Low fetal hemoglobin rates in patients carrying Thai (δβ)⁰-deletion and Turkish (δβ)⁰-deletion/inversion strengthen the hypothesis that the 5'δ BCL11A binding site plays a major role in its fetal hemoglobin inhibitory regulation. Response to "The 12.6 kb-deletion in the β-globin gene cluster is the known Thai/Vietnamese (δβ)⁰-thalassemia commonly found in Southeast Asia"

We read with interest the letter by Chalaow *et al.*[1] concerning 12.6 kb-deletion in the beta(β)-globin gene cluster known as the Thai/Vietnamese (δβ)⁰-thalassemia commonly found in Southeast Asia. The main purpose of our study[2] was not to report the discovery of new deletions but to focus on the impact of the loss of a regulatory element in the increase in fetal hemoglobin (HbF) by using short deletions. From the deletions described in our work, the 12610 pb del was claimed to be reported for the first time. However, it appears that this deletion was actually described under various names and referenced as: i) Thai (δβ)⁰-deletion[3] (5' breakpoint : 35432-35620 and 3'breakpoint: 23090 on NCBI_AC104389.8 co-ordinates;[4] ii) Laotian deletion (assumed to be a similar deletion, with stated 5' breakpoint between 775-781 in IVS2 of the δ-globin gene and 3' breakpoint laying 4.7kb downstream of the β-globin gene);[5] iii) Vietnamese (δβ)⁰-deletion (56009-68592del on Genbank HUMBB co-ordinates);[6] iv) SEA (δβ)⁰-deletion (55989-68573del on GenBank U01317 co-ordinates).[7] Clearly, we had not sufficiently searched the GenBank or compared our results with these data.

Thus, it would be more appropriate to report that, in a patient from India, we had identified a deletion known as being likely to be present more frequently in South-East Asian populations (Thailand, Laos and Vietnam). The lack of a standardized and exhaustive database of the known β-globin locus deletions is one reason for the mistake in identifying a known deletion as a new discovery. Moreover, since deletion mapping was performed in mid-2011, the breakpoint sequence loaded on the GenBank browser was not identified as being that of a previously known deletion. So, we propose to submit this deletion to the HbVAr database, with a table summarizing its main features, and including all the publications that have described this event with a unified co-ordinate. We will carry out this submission using the table presented here (Table 1) that summarizes the main features of patients described in these publications.

Interestingly, when we look at the phenotypes reported in these publications, we find that the fetal hemoglobin (HbF) rates are very close to those reported in our data (Table 1), i.e. Thai (δβ)⁰-del patients: mean HbF in meta-analysis 1.95 g/dL (standard deviation, SD=0.75); Turkish del/inv patients: mean HbF in meta-analysis 1.06 g/dL (SD=0.50). Then, the global low HbF rates observed in meta-analysis for all patients with both deletions (1.69 g/dL; SD=0.79) are in agreement with our statement that the loss of BCL11A 5'-δ binding site is a key element in the resulting increase in HbF observed in patients carrying deletions removing this site, highlighting the major role of

Table 1. Summary of publications describing patients displaying the Thai (δβ)⁰-deletion or the Turkish del/inv patients.

		Hgb (g/dL)	MCV (fl)	MCH (pg)	A2 %	Hb F %	Hb F (g/dL)	HbF quantifying method
Trent[3] 1988	Thai (δβ)⁰-del 1 heterozygote patient	12.2	74	23	2.7	9.9	1.20	modified Betke method
Zhang[5] 1988	Thai (δβ)⁰-del 1 heterozygote patient	12.4	71	22.8	3	11.5	1.43	not reported
Craig[6] 1994	Thai (δβ)⁰-del 1 heterozygote patient	13.8	76	26	2.5	20	2.76	Hb electrophoresis at pH8.9 cellulose acetate, HbF measured by alkaline denaturation
		12.1	70	22	2.5	13	1.573	
	Turkish del/inv	10.9	67	23	2.2	12.4	1.3516	
	4 heterozygote	12.8	62	20	2.8	6.8	0.87	
	patients	10.8	58	19	3	4.2	0.4536	
	Thai (δβ)⁰-del	10.9	76	25.2	2.2	22.2	2.41	
	3 heterozygote	11.7	73	23.8	2	23.9	2.79	
	patients	13	73	23	2.9	15.8	2.054	
Fucharoen[8] 2001	Thai (δβ)⁰-del compound heterozygote (cd 41/42 CTTT) severe thalassemia intermedia patient	6.5	70	22.3	1.9	91.7	5.96	cation exchange chromatography in conjunction with gradient elution (Hb Gold, Drew scientific Ltd, UK)
	Thai (δβ)⁰-del compound heterozygote HbE	12.3	64	20		48.3	5.9	
		13.9	69	22.5		49.8	6.92	

that BCL11A binding site in its HbF inhibitory regulation.

We would like to express our sincere thanks to Chalaow et al. for their letter[1] that we received following our publication,[2] and for the interest they have shown in our data.

Elyes Slim Ghedira,[1] and Serge Pissard[2]

[1]Faculty of Pharmacy, Monastir University, Monastir, Tunisia; [2]APHP-Molecular Genetics Department, Henri Mondor Hospital, Créteil, France

Correspondence: serge.pissard@inserm.fr.
doi:10.3324/haematol.2013.093716

Key words: Thai Vietnamese, thalassemia, Turkish, fetal hemoglobin, deletion, inversion.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Chalaow N, Thein SL, Viprakasit V, Phil D. The 12.6 kb-deletion in the β-globin gene cluster is the known Thai/Vietnamese (δβ)0-thalassemia commonly found in Southeast Asia. Haematologica. 2013;98(9):e117-8.
2. Ghedira ES, Lecerf L, Faubert E, Costes B, Moradkhani K, Bachir D, et al. Estimation of the difference in HbF expression due to loss of the 5' δ-globin BCL11A binding region. Haematologica. 2013; 98(2):305-8.
3. Trent RJ, Svirklys L, Jones P. Thai (δβ)0-thalassemia and its interaction with γ-thalassemia. Hemoglobin. 1988;12(2):101-14.
4. Tritipsombut J, Phylipsen M, Viprakasit V, Chalaow N, Sanchaisuriya K, Giordano PC, et al. A single-tube multiplex gap-polymerase chain reaction for the detection of eight β-globin gene cluster deletions common in Southeast Asia. Hemoglobin. 2012; 36(6):571-80.
5. Zhang JW, Stamatoyannopoulos G, Anagnou NP. Laotian (δβ) (0)-thalassemia: molecular characterization of a novel deletion associated with increased production of fetal hemoglobin. Blood. 1988; 72(3):983-8.
6. Craig JE, Barnetson RA, Prior J, Raven JL, Thein SL. Rapid detