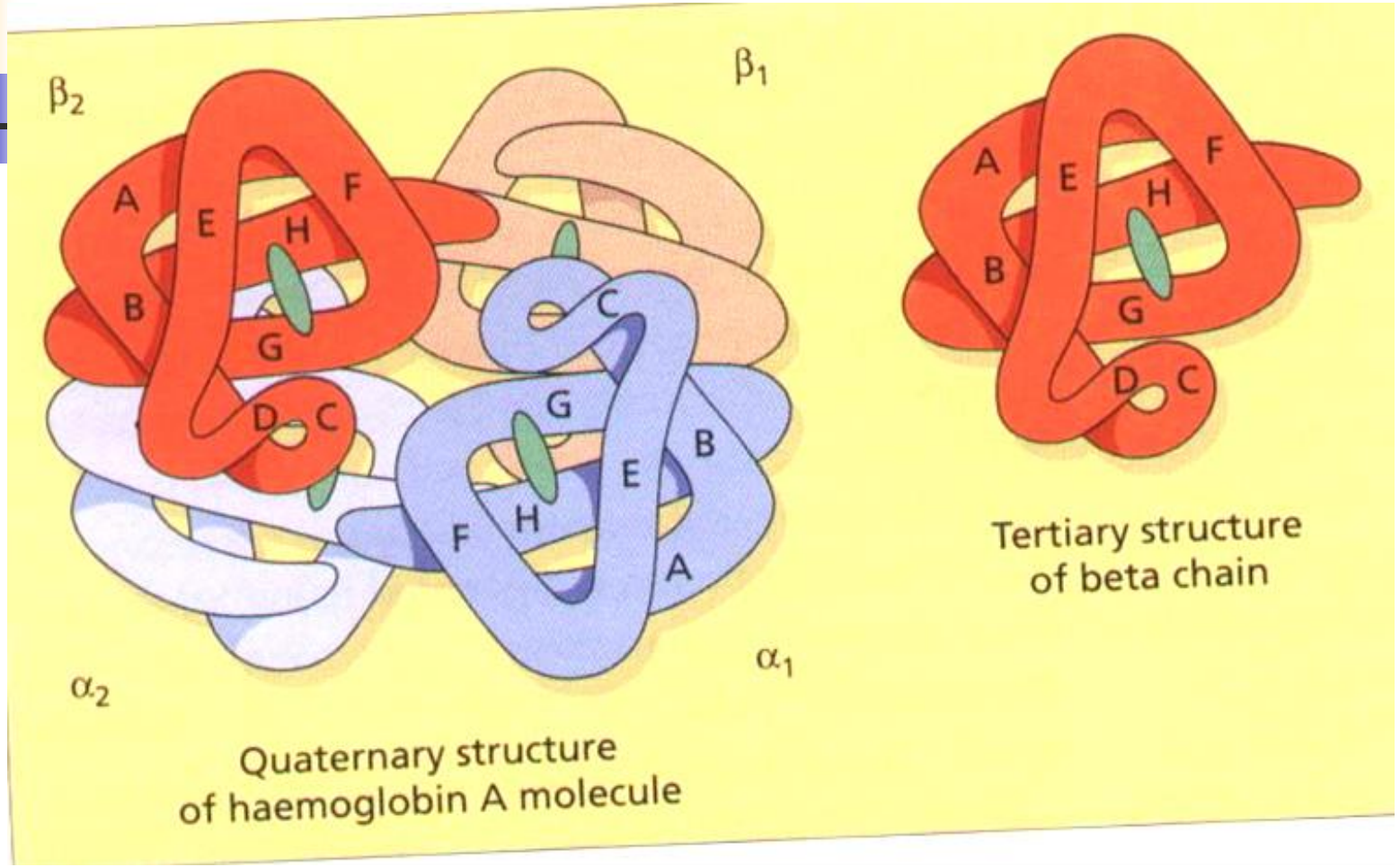
คณะเทคนิคการแพทย์ มหาวิทยาลัยขอนแก่น

Disclosure

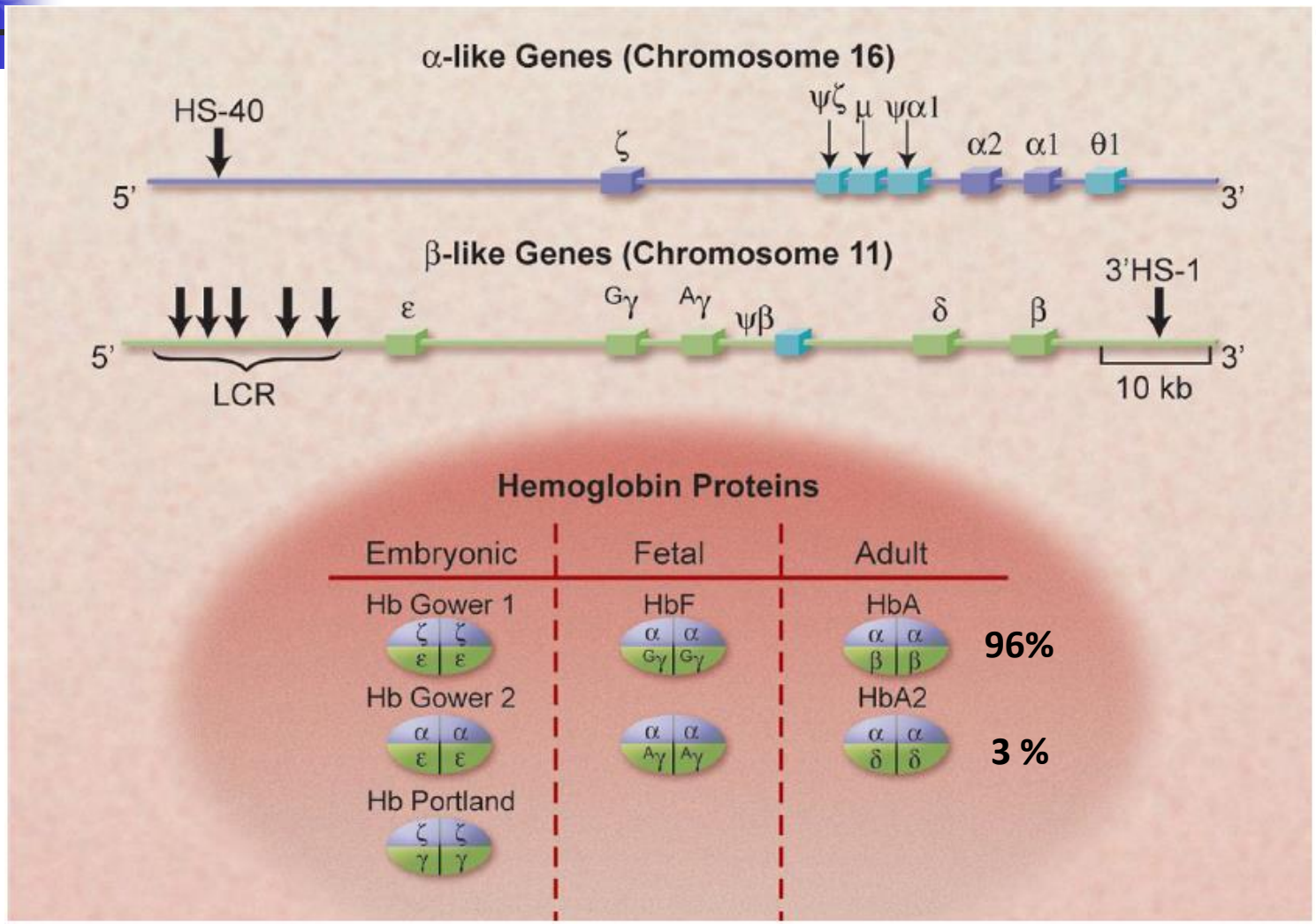
Nothing to disclose

Globin chain



Hemoglobin (2 α + 2 non α)

… Hb genes …


α-like Genes (Chromosome 16)
HS-40
5'
ζ
ψζ μ ψα1
α2 α1 θ1
3'
β-like Genes (Chromosome 11)
3'HS-1
5'
LCR
ε
Gγ Aγ
ψβ
δ
β
3'
10 kb
Hemoglobin Proteins
Embryonic
Fetal
Adult
Hb Gower 1
ζ2ε2
HbF
α2Gγ2
HbA
α2β2
96%
Hb Gower 2
α2ε2
α2Aγ2
HbA2
α2δ2
3 %
Hb Portland
ζ2γ2

Classification of hemoglobin disorders

Quantitative defect (Reduced synthesis)

Thalassemia syndrome

พาหะแฝงไม่แสดงอาการ

เป็นโรค

แสดงอาการ

- ***Structural defect***

  …….. Variant in one of the globin subunits

  (ปริมาณการสังเคราะห์ ไม่เปลี่ยนแปลง)

  Hb variant / Abnormal Hb

- ***Quantitative & Structural defect***

  Thalassemic hemoglobinopathy

ธาลัสซีเมียกับปัญหาโลหิตจางในคนอีสาน .....

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Blood Cells, Molecules, and Diseases 37 (2006) 8–11

BLOOD CELLS, MOLECULES, & DISEASES

www.elsevier.com/locate/ybcmd

Thalassemia and hemoglobinopathies rather than iron deficiency are major causes of pregnancy-related anemia in northeast Thailand

Kanokwan Sanchaisuriya [a,b], Supan Fucharoen [b,*], Thawalwong Ratanasiri [c], Pattara Sanchaisuriya [d], Goonnapa Fucharoen [b], Ekkahart Dietz [e], Frank P. Schelp [e]

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Study on pregnancy related anemia in northeast Thailand

Subjects : ***412 pregnant women***

Hospitals : ***Chumpae & Nampong***

Duration : ***Jan 2003 – May 2004***

Mean age : ***25.5 ± 6.0 yr***

Mean GA : ***12.8 ± 3.7 wk.***

Inclusion criteria

Normal pregnancy with GA < 20 wks.

Hb ≤ 11 g/dl at GA ≤ 12 wks.

Hb ≤ 10.5 g/dl at GA ≤ 20 wks.

Methods : *CBC , Hb & DNA analyses , Serum ferritin assay*

Results : ***From 412 pregnant women***

71 cases (17.2 %) : Anemic

42 (59.2 %) : Thalassemia
5 (7.0 %) : Iron deficiency
18 (25.4 %) : Thalassemia + Iron def.
6 (8.5 %) : Non thal, Non iron def.

Thalassemias are major causes of anemia in northeast Thailand

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Blood Cells, Molecules, and Diseases 37 (2006) 8–11

Thalassemia and hemoglobinopathies rather than iron deficiency are causes of pregnancy-related anemia in northeast Thailand

Kanokwan Sanchaisuriya [a,b], Supan Fucharoen [b,*], Thawalwong Ratanasiri [c], Pattara Sanchaisuriya [d], Goonnapa Fucharoen [b], Ekkahart Dietz [e], Frank P. Schelp [e]

Eur J Pediatr
DOI 10.1007/s00431-010-1218-3

ORIGINAL PAPER

(2011; 169: 1317-1322.)

Thalassemia and iron deficiency in a group of northeast Thai school children: relationship to the occurrence of anemia

Nichathorn Panomai · Kanokwan Sanchaisuriya · Supawadee Yamsri · Pattara Sanchaisuriya · Goonnapa Fucharoen · Supan Fucharoen · Frank P. Schelp

Acta Haematologica

(2011; 125: 186-192.)

Anemia, Iron Deficiency and Thalassemia among Adolescents in Northeast Thailand: Results from Two Independent Surveys

Anupong Pansuwan [a, b] Goonnapa Fucharoen [b] Supan Fucharoen [b]
Boonmee Himakhun [c] Samrit Dangwiboon [d]

บทนำ

Average statistics for Thalassemia .....

โรคโลหิตจางธาลัสซีเมีย (thalassemia) เป็นโรคพันธุกรรมทางโลหิตวิทยา ซึ่งมีอุบัติการณ์สูงมากในประเทศไทย ประมาณร้อยละ 20-30 ของประชากรมียีน alpha (α)-thalassemia ร้อยละ 3-9 มียีน beta (β)-thalassemia และพบยีนของฮีโมโกลบินผิดปกติ 2 ชนิด คือ hemoglobin E (Hb E) โดยเฉลี่ยประมาณร้อยละ 13 และพบสูงขึ้นในคนอีสานถึงร้อยละ 30-40 ที่จังหวัดสุรินทร์พบ Hb E สูงถึงร้อยละ 52 ฮีโมโกลบินผิดปกติอีกชนิดหนึ่งที่พบได้บ่อย คือ Hb Constant Spring (Hb CS) พบประมาณร้อยละ 1-8 อุบัติการณ์ดังตารางที่ 1

ข้อมูลจากการทำ micromappingใหม่

ORIGINAL ARTICLE

MICROMAPPING OF THALASSEMIA AND HEMOGLOBINOPATHIES IN DIFERENT REGIONS OF NORTHEAST THAILAND AND VIENTAINE, LAOS PEOPLE'S DEMOCRATIC REPUBLIC

Jaruwan Tritipsombut,[1,2] Kanokwan Sanchaisuriya,[2] Prachatip Phollarp,[2] Dalouny Bouakhasith,[3] Pattara Sanchaisuriya,[4] Goonnapa Fucharoen,[2] Supan Fucharoen,[2] and Frank P. Schelp[4]

[1] *Biomedical Science Program, Graduate School, Khon Kaen University, Khon Kaen, Thailand*

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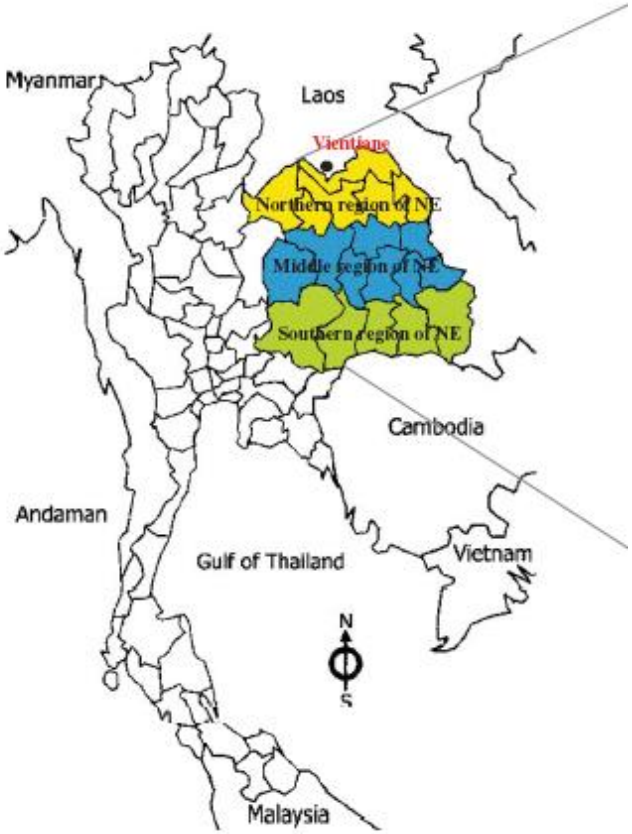


Hemoglobin 2012; 36: 47-56.

SGF.-

ภาคอีสานมี Hb E มาก
แต่ β – thalassemia น้อย

TABLE 1 Prevalence and Gene Frequency of Hb E, α^0- and β-Thalassemia in 1,460 Northeast Thai and 349 Laotian Subjects (95% confidence interval in parentheses)

	Northeast Thailand			Vientiane, Laos PDR			
Types of Thalassemia	*n*	Prevalence	Gene Frequency	*n*	Prevalence	Gene Frequency	*p* Value[a]
Hb E[b]	609	41.7 (39.2–44.3)	0.238 (0.223–0.253)	105	30.1 (25.3–35.2)	0.173 (0.145–0.202)	<0.001
α^0-Thalassemia[c]	85	5.8 (4.7–7.1)	0.029 (0.024–0.036)	30	8.6 (5.9–12.0)	0.043 (0.029–0.061)	0.089
β-Thalassemia	13	0.9 (0.5–1.5)	0.005 (0.003–0.008)	8	2.3 (1.0–4.5)	0.011 (0.005–0.022)	0.110

[a]Test for prevalence difference.
[b]Including individuals with heterozygous and homozygous states.
[c]Most carried the SEA deletion except one Thai subject with the THAI deletio

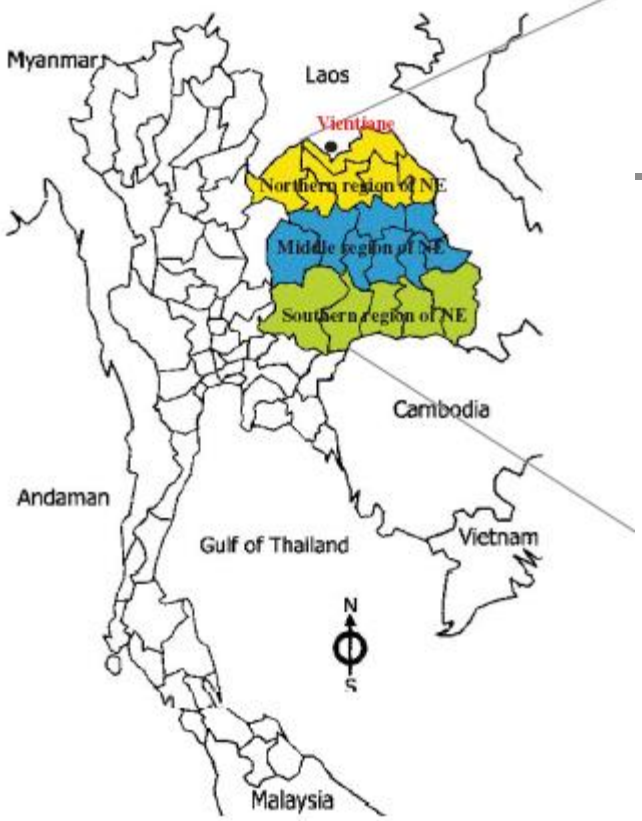
ลาวมี มากกว่า

Updated data for Northeast Thailand

TABLE 4 Comparison of Frequencies of Thalassemia and Hemoglobinopathies in Populations of Northeast Thailand and Neighboring Countries

Types of Thalassemia	NE Thailand	Vientiane, Laos PDR	South Laos (15,16)	Cambodia (17,18)	South Vietnam (19)
α^0-Thalassemia[a]	0.029	0.043	0.006[b]	0.010[c]	0.017–0.034[d]
α^+-Thalassemia[e]	0.107	0.046	0.381[b]	0.162[c]	0.017–0.220[d]
β-Thalassemia	0.005	0.011	N.A.	0.0156 – 0.017[f]	0.001–0.046[g]
Hb E	0.238	0.172	0.253 – 0.433[h]	0.151 – 0.299[f]	0–0356[g]
Hb CS	0.053	0.029	0.113[b]	0.023	0–0.030[d]
Hb Paksé	0.004	0.003	N.A.	0.002	0–0.002[d]

α^+ - thalassemia is ~ 5 times more common than α^0 - thalassemia



... แต่ละภูมิภาคมีข้อมูลต่างกัน ...

... ควรเลือกแนวทางการตรวจ
การวินิจฉัย และ การให้คำปรึกษา
แนะนำทางพันธุกรรม
อย่างเหมาะสม ...

Phenotypic classification of thalassemia in Thailand …..

β - thalassemia

β^{+} - thalassemia
β^{o} - thalassemia
Hb E

α – thalassemia

α ^{o}-thalassemia / α -thal 1
α $^{+}$-thalassemia / α -thal 2
Hb Constant Spring
Hb Pakse'

αβ -thalassemia

AEBart's disease
EFBart's disease , etc.

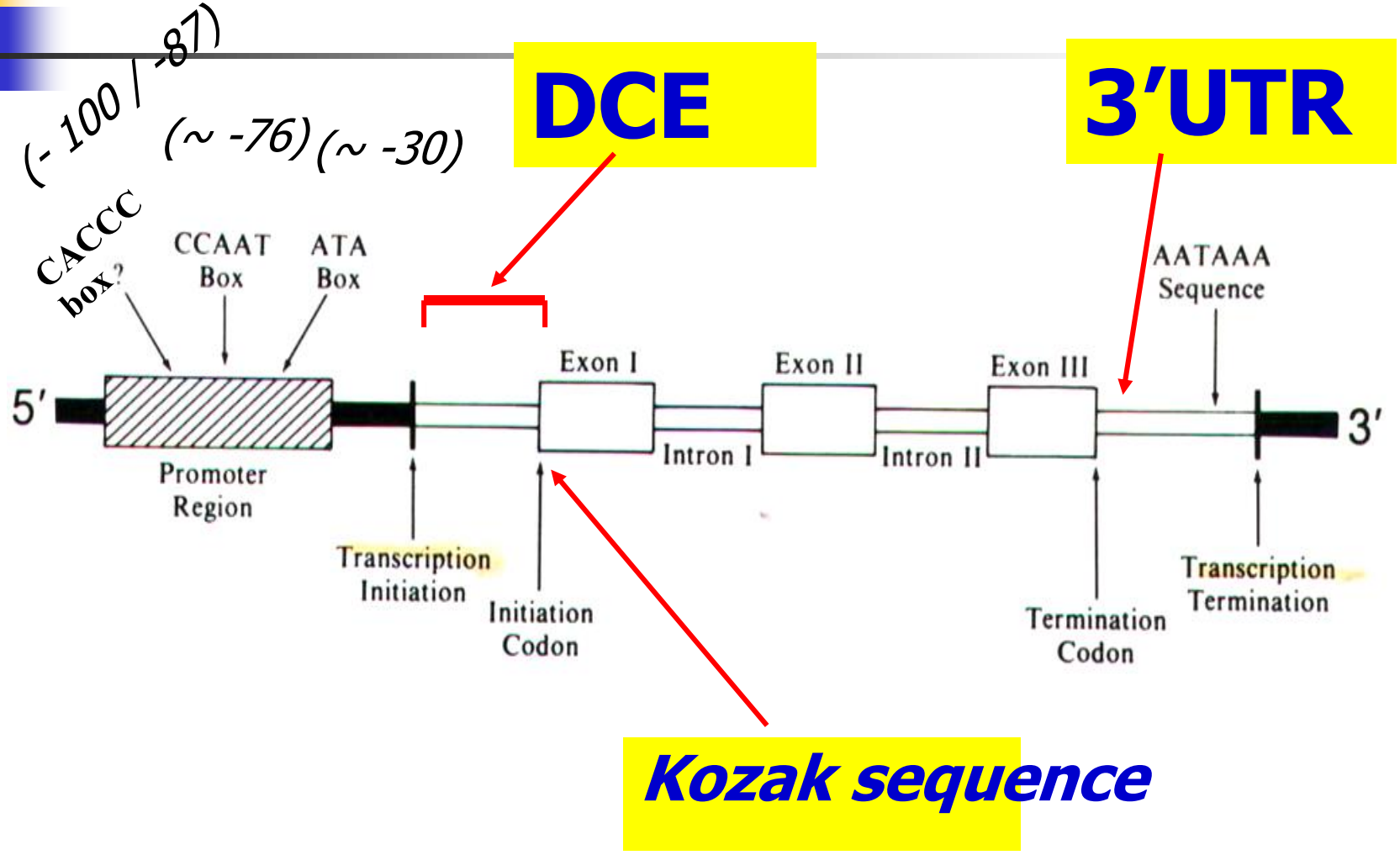
δβ -thalassemia / HPFH

Highly heterogeneous in Thai population

Thalassemia gene interactions

More than 60 thalassemia syndromes

Structure of Human globin gene



Hum Genet (1989) 84:41–46

Human Genetics

Molecular basis of β-thalassemia in Thailand: analysis of β-thalassemia mutations using the polymerase chain reaction

Supan Fucharoen[1], Goonnapa Fucharoen[1,2], Wimonman Sriroongrueng[1,3], Vichai Laosombat[4], Arunee Jetsrisuparb[5], Sutthipan Prasatkaew[2], Voravarn S. Tanphaichitr[6], Vinai Suvatte[6], Soodsarkorn Tuchinda[6], and Yasuyuki Fukumaki[1]

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[3] Department of Pathology and [4] Department of Pediatrics, Faculty of Medicine, Prince of Songkhla University, Songkhla, Thailand
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Summary. β-Thalassemia mutations in 71 chromosomes of Thai patients from the northeast, the middle and the south of the country were investigated using dot blot hybridization of PCR (polymerase chain reaction)-amplified DNA with allele-specific oligonucleotide probes. Eight different known molecular defects were detected, at different frequencies. There was an amber mutation in codon 17, a C-T transversion at position 654 of IVS-2, a frameshift mutation between codons 71 and 72, an A-G transition at nucleotide −28 within northeast, middle and south of Thailand. Mutations previously detected in two related ethnic groups, Chinese and Indians (Kazazian and Boehm 1988), and also the β^{35} ochre mutation were screened using PCR and dot-blot hybridization with specific oligonucleotide probes.

Materials and methods

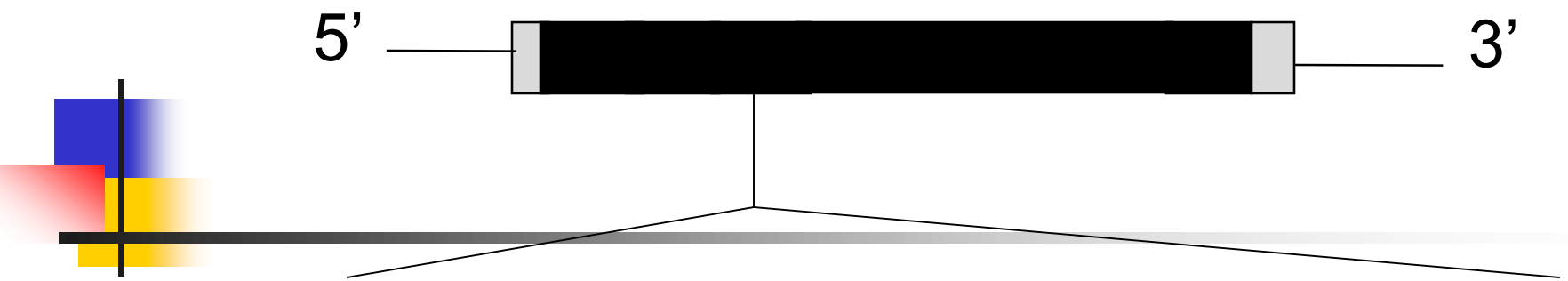
แต่ละภูมิภาคมีชนิดและความถี่ของมิวเตชั่นแตกต่างกัน

Table 2. Distribution of β-thalassemia mutations in Thailand

	The northeast	The middle	The south	Total (%)
−28 TATA	0	1	1	2 (2.8)
Codon 17	10	4	0	14 (19.7)
Codons 71, 72	2	0	0	2 (2.8)
IVS-2 # 654	4	5	0	9 (12.8)
Codons 41/42	10	10	11	31 (43.7)
IVS-1 # 5	0	1	7	8 (11.2)
IVS-1 # 1	0	0	1	1 (1.4)
Codon 35	0	1	0	1 (1.4)
Codon 19	0	0	3	3 (4.2)
Total number of alleles examined	26	22	23	71 (100)

Mostly caused by point mutations

Frame shift mutation
(4 bp deletion at codons 41/42)



	40	41	42	43	44	59	60
	Arg	Phe	Phe	Glu	Ser	Lys	Val
β^A	AGG	**TTC**	**T**TT	GAG	TCC----------	AAG	GTG
	AGG	TTG	AGT	CCT	TTG	----------TGA	
$\beta^{41/42}$	Arg	Leu	Ser	Pro	Leu	Termination codon	

β^0-thalassemia

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

A large cohort of β^+-thalassemia in Thailand: Molecular, hematological and diagnostic considerations

Supawadee Yamsri [a], Kritsada Singha [a,b], Thanet Prajantasen [a,b], Wachiraporn Taweenan [a], Goonnapa Fucharoen [a], Kanokwan Sanchaisuriya [a], Supan Fucharoen [a,*]

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ABSTRACT

We report the molecular and hematological characteristics associated with a large cohort of β^+-thalassemia in Thailand. Study was done on 21,068 unrelated subjects referred to our center in northeast Thailand for hemoglobinopathies investigation. Among 21,068 subjects, 2637 (12.5%) were found to carry β-thalassemia. Of these 2637 cases, 705 (26.7%) carried β^+-thalassemia with eight different mutations including 6 promoter mutations; NT-28 (A–G), NT-31 (A–G), NT-50 (G–A), NT-86 (C–G), NT-87 (C–A) and NT-90 (C–T) and two missense mutations; Hb Malay (codon 19; *AAC-AGC*) and Hb Dhonburi (codon 126; *GTG-GGG*). Hematological features of carriers with these β^+-thalassemia (n = 528) were compared with those with β^0-thalassemia (n = 309). Data for Hb E-β^+-thalassemia (n = 177) were also presented along with Hb E-β^0-thalassemia in our series (n = 94). All

Total **21,068** subjects examined ……

2,637 *β – thalassemia carriers*

1,932 β^0 – thalassemia (73.3%)

705 β^+ - thalassemia (26.7%)

Blood Cells, Molecules, and Diseases 47 (2011) 120–124

Contents lists available at ScienceDirect

Blood Cells, Molecules, and Diseases

journal homepage: www.elsevier.com/locate/ybcmd

Genotype and phenotype characterizations in a large cohort of β-thalassemia heterozygote with different forms of α-thalassemia in northeast Thailand

Supawadee Yamsri [a,b], Kanokwan Sanchaisuriya [b], Goonnapa Fucharoen [b], Nattaya Sae-ung [b], Supan Fucharoen [b,*]

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heterozygotes.

β-thalassemia mutation	Type	No.	%
CD 41/42; (−TTCT)	β^0	307	36.16
CD 17; (A-T)	β^0	215	25.32
NT-28; (A-G)	β^+	191	22.50
CD 71/72; (+A)	β^0	36	4.24
IVSI-1; (G-T)	β^0	26	3.06
IVSII-654; (C-T)	β^0	19	2.23
3.4 kb deletion	β^0	19	2.23
IVSI-5; (G-C)	β^+	14	1.65
CD 43; (G-T)	β^0	6	0.71
CD 35; (C-A)	β^0	4	0.47
CD 26; (G-T)	β^0	4	0.47
NT-87; (C-A)	β^+	2	0.24
CD 15; (−T)	β^0	2	0.24
CD 27; (+C)	β^0	1	0.12
CD19; (A-G), Hb Malay	β^+	1	0.12
CD 95; (+A)	β^0	1	0.12
NT-31 (A-G)	β^+	1	0.12
Total		849	100

Accumulative data at KKU
… 849 genes…

~ 22.5 %
β^+ - thalassemia

β^0 – thalassemia	:	Severe
β^+ - thalassemia	:	Mild

Similar hematological characteristics i.e. .....

Low MCV
Low MCH
Elevated Hb A_2

Differential diagnosis is only made possible by DNA analysis

... ตรวจหา mutation ในคู่สมรสก่อนส่งไปทำ PND น่าจะดีกว่า ...

β^+ - thalassemia mutations observed

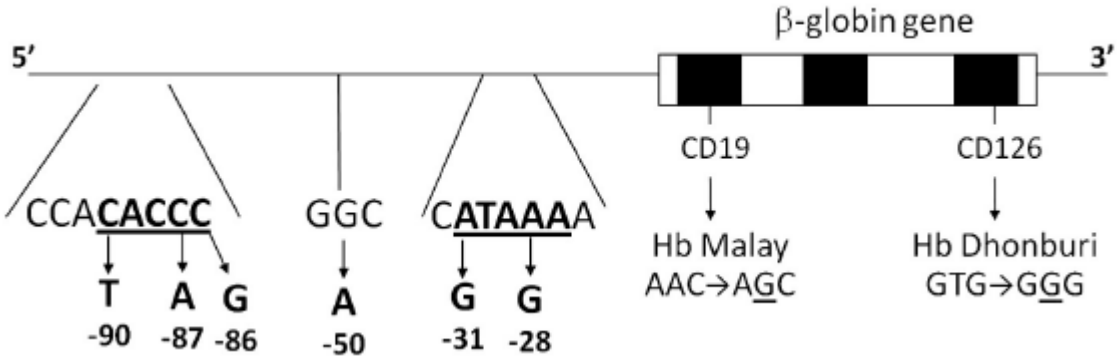


Table 1
Hematological parameters and Hb profiles of 528 β^+-thalassemia heterozygotes. Values are presented as mean ± SD (min–max) or as raw data where appropriate.

β-Thal genotypes	n (%)	Sex (n) female/male	Hb A_2 (%)	Hb F (%)	Rbc ($\times 10^{12}$/L)	Hb (g/dl)	MCV (fl)	MCH (pg)	RDW (%)
$\beta^{NT-28;\ (A-G)}/\beta^A$	431 (81.6)	225/206	5.7 ± 0.6 (3.6–7.5)	1.7 ± 1.5 (0–9.4)	5.3 ± 0.7 (3.8–7.8)	12.5 ± 1.9 (8.1–16.9)	72.1 ± 5.3[a] (56.3–89.0)	23.3 ± 1.8[a] (18.1–29.9)	15.3 ± 2.2 (10.7–23.4)
$\beta^{NT-31;\ (A-G)}/\beta^A$	41 (7.8)	23/18	4.7 ± 0.4 (3.9–5.2)	1.2 ± 1.1 (0.2–3.9)	5.0 ± 0.7 (3.7–6.2)	12.9 ± 1.5 (10.4–16.1)	77.4 ± 4.5[a] (67.7–85.0)	25.4 ± 1.3[a] (23.0–28.1)	14.7 ± 1.2 (12.5–16.2)
β^{Malay}/β^A	29 (5.5)	12/17	4.4 ± 0.4 (3.5–5.2)	1.3 ± 1.4 (0–5.2)	5.3 ± 0.9 (3.8–6.5)	12.0 ± 1.6 (9.4–14.6)	70.2 ± 5.1[a] (61.9–82.6)	23.4 ± 2.5[a] (19.7–31.3)	15.6 ± 1.8 (13.5–18.8)
$\beta^{NT-87;\ (C-A)}/\beta^A$	13 (2.5)	9/4	5.6 ± 0.5 (5.4–6.3)	3.2 ± 2.1 (1.2–8.4)	5.5 ± 0.7 (4.5–6.4)	13.3 ± 1.4 (11.4–15.3)	74.9 ± 3.1 (70.0–78.0)	24.4 ± 1.4 (22.6–26.1)	13.5 ± 0.6 (13.0–14.4)
$\beta^{Dhonburi}/\beta^A$	10 (1.9)	5/5	4.5 ± 0.3 (4.1–4.9)	0.5 ± 0.4 (0–1.0)	5.3 ± 0.7 (4.1–5.9)	13.1 ± 2.1 (10.9–15.5)	75.1 ± 4.1 (70.8–80.3)	25.2 ± 1.4 (23.4–26.6)	14.1 ± 1.1 (12.7–15.6)
$\beta^{NT-90;\ (C-T)}/\beta^A$	2 (0.4)	0/2	6.4, 5.9	0, 3.5	4.6, na	11.1, na	67.3, na	23.9, na	17.3, na
$\beta^{NT-86;\ (C-G)}/\beta^A$	1 (0.2)	1/0	5.0	0.4	na	na	na	na	na
$\beta^{NT-50;\ (G-A)}/\beta^A$	1 (0.2)	1/0	4.0	1.6	5.5	14.3	77.5	26	14.4
β^0/β^{Ab}	309	157/152	5.7 ± 0.7 (4.0–7.6)	1.4 ± 1.1 (0–7.0)	5.5 ± 0.9 (3.4–7.8)	11.4 ± 1.9 (10.7–17.1)	63.6 ± 4.0[a] (55.8–77.6)	20.6 ± 1.8[a] (18.7–25.4)	17.2 ± 2.0 (12.6–18.6)

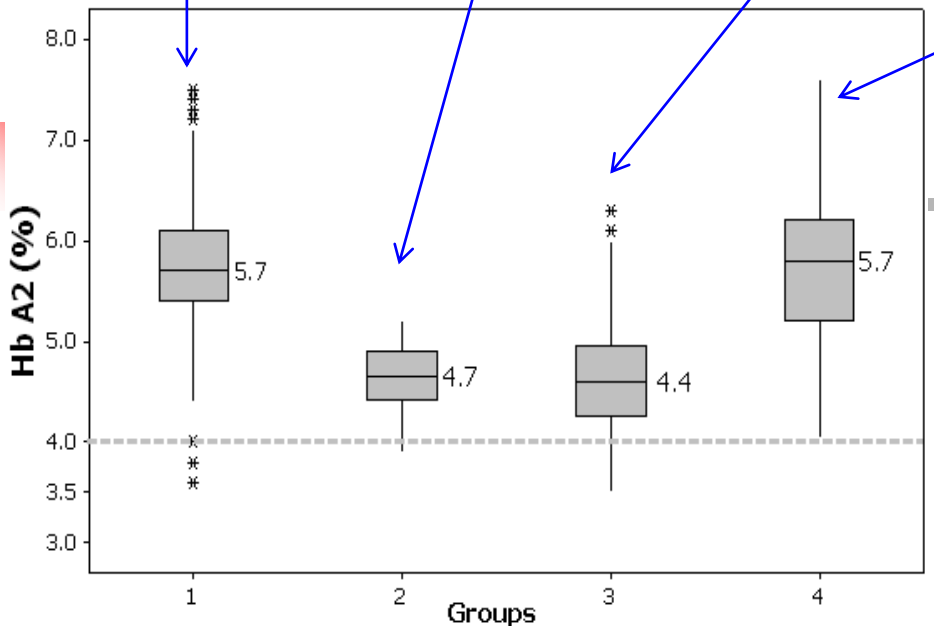
[a] Significant different from β^0-thalassemia trait ($P < 0.001$; Mann–Whitney U-test).
[b] Heterozygous β^0-thalassemia: Data from our series including CD 41/42 (−TTCT); (N = 195) and CD17 (A–T); (N = 114), NT: Nucleotide na: not available.

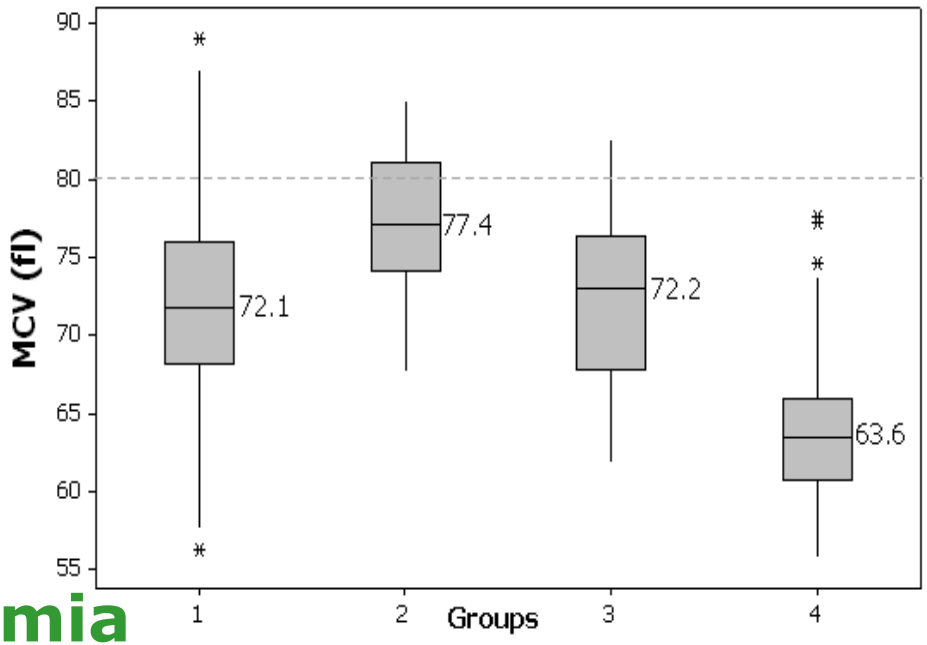
-28 A-G (431)

-31 A-G (41)

-87 C-A (13)
Hb Malay (29)
Hb Dhonburi (10)

β^0 - thal (n=309)





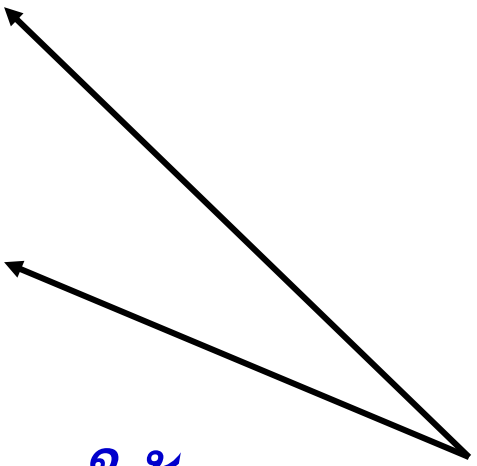
มีส่วนน้อยที่ < 4 %

และส่วนใหญ่เป็น β^+ - thalassemia

Laosombat V, et al. Am J Hematol 1992; 41: 194-198.
….. Data in Southern Thailand ….

Six most common mutations (not including Hb E) are …..

- Codons 41/42	β^o	Thai & Chinese Thai
- IVS1#5 G – C	severe β^+	Thai muslim
- Codon 19 A – G	β^+	Hb Malay
- Codon 17 A – T	β^0	
- - 28 A – G	β^+	
- IVS1#1 G – T	β^0	



… ข้อมูลภาคใต้ …

วารสาร
เทคนิคการแพทย์และกายภาพบำบัด
JOURNAL OF MEDICAL TECHNOLOGY AND PHYSICAL THERAPY

นิพนธ์ต้นฉบับ
ORIGINAL ARTICLE

พื้นฐานการเกิดโรคระดับโมเลกุลของบีตาธาลัสซีเมียที่จังหวัดนราธิวาส

อับดุลเลาะ หะมะ *

Received: *July 10, 2014*
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บทคัดย่อ

เพื่อเป็นการเตรียมข้อมูลที่มีประโยชน์สำหรับการวางแผนงานการควบคุมและป้องกันโรคบีตาธาลัสซีเมียในจังหวัดนราธิวาส จึงได้ศึกษาและรวบรวมข้อมูลย้อนหลัง พื้นฐานการเกิดโรคบีตาธาลัสซีเมียในระดับโมเลกุล ศึกษาจากตัวอย่างจำนวน

ตารางที่ 1 ชนิดและความถี่ของการกลายพันธุ์ที่ตรวจพบที่โรงพยาบาลราธิวาสราชนครินทร์ ตรวจพบทั้งชนิด β^0- และ β^+ - thalassemia (+) รวมทั้ง deletion ที่ทำให้เกิดลักษณะ high Hb F ในผู้ใหญ่

Mutation	Type	No.	%
Non deletion			
IVS I # 5 (G-C)	0	77	43.5
codons 41/42 (-TTCT)	0	30	16.9
codon19 (Hb Malay)	+	18	10.6
codon17 (A–T)	0	15	8.4
- 28 (A-G)	+	10	5.6
IVS I # 1 (G-T)	0	8	4.5
IVS II # 654 (C-T)	0	4	2.2
codon 41 (-C)	0	3	1.6
codons 71/72 (+A)	0	1	0.6
Deletion			
3.4 kb del β^0-thalassemia	0	3	1.6
12.5 kb del $\delta\beta^0$-thalassemia	high Hb F	3	1.6
45 kb del β^0-thalassemia	0	2	1.1
79.2 kb del HPFH	high Hb F	2	1.1
$^{G}\gamma(^{A}\gamma\delta\beta)^0$-thal	high Hb F	1	0.6
รวม		177	100

Expression of Hbs A_2, E and F in various Hb E related disorders

Blood Cells, Molecules, and Diseases 48 (2012) 11–16

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Blood Cells, Molecules, and Diseases

journal homepage: www.elsevier.com/locate/ybcmd

Phenotypic expression of hemoglobins A_2, E and F in various hemoglobin E related disorders

Nattaya Sae-ung [a], Hataichanok Srivorakun [a,b], Goonnapa Fucharoen [a], Supawadee Yamsri [a], Kanokwan Sanchaisuriya [a], Supan Fucharoen [a,*]

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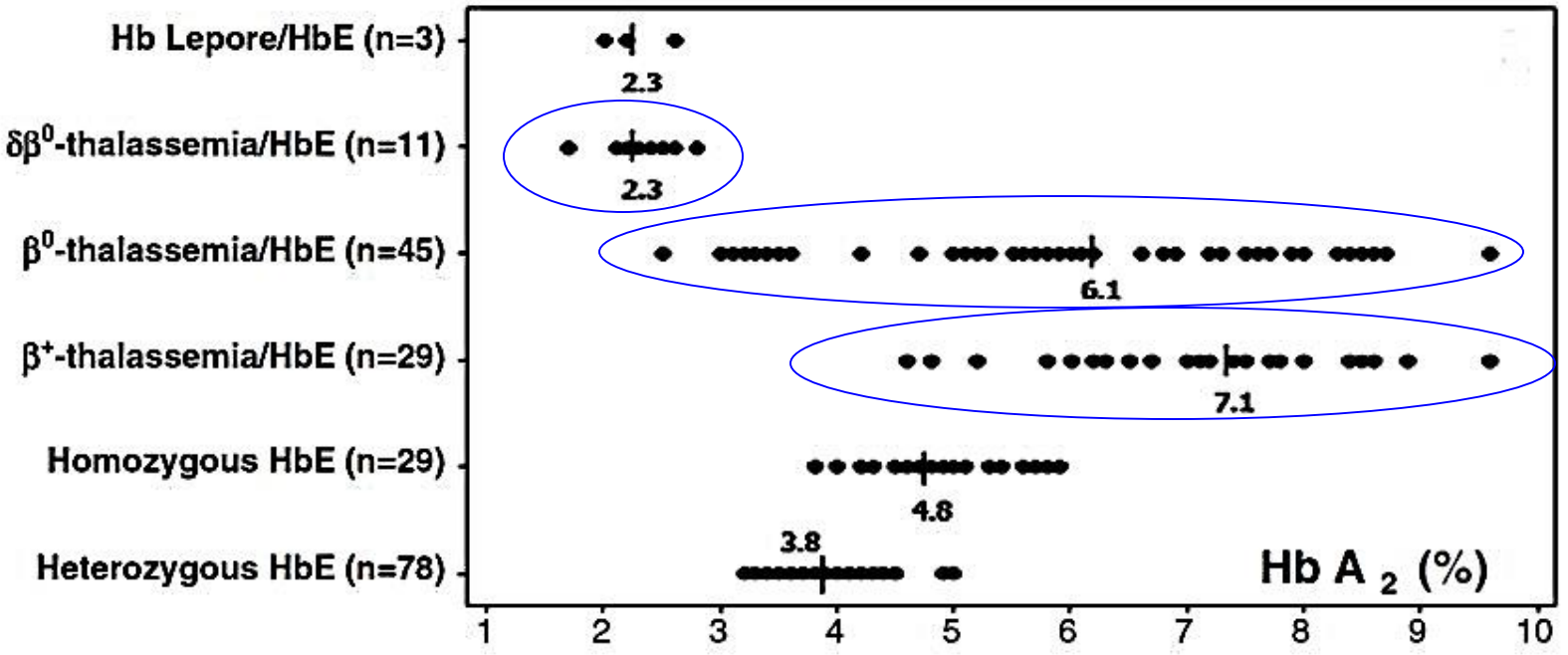
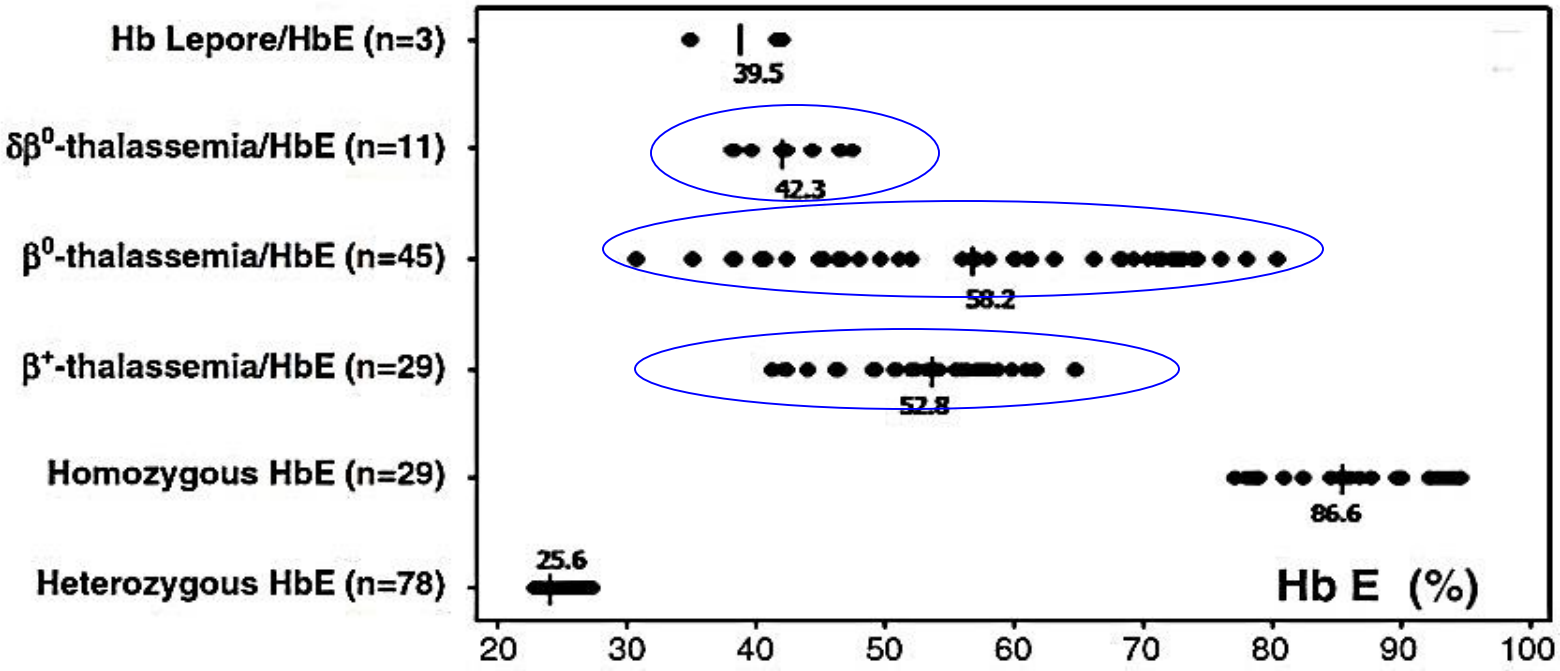

Hb Lepore/HbE (n=3)
2.3
δβ0-thalassemia/HbE (n=11)
2.3
β0-thalassemia/HbE (n=45)
6.1
β+-thalassemia/HbE (n=29)
7.1
Homozygous HbE (n=29)
4.8
Heterozygous HbE (n=78)
3.8
Hb A 2 (%)
1
2
3
4
5
6
7
8
9
10


Hb Lepore/HbE (n=3)
39.5
δβ0-thalassemia/HbE (n=11)
42.3
β0-thalassemia/HbE (n=45)
58.2
β+-thalassemia/HbE (n=29)
52.8
Homozygous HbE (n=29)
86.6
Heterozygous HbE (n=78)
25.6
Hb E (%)
20
30
40
50
60
70
80
90
100

α - thalassemia

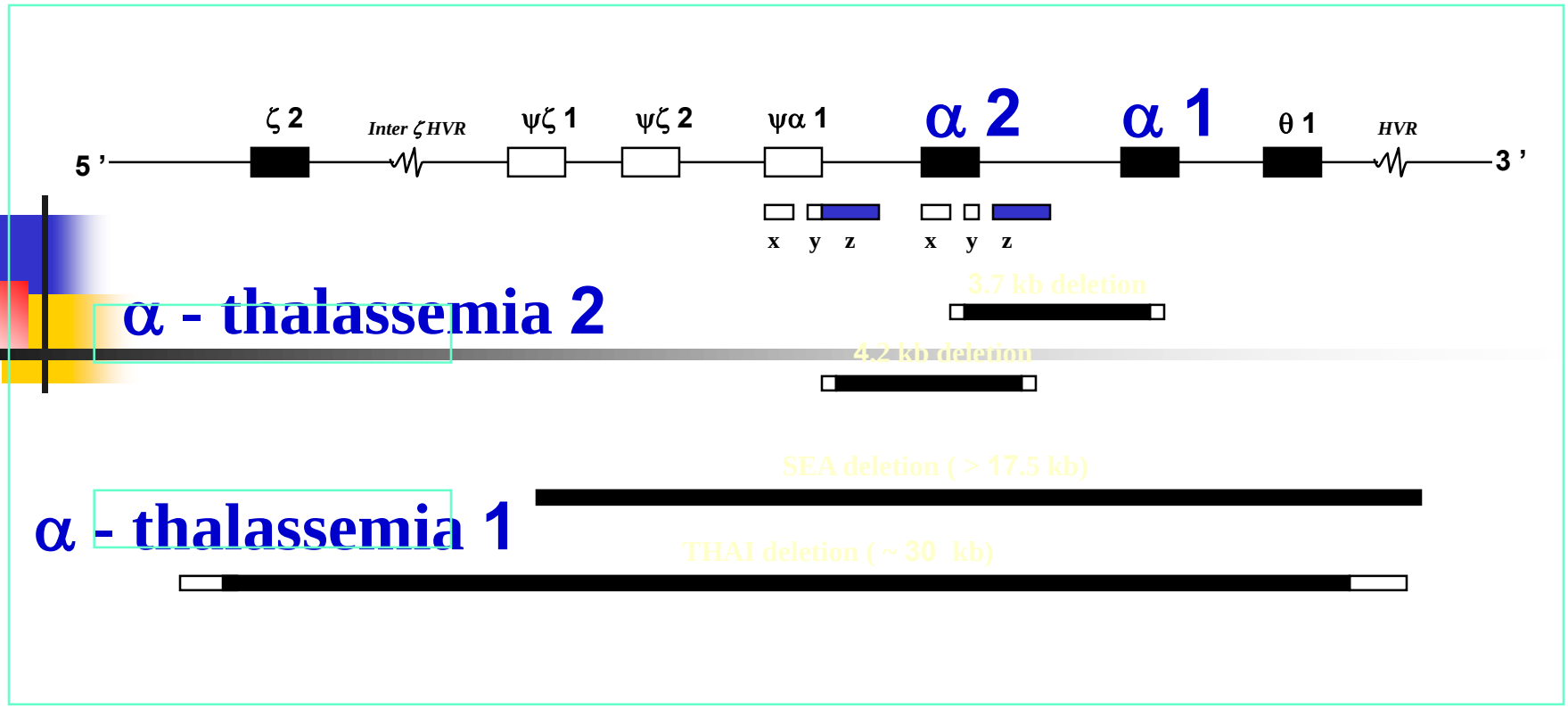
α^o - thalassemia (α – thalassemia 1)

no α - globin chain production

α^+ - thalassemia (α – thalassemia 2)

low α - globin chain production

α - thalassemia gene in Thailand



Mostly caused by DNA deletions

Molecular basis of α – thalassemia

Gene deletions

- α - thalassemia 1 deletion (SEA & THAI)
- α - thalassemia 2 deletion (3.7 kb & 4.2 kb)

Non deletion

- *Hb Constant Spring*
- *Hb Pakse'*
- *Hb Q - Thailand*
- *Hb Quong Sze* *(less common)*
- *Codon 30 (GAG deletion)* *(less common)*
- *Poly A mutation* *(less common)*
- *Hb Pak Nam Pho* *(less common)*

Data from ongoing thalassemia screening at KKU

1,541 positives at preliminary screening

397 α – thalassemia 1 carriers (25.8%)

- 396 SEA deletion
- 1 THAI deletion

Fetal Diagnosis and Therapy

Fetal Diagn Ther 2007;22:264–268
DOI: 10.1159/000100787

Received: March 29, 2006
Accepted after revision: June 7, 2006
Published online: March 16, 2007

Prenatal Diagnosis of Hb Bart's Hydrops Fetalis Caused by a Genetic Compound Heterozygosity for Two Different α^0-Thalassemia Determinants

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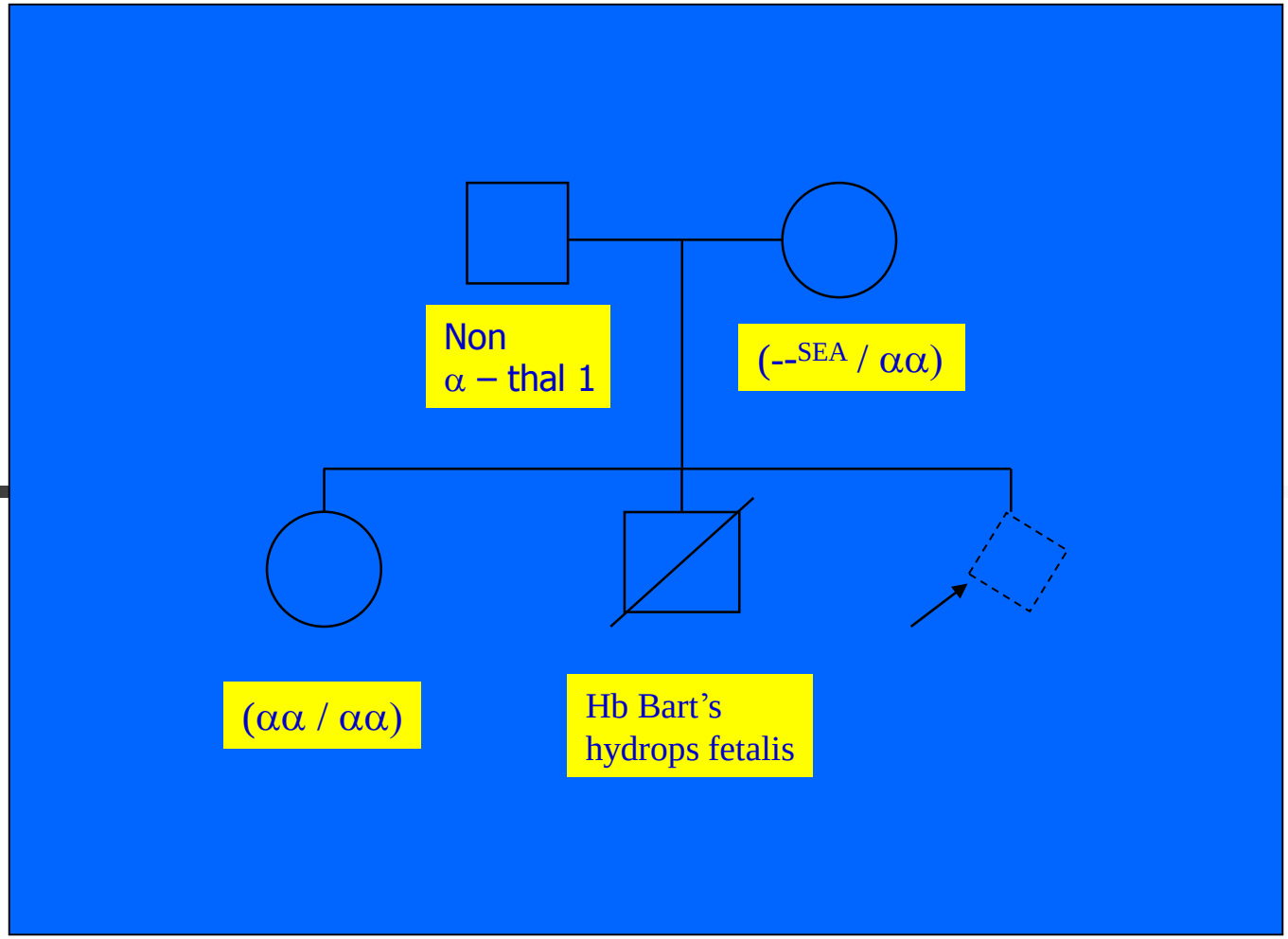
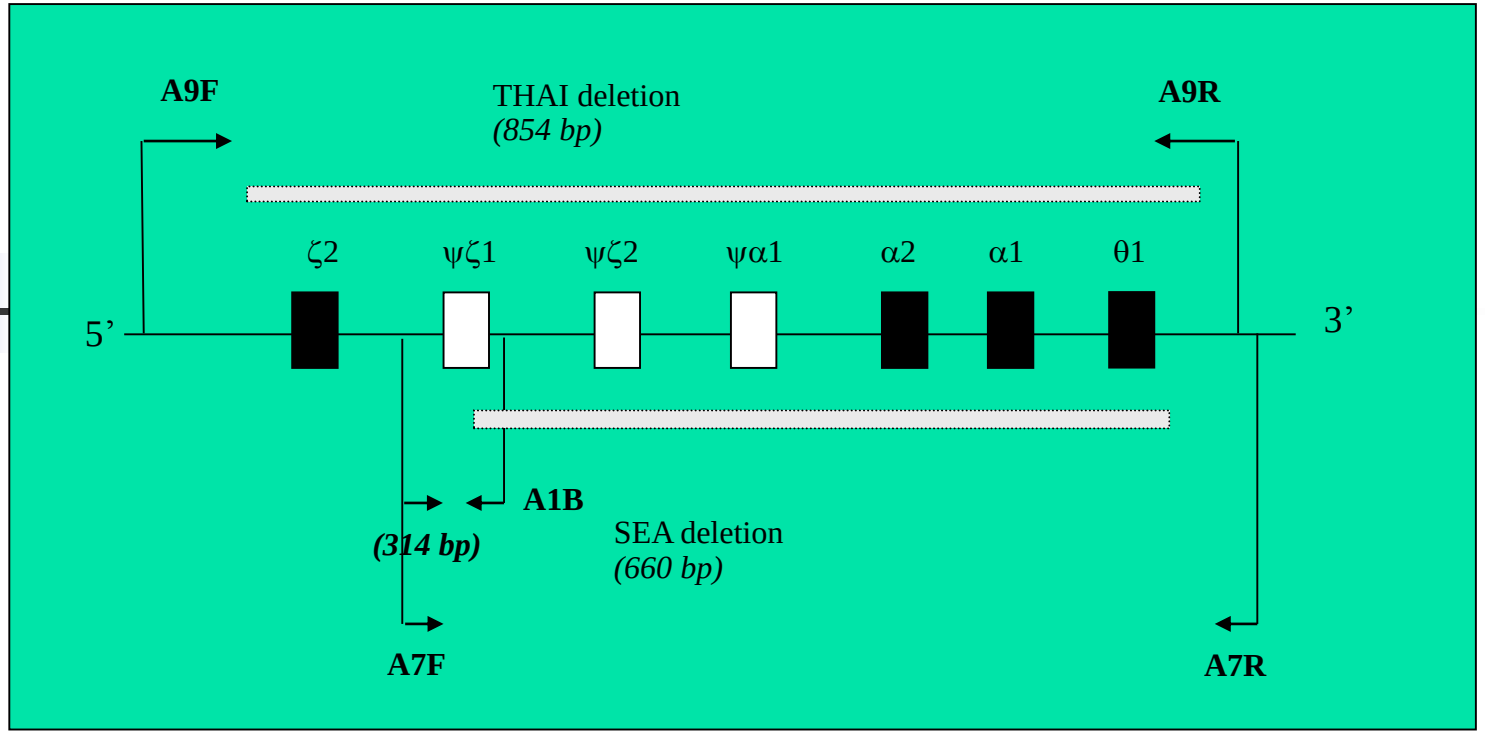
Supan Fucharoen[b]

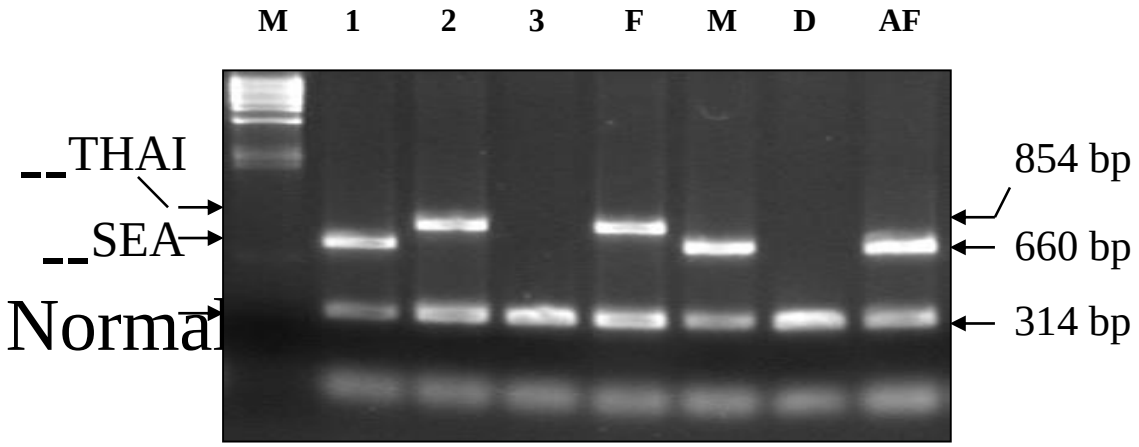
[a]Regional Health Center 8, Nakhon Sawan, and [b]Centre for Research and Development of Medical Diagnostic Laboratories, Faculty of Associated Medical Sciences, Khon Kaen University, Khon Kaen, Thailand

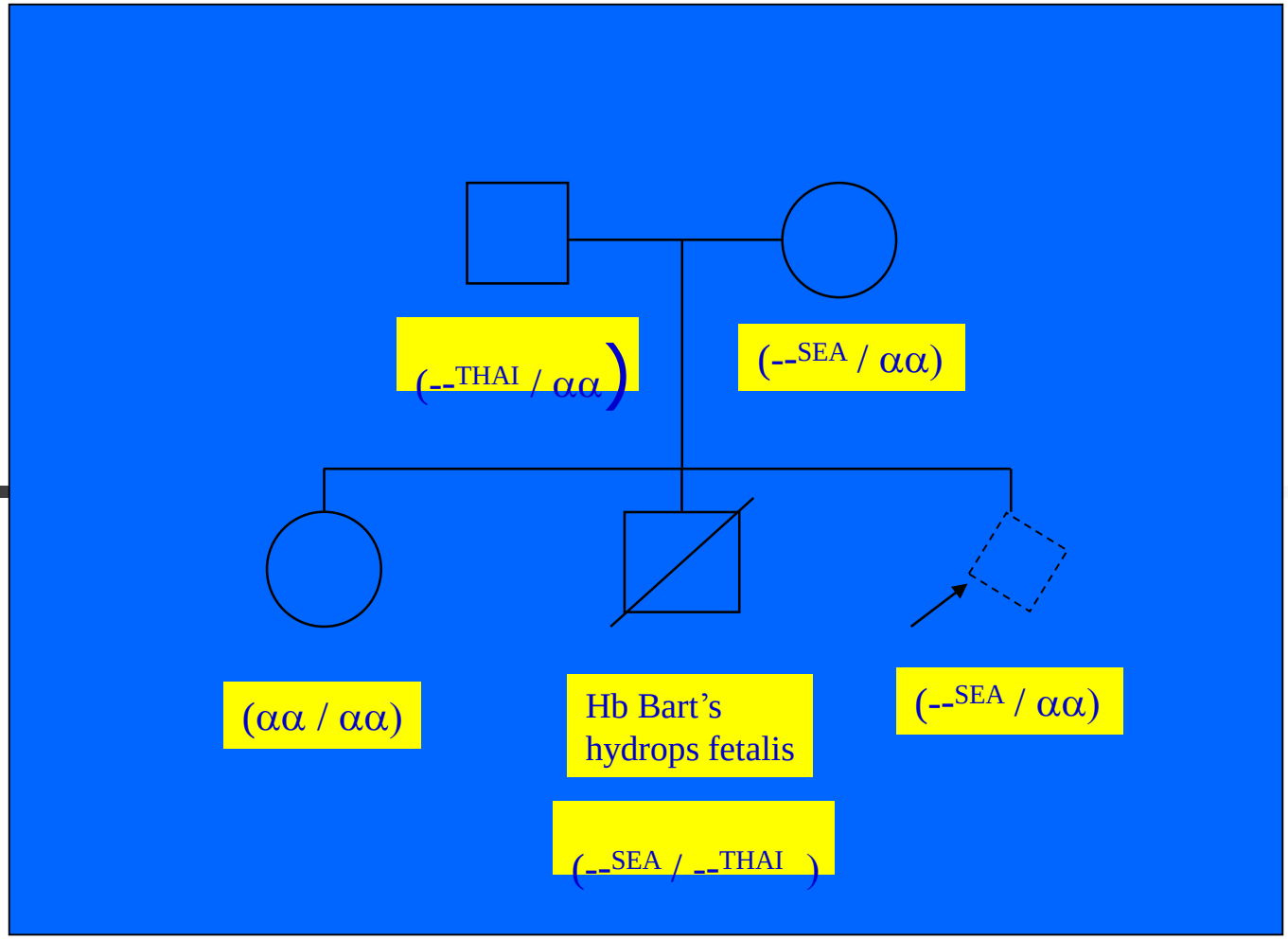
Table 1 Hematological data of a pregnant Thai woman and her family members.

Parameters	Proband	Husband	Daughter
OF	positive	positive	negative
DCIP	negative	negative	negative
Rbc (10^{12}/L)	4.5	6.3	3.3
Hb (g/dL)	9.8	14.6	12.5
Hct (%)	32	44	36
MCV (fL)	72.4	63	80.7
MCH (pg)	21.9	23.1	38.5
MCHC (g/dL)	30.3	36.9	47.7
RDW (%)	13.3	13.0	12.3
Hb A_2 (%)	2.4	2.6	2.4
Hb F (%)	0.3	0.1	0.3
α – thal 1 (SEA)	Positive	Negative	Negative


Non
α – thal 1
(--SEA / αα)
(αα / αα)
Hb Bart's
hydrops fetalis


A9F
THAI deletion
(854 bp)
A9R
ζ2
ψζ1
ψζ2
ψα1
α2
α1
θ1
5'
3'
A1B
(314 bp)
SEA deletion
(660 bp)
A7F
A7R


M
1
2
3
F
M
D
AF
THAI
SEA
Normal
854 bp
660 bp
314 bp


(--THAI / αα)
(--SEA / αα)
(αα / αα)
Hb Bart's hydrops fetalis
(--SEA / --THAI)
(--SEA / αα)

Referral cases commonly encountered at KKU for molecular analysis

Prenatal diagnosis

Diagnosis of complex thalassemias

Determine genotype – phenotype relationship

Diagnosis of unknown Hb variants

Example of Family analysis

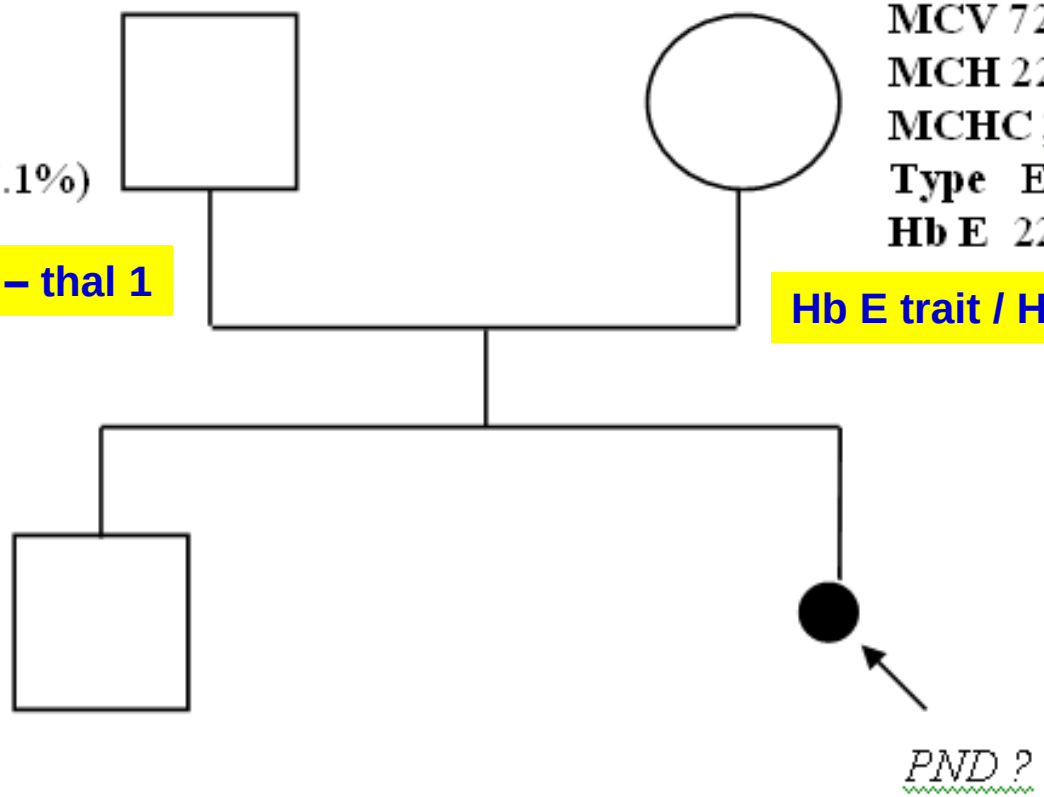
ครอบครัวที่ 1

OF + / DCIP -
Hb 12.9 g/dl
Hct 41.4 %
MCV 65.0 fl
MCH 20.2 pg
MCHC 30.9 g/dl
Type A_2A (A_2 = 7.1%)

β^0 – thalassemia trait / α – thal 1

OF + / DCIP +
Hb 10.4 g/dl
Hct 33.7 %
MCV 72.0 fl
MCH 22.2 pg
MCHC 31.0 g/dl
Type EA
Hb E 22.4 %

Hb E trait / Homo α – thal 2



OF + / DCIP -
Hb 9.9 g/dl
Hct 27.4 %
MCV 62.2 fl
MCH 22.3 pg
MCHC 22.9 g/dl
Type A_2ABart'sH
HbA_2 1.5 %

α – thal 1 / α – thal 2

Risk for … β^0 – thal / Hb E disease
Others: … Hb H disease
… EABart's disease

ระมัดระวังการแปลผล

…complex thalassemia syndrome…

พบได้บ่อยและวินิจฉัยพลาดได้

Example 1 ….. αβ - ***thalassemia***

mis - interpreted case of αβ - thalassemia

Patient : 7-year-old Thai boy

Initial laboratory findings:-

DCIP	Positive	
Hb	6.8	%
Hct	24.7	%
MCV	56.3	fl
MCH	15.5	pg
MCHC	27.6	g/dl
RDW	28.4	%

Hb typing A_2A (A_2 8.5 %, F 1.6 %, A 81.1 %)

↓

Suspected β - thalassemia

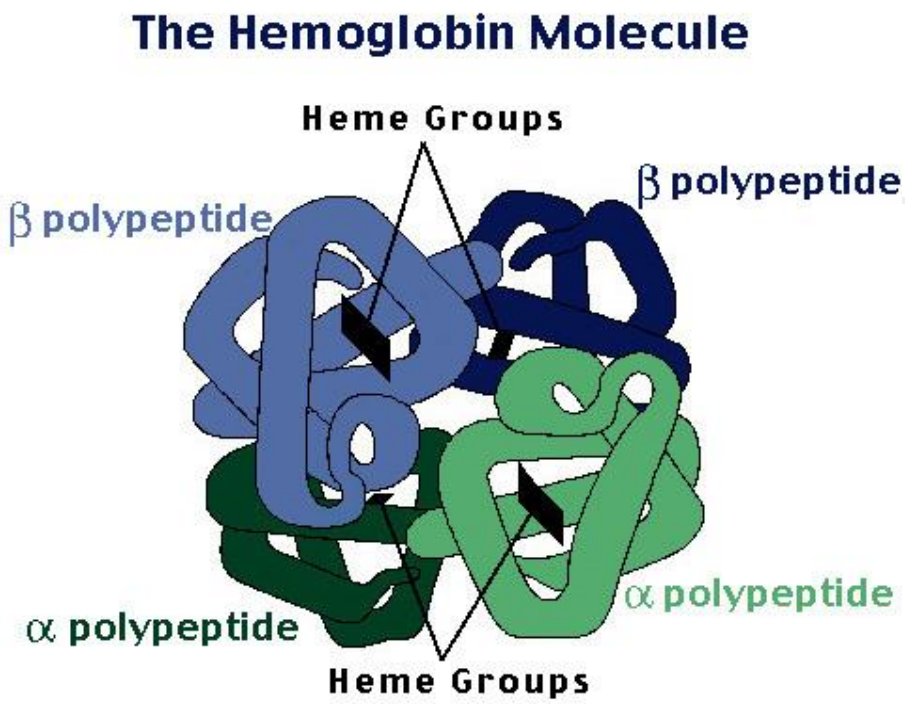
Refer for β – thalassemia gene analysis

Analysis at KKU

Repeated DCIP	:	Positive
β - thal gene analysis	:	Negative for all mutations
Hb E gene analysis	:	Positive (heterozygous)
α – thal gene analysis	:	Positive for α – thal 1 (SEA) Positive for α^{CS} gene

Repeated Hb typing : CS EA (E = 16.3 %)

Final diagnosis : CS EABart's disease



Abnormal Hemoglobins

...พบบ่อย... วินิจฉัยยาก....

Please refer to this recent paper for more information

OPEN ACCESS Freely available online

PLOS | ONE

A Large Cohort of Hemoglobin Variants in Thailand: Molecular Epidemiological Study and Diagnostic Consideration

Hataichanok Srivorakun[1], Kritsada Singha[1,2], Goonnapa Fucharoen[1], Kanokwan Sanchaisuriya[1], Supan Fucharoen[1]*

1 Centre for Research and Development of Medical Diagnostic Laboratories, Faculty of As sity, Khon Kaen, Thailand, 2 Graduate School, Khon Kaen University, Khon Kaen, Thailand

พบประมาณ 2.4 %

Abstract

Background: Hemoglobin (Hb) variants are structurally inherited changes of globin chains. Accurate diagnoses of these variants are important for planning of appropriate management and genetic counseling. Since no epidemiological study has been conducted before, we have investigated frequencies, molecular and hematological features of Hb variants found in a large cohort of Thai subjects.

Materials and Methods: Study was conducted on 26,013 unrelated subjects, inhabiting in all geographical parts of Thailand over a period of 11 years from January 2002-December 2012. Hb analysis was done on high performance liquid chromatography (HPLC) or capillary electrophoresis (CE). Mutations causing Hb variants were identified using PCR and related techniques.

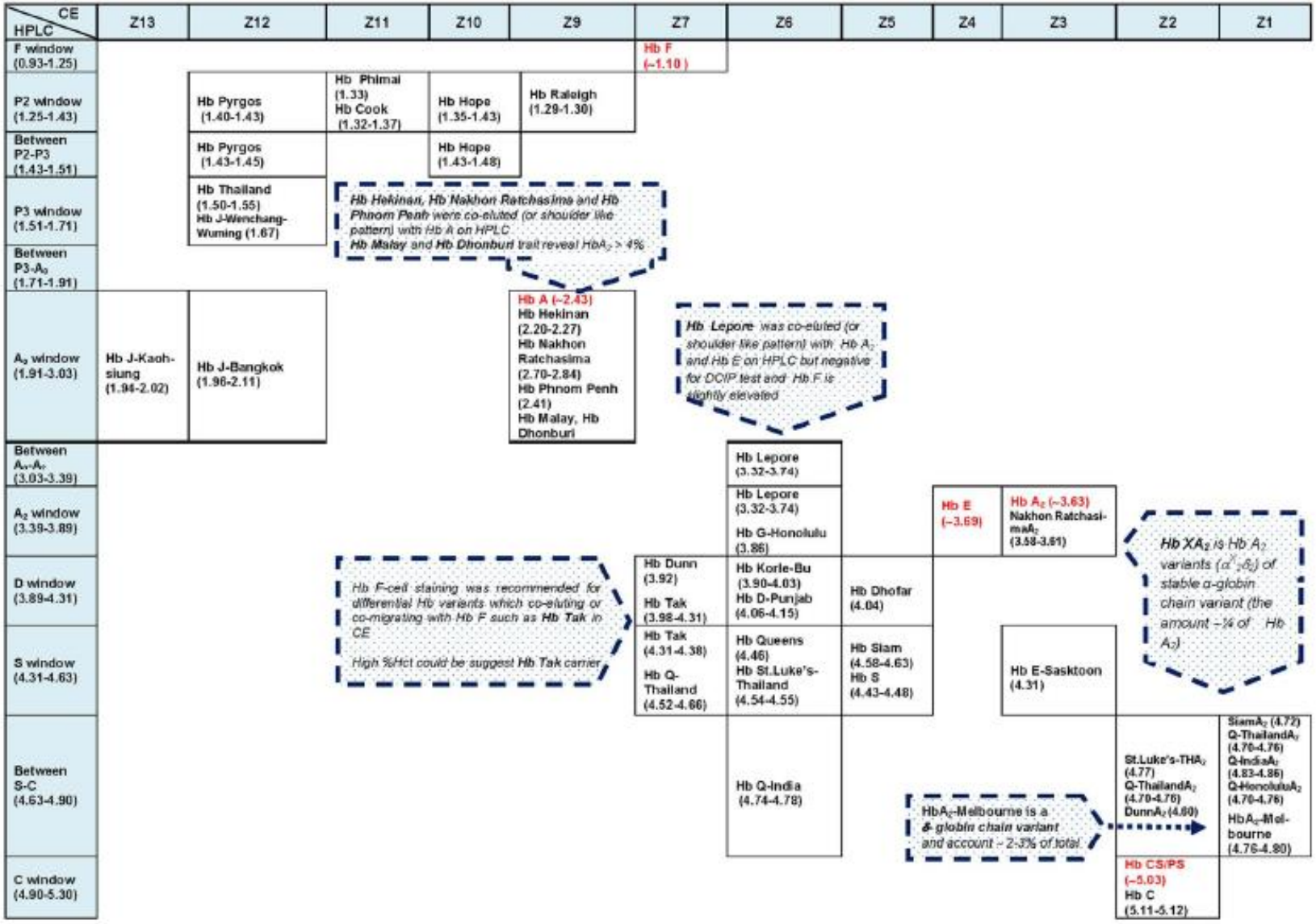
Results: Among 26,013 subjects investigated, 636 (2.4%) were found to carry Hb variants. Of these 636 subjects, 142 (22.4%) carried α-chain variants with 13 different mutations. The remaining included 451 (70.9%) cases with 16 β-chain variants, 37 (5.8%) cases with Hb Lepore (δβ-hybrid Hb) and 6 (0.9%) cases with a single δ-chain variant. The most common α-globin chain variant was the Hb O-Thailand ($\alpha^{74GAC\text{-}CAC,\ Asp\text{-}His}$) which was found in 101 cases (15.8%). For β-globin chain variants

Table 1. The frequency and Hb variant types found in 636 Thai referral cases throughout the countries.

Hb Variant (32 mutations)	Total no. (%)	Part of Thailand (n)					
		Center	Northeast	South	North	East	
α-Variant (13 mutations)							
Hb Q-Thailand ($\alpha1^{74GAC-CAC, Asp-His}$)	**101 (15.8)**	55	40	5		1	
Hb Siam ($\alpha1^{15GGT-CGT, Gly-Arg}$)	**8 (1.2)**	5	3				
Hb Queens ($\alpha1^{34CTG-CGG, Leu-Arg}$)	**6 (0.9)**	1		5			
Hb Beijing ($\alpha2^{16AAG-AAC,}$							
Hb Hekinan ($\alpha1^{27GAG-GA}$							
Hb Nakhonratchasima (							
Hb Dunn ($\alpha^{6GAC-AAC, Asp}$							
Hb Thailand ($\alpha1^{56AAG-AC}$							
Hb St. Luke's-Thailand (							
Hb Q-India ($\alpha1^{64GAC-CAC,}$							
Hb Phnom Penh ($\alpha1^{117}$							
Hb G-Honolulu ($\alpha2^{30GAC}$							
HbJ-Wenchang-Wuming							
β-Variant (16 mutations)							
Hb Hope ($\beta^{136GGT-GAT, Gly-Asp}$)	**121 (19.0)**	86	27	2	5	1	
Hb Tak ($\beta^{146+AC, Ter-Thr}$)	**90 (14.2)**	39	37	12	2		
Hb Malay ($\beta^{19AAC-AGC, Asn-Ser}$)	**46 (7.2)**	9	10	27			
Hb J-Bangkok ($\beta^{56GGC-GAC, Gly-Asp}$)	**43 (6.8)**	23	19	1			
Hb Pyrgos ($\beta^{83GGC-GAC, Gly-Asp}$)	**42 (6.6)**	14	28				
Hb D-Panjab ($\beta^{121GAA-CAA, Glu-Gln}$)	**38 (5.9)**	11	5	22			
Hb C ($\beta^{6GAG-AAG, Glu-Lys}$)	**24 (3.8)**	8		16			
Hb Korle-Bu ($\beta^{73GAT-AAT, Asp-Asn}$)	**19 (2.9)**	9	9	1			
Hb Cook ($\beta^{132AAA-ACA, Lys - Thr}$)	**10 (1.6)**	2	8				
Hb Dhonburi ($\beta^{126GTG-GGG, Val-Gly}$)	**8 (1.2)**		8				
Hb J-Kaohsiung ($\beta^{59AAG-ACG, Lys-Thr}$)	**3 (0.5)**		3				
Hb Phimai ($\beta^{72AGT-ACT, Ser-Thr}$)	**2 (0.3)**		2				
Hb Dhofar ($\beta^{58CCT-CGT, Pro-Arg}$)	**2 (0.3)**	2					
Hb S ($\beta^{6GAG-GTG, Glu-Val}$)	**1 (0.2)**			1			
Hb Raleigh ($\beta^{1GTG-GCG, Val-Ala}$)	**1 (0.2)**		1				
Hb E-Saskatoon ($\beta^{22GAA-AAA, Glu-Lys}$)							
δβ hybrid Hemoglobin (2 mutations)	**37 (5.8)**						
Hb Lepore-Hollandia ($\delta^{IVS\ I-42}/\beta^{IVS\ I-56}$)		11	14				
Hb Lepore-Washington-Boston ($\delta^{87}/\beta^{IVS\ II-8}$)		10	2				
δ variant (1 mutations)	**6 (0.9)**						
Hb A_2-Melbourne ($\delta^{43GAG-AAG, Glu-Lys}$)		4	2				
Total (%)	**636 (100)**	**294 (46.2)**	**237 (37.3)**	**92 (14.5)**	**11 (1.7)**	**2 (0.3)**	

~ 40 variants

Two dimensional diagnostic diagram using CE & HPLC



*Example 2 ….. **Abnormal Hb***

Unnecessary PND

Specimen
☐ Blood ☐ CVS
☐ Amniotic fluid ☐ Fetal Blood
☐ Other……

Patient history…… G3P2 GA 19+4 wks. Hb A_2A c Unidentify Hb.

Transfusion history……

Lab Finding	Father	Mother	Affected child
Name			
Rbc ($x10^{12}$/L)			
Hb (g/dl)			
HCT (%)			
MCV (fl)	MCV 89.3 DCIP+ve	MCV 75.8 DCIP+ve	
MCH (pg)			
MCHC (g/dl)			
RDW (%)			
Hb typing	A2A + unidentify Hb	EA	
HbA_2/HbE (%)	A2=2.1 + unidentify Hb	2.9% E 26.8%	
HbF (%)			

Fetal Risk ☐ Homozygous α-thalassemia 1
☐ Homozygous β-thalassemia
☑ β-thalassemia-Hb E disease
☐ Other (specify)……

MCV 89.3
A_2A (A_2 2.1%)
+ unidentified Hb

Father	:	*Carrier of unknown Hb variant*
Mother	:	*Hb E trait (Hb E = 26.8 %)*

Centre for Research and Development of
Medical Diagnostic Laboratories (CMDL) KKU

4123/55

Hemoglobin typing report

Recieved date: 5/6/2558

Working date : 5/6/2558

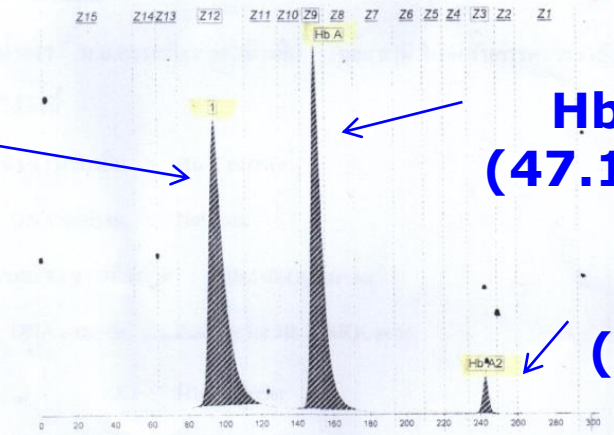
Type of sample: EDTA blood

ID : Fa58-256

Principle : Capillary Electrophoresis

Sample No. : 29

Name : rack: SEBIA Pos.: 5



Hb variant (50.4 %)

Hb A (47.1 %)

Hb A2 (2.5 %)

Hemoglobin Electrophoresis

Fractions	%	Ref. %	Ref. g/dl
1	50.4		
Hb A	47.1		
Hb A2	2.5		

DNA testing

Positive for Hb J Bangkok

ได้รับตัวอย่าง 5 มิ.ย. 58

ตามที่ได้ส่งน้ำคร่ำ [redacted] และ สามี ไปขอรับการตรวจธาลัสซีเมีย นั้น ผลการตรวจสรุปได้ดังนี้

[redacted] : **Hb E carrier** ← **Mother**

DNA analysis : Not done

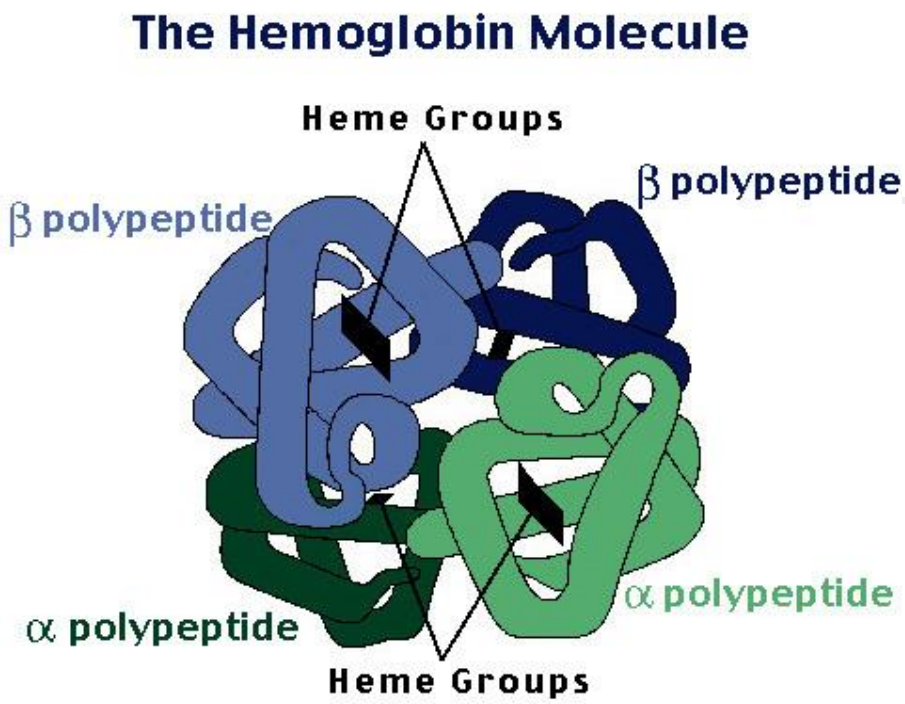
สามี [redacted] : **Hb J-BKK carrier** ← **Father**

DNA analysis : Positive for **Hb J-BKK** gene

AF : **Hb E carrier** ← **AF**

DNA analysis : Positive for **Hb E** gene

: **Negative** for Hb J-BKK gene



High Hb F determinants

...เจอได้บ่อยในภาคใต้...

Increased Hb F in adult

HPFH : ***Hereditary Persistence of Fetal Hemoglobin***

: increased Hb F in adult life with no clinical condition

: no hypochromic microcytosis / normal MCV & MCH

δβ-thalassemia : ***δ - & β - globin genes defect***

: increased Hb F in adult life with mild clinical condition

: hypochromic microcytosis / reduced MCV & MCH

Molecular basis

Mostly caused by

DNA deletion in β - globin gene cluster

Haematologica 2004;89:777-781.

[haematologica]
2004;89:xxxxx

SITTHICHAI PANYASAI
SUPAN FUCHAROEN
SATJA SURAPOT
GOONNAPA FUCHAROEN
KANOKWAN SANCHAISURIYA

Red Cell Disorders • Research Paper

Molecular basis and hematologic characterization of δβ-thalassemia and hereditary persistence of fetal hemoglobin in Thailand

A B S T R A C T

Background and Objectives. This study aims to characterize hematologically and molecularly the high hemoglobin (Hb) F determinants in Thailand, as well as to establish a rapid DNA-based assay to facilitate diagnosis in a routine laboratory.

Design and Methods. A multiplex allele-specific polymerase chain reaction (PCR) system for rapid detection of three common DNA deletions causing $(\delta\beta)^0$-thalassemia and hereditary persistence of fetal Hb (HPFH) in South-east Asians was developed and used to examine the molecular basis for the high Hb F phenotypes in 273 unrelated Thai individuals. Hematologic data were assessed comparatively.

Results. The multiplex PCR system was validated and results were completely concordant with those of other established methods. DNA analysis identified $^{G}\gamma^{A}\gamma(\delta\beta)^0$-thalassemia in 148 cases (54.2%), deletional HPFH-6 in 83 (30.4 %) and the deletion-inversion $^{G}\gamma(^{A}\gamma\delta\beta)^0$-thalassemia in 22 (8.1 %) cases, while another 20 (7.3 %) subjects remained uncharacterized. Genotype-phenotype relationships are discussed.

Interpretation and Conclusions. These data emphasize the high frequencies of δβ-thalassemia and HPFH in Thailand and the need for differential diagnostic methods as the hematologic parameters associated with them are very similar and overlapping. The multiplex allele-specific PCR approach should prove useful in complementing routine Hb analysis for differential diagnosis of these three common high Hb F determinants and should facilitate a program of hemoglobinopathy screening in the region.

Key words: δβ thalassemia, HPFH-6, deletion-inversion, multiplex PCR.

EUROPEAN JOURNAL OF Haematology

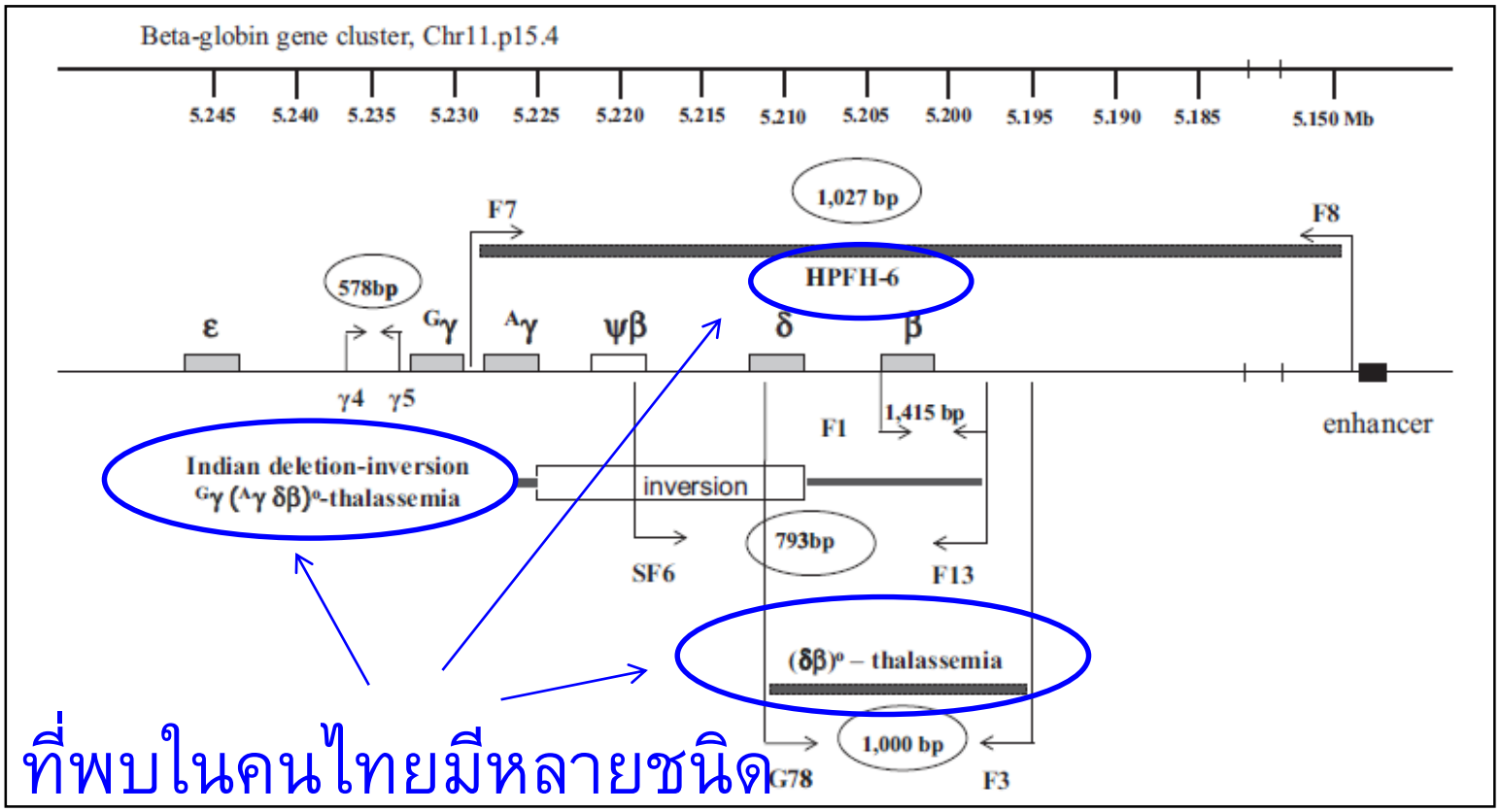
European Journal of Haematology 92 (73–79)

ORIGINAL ARTICLE

Phenotypic expression of Hb F in common high Hb F determinants in Thailand: roles of α-thalassemia, 5′ δ-globin BCL11A binding region and 3′ β-globin enhancer

Nattaphol Prakobkaew[1,2], Supan Fucharoen[2], Goonnapa Fuchareon[2], Nirut Siriratmanawong[3]

[1]The Graduate School, Khon Kaen University, Khon Kaen; [2]Centre for Research and Development of Medical Diagnostic Laboratories, Faculty of Associated Medical Sciences, Khon Kaen University, Khon Kaen; [3]Regional Health Promotion Center, region 8, Nakhon Sawan, Thailand

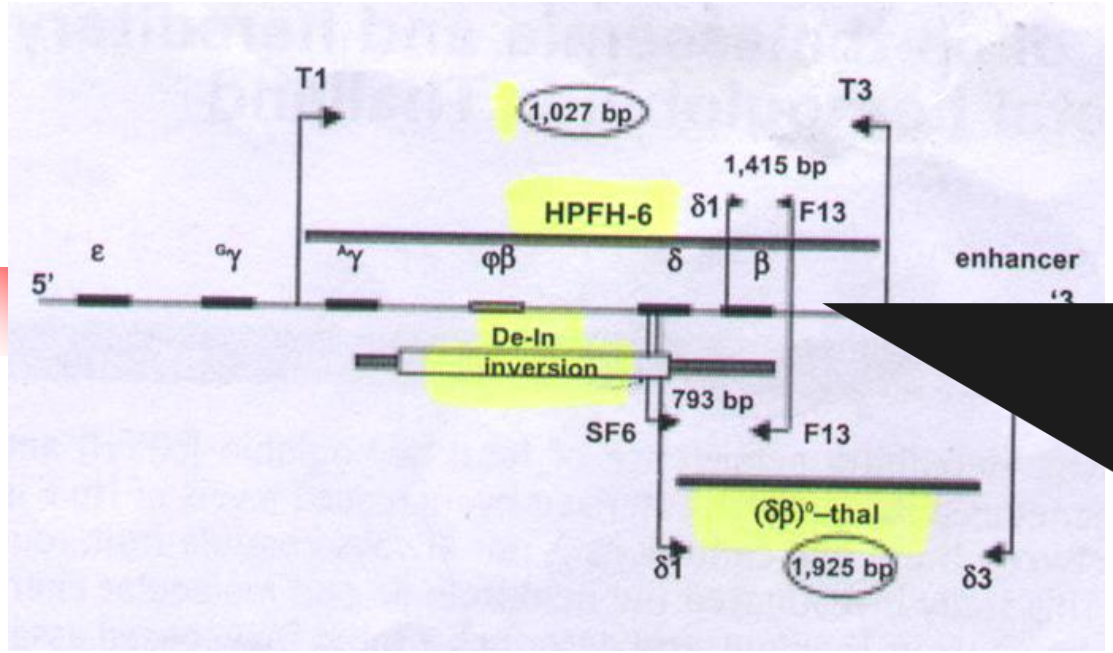


ที่พบในคนไทยมีหลายชนิด

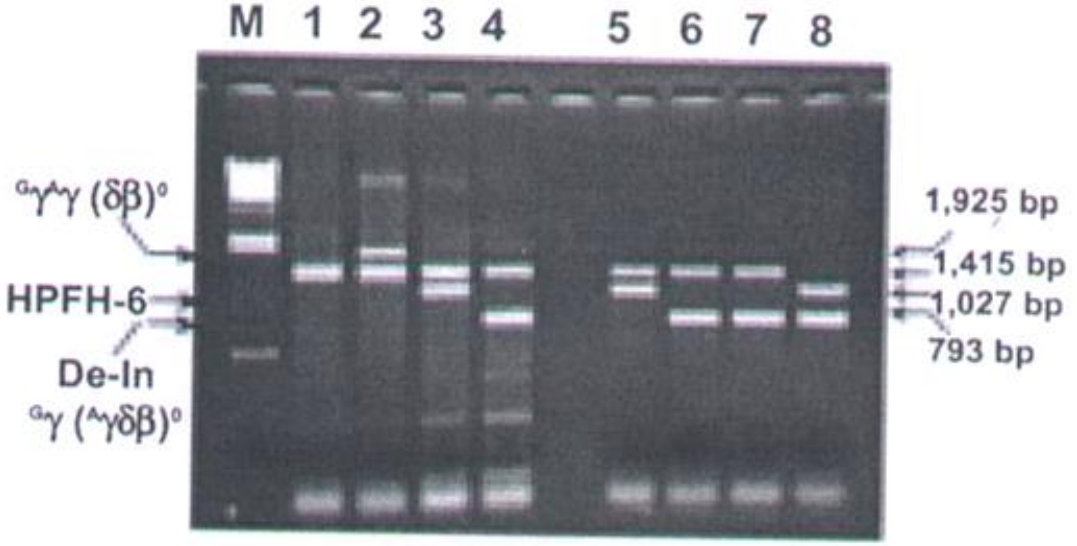
Table 1. Results of hematologic analyses of 253 adult Thai carriers of three different high Hb F determinants and 58 normal individuals. Values are expressed as mean ± standard deviation. The three determinants were statistically compared using the Kruskal-Wallis non-parametric test.

Parameters	*$(\delta\beta)^0$ -thal*	*HPFH-6*	*Deletion-Inversion*	*Difference*	*Normal*
N. (%)	148 (58.6)	83 (32.8)	22 (8.6)	–	58
Sex (male/female)	34/114	16/67	2/20	–	21/37
Age (year)	3–68	1.3–61	4–61	–	20–33
Rbc ($\times 10^6/mm^3$)	4.8±0.8	4.7±0.6	4.9±0.6	–	4.5±0.4
Hb (g/dL)	11.5±1.5	12.3±1.4	12.1±1.3	–	13.3±1.4
Hct (%)	35.7± 4.5	37.5±4.4	37.3±3.6	–	39.8±4.0
MCV (fL)	75.4± 7.0	79.9±6.8	76.4±5.6	< 0.001	87.9±3.6
MCH (pg)	24.4±2.0	25.7±2.2	24.3±1.9	< 0.001	29.5±1.6
MCHC (g/dL)	32.3±1.0	32.8±1.1	32.4±1.1	–	33.5±0.9
RDW-CV (%)	20.5±2.4	16.6±2.7	16.8±2.4	< 0.001	13.3±0.8
Hb-type	A_2FA	A_2FA	A_2FA	–	A_2A
Hb A_2 (%)	2.2±0.4	2.0±0.4	2.3±0.3	–	2.5±0.4
Hb F (%)	20.6±5.6	24.6±4.4	19.6±3.0	< 0.001	< 1.0
Hb F subunit	$^G\gamma$ & $^A\gamma$	$^G\gamma$	$^G\gamma$	–	–

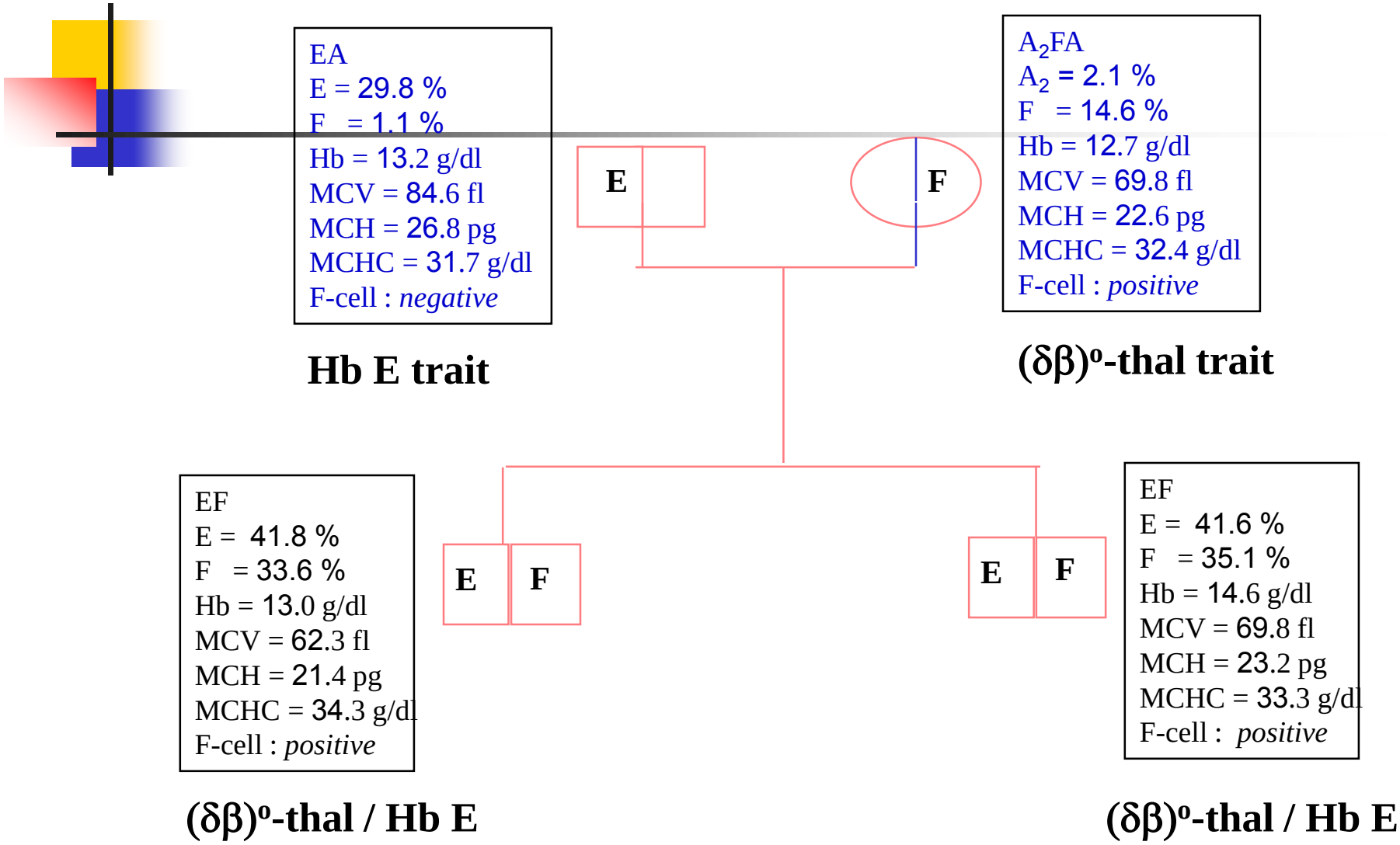
SGF.-



Development of multiplex PCR system



Family SP : *δβ - thalassemia / Hb E*



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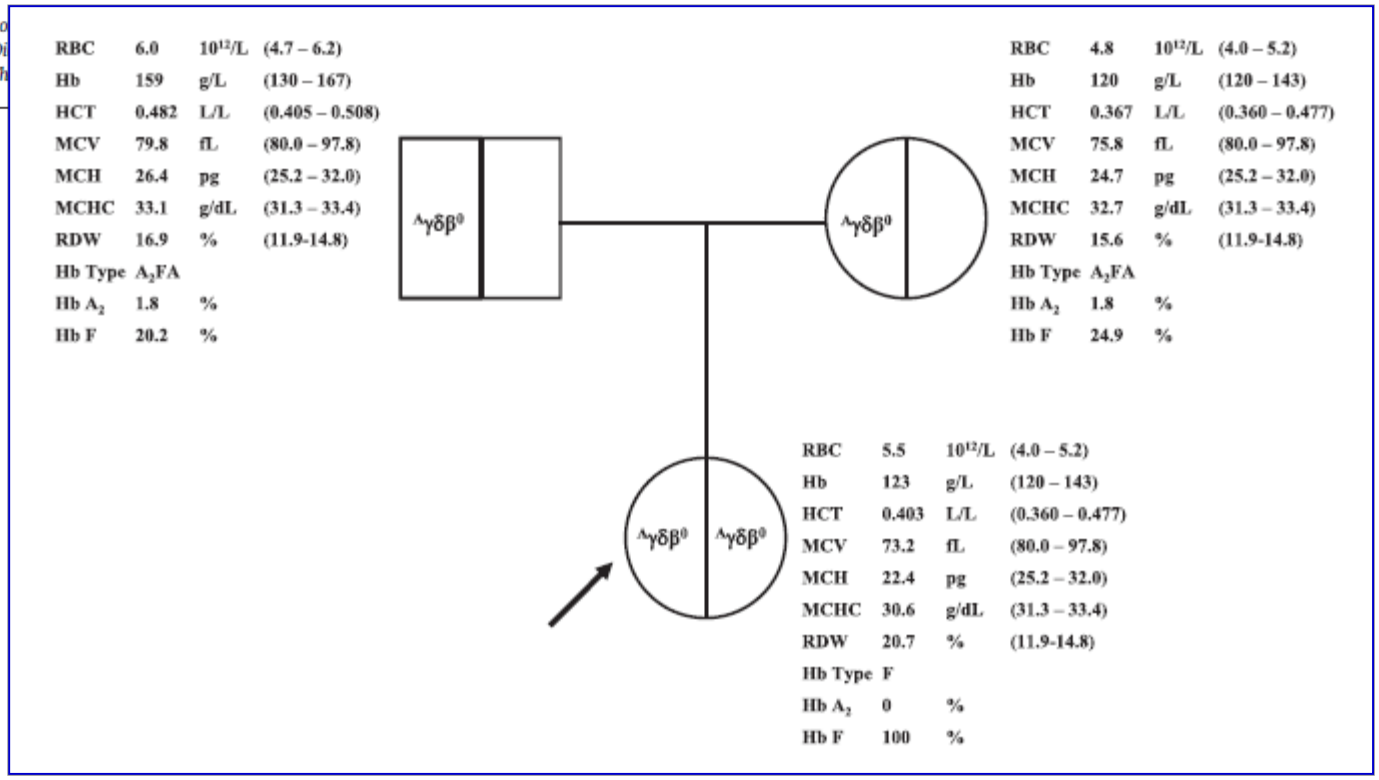
journal homepage: www.elsevier.com/locate/clinbiochem

A novel $^{A}\gamma\delta\beta^{0}$-thalassemia caused by DNA deletion–inversion–insertion of the β-globin gene cluster and five olfactory receptor genes: Genetic interactions, hematological phenotypes and molecular characterization

Kritsada Singha [a,b], Goonnapa Fucharoen [b], Abdulloh Hama [c], Supan Fucharoen [b,*]

[a] The Medical Science Program, Graduate School, Kho
[b] Centre for Research and Development of Medical Di
[c] Narathiwasrajanagarindra Hospital, Narathiwas, Th



12 มิ.ย. 2558

S58-909

15 มิ.ย. 2558
15.50 น.

เรียน รศ.ดร.สุพรรณ ฟูเจริญ ที่เคารพ

เรื่อง ขอความอนุเคราะห์ตรวจยืนยันชนิดของยีนฮีโมโกลบินของคนไข้ 1 ราย ดังนี้

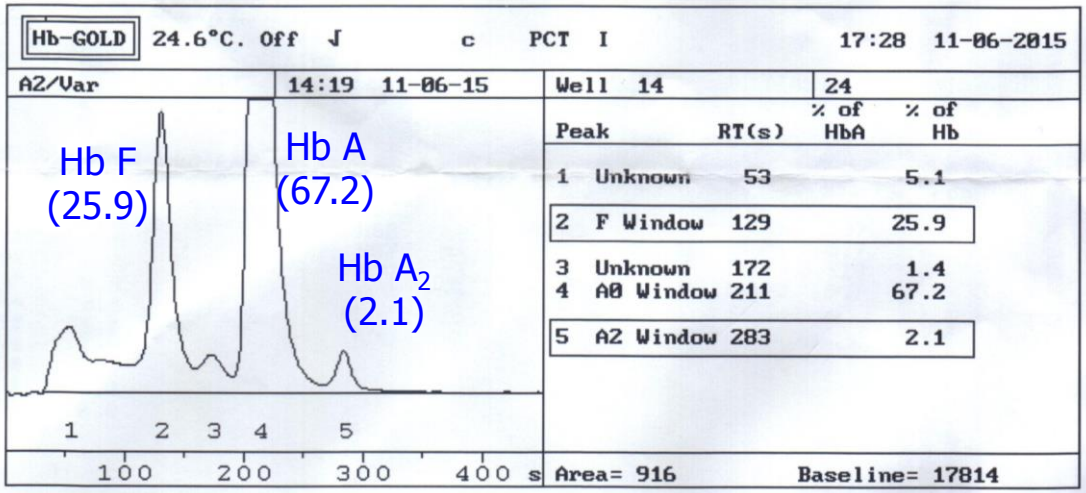
1. เด็กธนาเทพ ขนอม ส่งตรวจ PCR for Beta-common +rare mutations

สิ่งที่ส่งมาด้วย

1. ตัวอย่างเลือด จำนวน 1 หลอด
2. Hemoglobin typing 1ราย
3. ผล CBC 1 แผ่น

ผลการตรวจทางห้องปฏิบัติการ

Hb typing : ตามแนบ CBC : ตามแนบ



เพราะมี Hb F

สงสัย β – thal

จึงส่งตรวจ β - thal

DNA analysis : Positive for $(\delta\beta)^0$ – thalassemia trait)

Total Area : 1,525,707

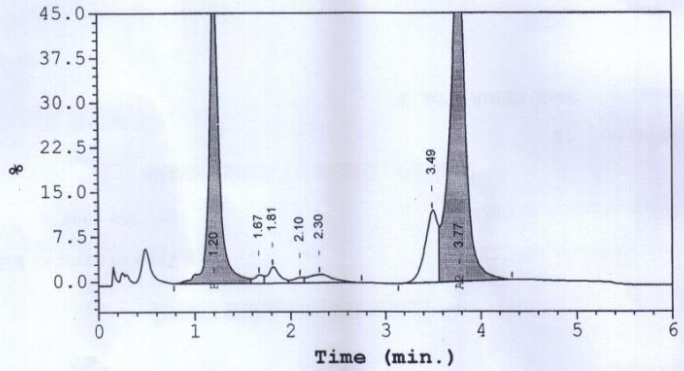
F Concentration = 33.2* %
A2 Concentration = 56.2* %

958-1046

Analysis comments:

*Values outside of expected ranges

อ่านผลเป็น Hb E เมื่อ % A_2 > 10%



Type of Hb : EF with Abnormal Hb

DNA analysis : Negative for α- thalassemia 1 gene (SEA& THAI)

Suggestion : ศูนย์อนามัยที่ 5 ส่งต่อเพื่อตรวจหา β – thalassemia mutation

Reported by : ทนพญ. รวิวรรณ พวงพฤกษ์ ท.น.9078 นักเทคนิคการแพทย์ชำนาญการ

Approved by : ดร.ทนพญ. ยุพิน โจ้แปง ท.น.1520 นักเทคนิคการแพทย์ชำนาญการพิเศษ

Rbc	-
Hb	-
Hct	-
MCV	60.9
MCH	-
MCHC	-
RDW	-

Centre for Research and Development of Medical Diagnostic Laboratories (CMDL) KKU

CMDL THAI SERVICE UNIT

QUALITY ASSURANCE DMSc หมายเลขทะเบียน 4123/55

Hemoglobin typing report

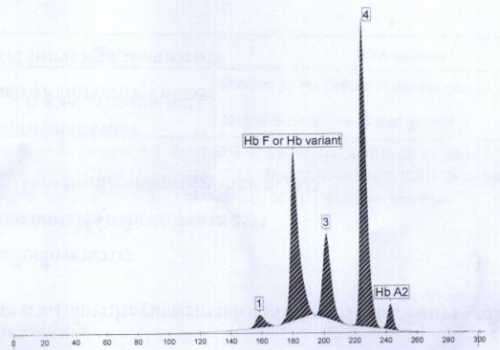
Recieved date: 7/7/2558 Type of sample: EDTA blood

Working date : 10/7/2558 ID : S58-1046

Principle : Capillary Electrophoresis

Sample No. : 16

Name : rack: SEBIA Pos.: 8



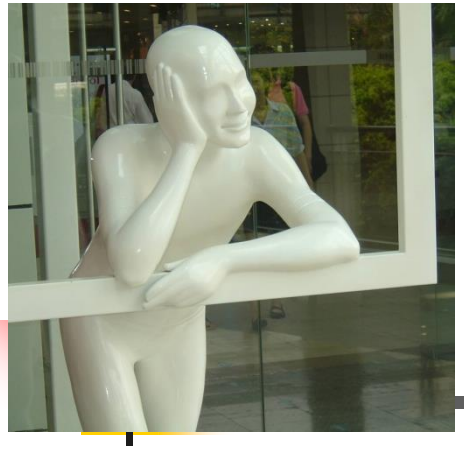
Hemoglobin Electrophoresis

Fractions	%	Ref. %	Ref. g/dl
1	2.6		
Hb F or Hb variant	31.9		
3	16.2		
4	46.1		
Hb A2	3.2		

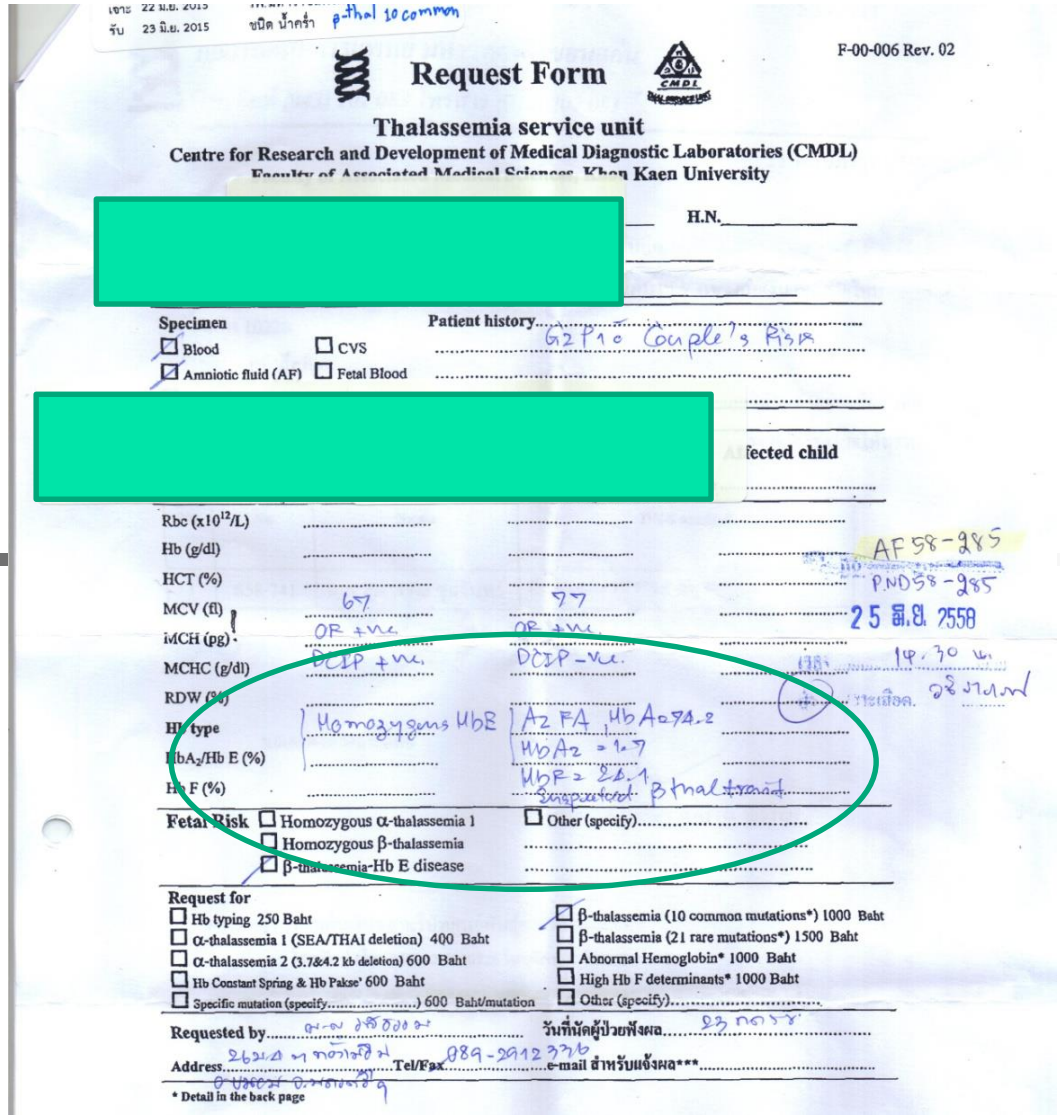
EF Abn…. Positive for

Hb E / Hb Lepore-Hollandia

*Example 3 ….. **High Hb F determinant***



Unnecessary PND



Request Form

F-00-006 Rev. 02

Thalassemia service unit

Centre for Research and Development of Medical Diagnostic Laboratories (CMDL)

Faculty of Associated Medical Sciences, Khon Kaen University

H.N.

Specimen: ☐ Blood ☐ CVS ☑ Amniotic fluid (AF) ☐ Fetal Blood

Patient history: G2P1 Couple's Risk

fected child

Rbc ($x10^{12}$/L)			
Hb (g/dl)			
HCT (%)			
MCV (fl)	67	97	
MCH (pg)	OR +ve.	OR +ve.	
MCHC (g/dl)	DCIP +ve.	DCIP -ve.	
RDW (%)			
Hb type	Homozygous HbE	A_2 FA, HbA_2 4.2	
HbA_2/Hb E (%)		HbA_2 = 1.7	
Hb F (%)		HbF = 24.1 suspected β thal trait	

AF 58-985

PND 58-985

25 มิ.ย. 2558

Fetal Risk: ☐ Homozygous α-thalassemia 1 ☐ Homozygous β-thalassemia ☑ β-thalassemia-Hb E disease ☐ Other (specify)

Request for:

- ☐ Hb typing 250 Baht
- ☐ α-thalassemia 1 (SEA/THAI deletion) 400 Baht
- ☐ α-thalassemia 2 (3.7&4.2 kb deletion) 600 Baht
- ☐ Hb Constant Spring & Hb Pakse' 600 Baht
- ☐ Specific mutation (specify.....) 600 Baht/mutation
- ☑ β-thalassemia (10 common mutations*) 1000 Baht
- ☐ β-thalassemia (21 rare mutations*) 1500 Baht
- ☐ Abnormal Hemoglobin* 1000 Baht
- ☐ High Hb F determinants* 1000 Baht
- ☐ Other (specify).....

Requested by..... วันที่นัดผู้ป่วยฟังผล.....

Address..... Tel/Fax 089-2912376 e-mail สำหรับแจ้งผล***.....

* Detail in the back page

Father *Homozygous Hb E*

Mother *High Hb F carrier*

DNA analysis for Thalassemia S58 /741

คณะเทคนิคการแพทย์ มหาวิทยาลัยขอนแก่น

โทรศัพท์ (043) 202 083 โทรสาร (043) 202 083

11 พฤษภาคม 2558

RE : ผลการตรวจ DNA analysis

เรียน ผู้อำนวยการ บริษัทศูนย์พันธุ์ศาสตร์การแพทย์ ที่นับถือ

บริษัทศูนย์พันธุ์ศาสตร์การแพทย์ 6/3 หมู่ 6 ถ.สุขาภิบาล 5 แขวงออเงิน เขตสายไหม กรุงเทพ 10220

อ้างถึง หนังสือที่ -

ตามที่ได้ส่งเลือดไปตรวจดีเอ็นเอธาลัสซีเมียนั้น ซึ่งห้องปฏิบัติการได้รับตัวอย่างเลือด เมื่อวันที่ 6 พฤษภาคม 2558 เวลา 10.30 น. จำนวน 1 ตัวอย่าง ผมใคร่ขอแจ้งสรุปผลการตรวจให้ทราบดังนี้

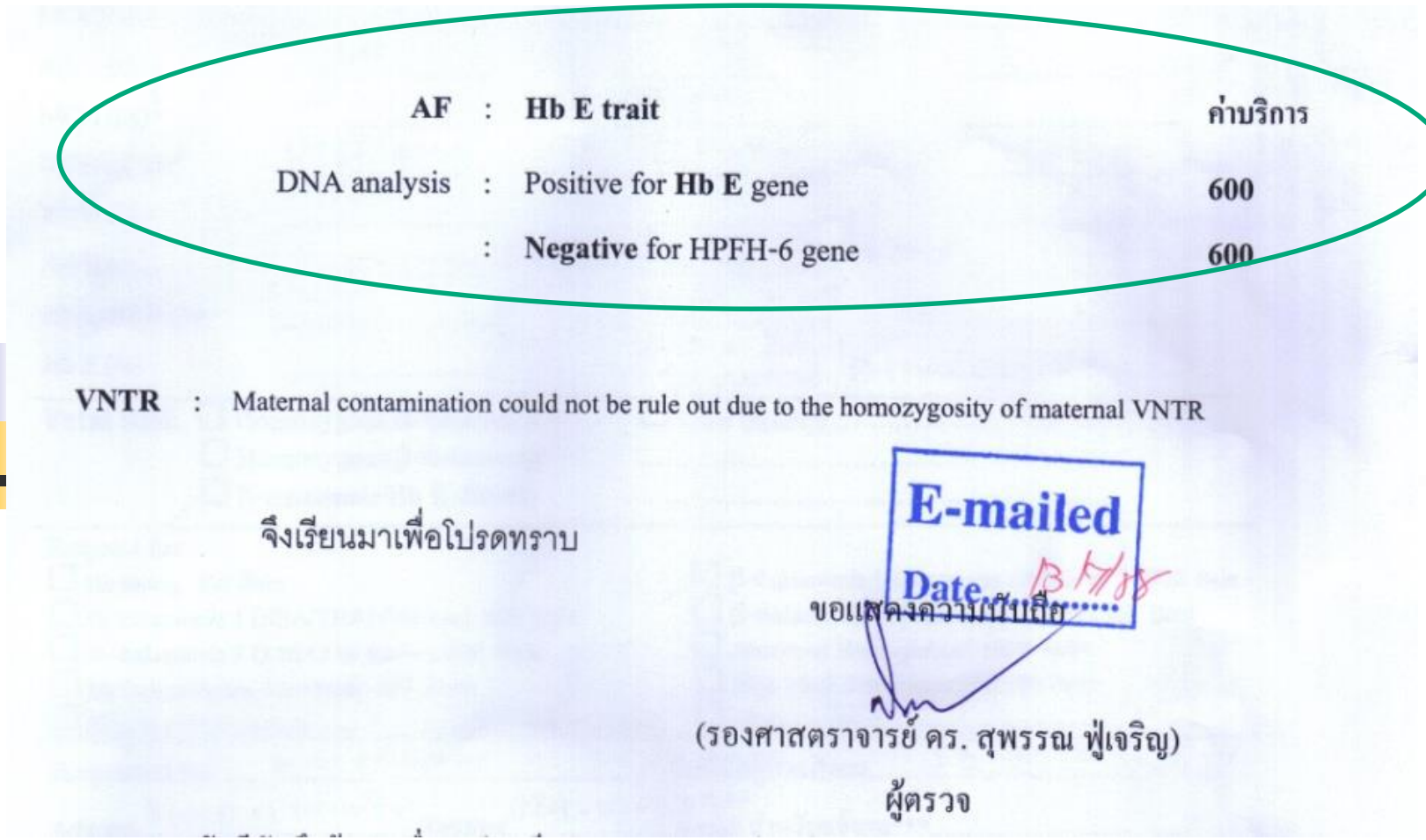
No	No	Name	DNA analysis
1	[redacted]		Positive for HPFH-6 gene

ขอแสดงความนับถือ

(รองศาสตราจารย์ ดร.สุพรรณ ฟู่เจริญ)

ผู้ตรวจ

Positive for HPFH-6 trait



AF	:	**Hb E trait**	ค่าบริการ
DNA analysis	:	Positive for **Hb E** gene	**600**
	:	**Negative** for HPFH-6 gene	**600**

VNTR : Maternal contamination could not be rule out due to the homozygosity of maternal VNTR

จึงเรียนมาเพื่อโปรดทราบ

E-mailed
Date 13/7/58

ขอแสดงความนับถือ

(รองศาสตราจารย์ ดร. สุพรรณ ฟู่เจริญ)

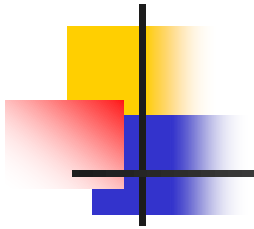
ผู้ตรวจ

PND : ทารกในครรภ์เป็น Hb E trait

ตรวจ Lab ให้ถูกต้อง
และใช้ผล Lab ทุกอย่าง
ร่วมกันในการ
วินิจฉัยและประเมินคู่เสี่ยง

..... ตอบว่าไม่รู้บ้างก็ได้ .....

..... แล้วปรึกษาผู้รู้เอา .....



The End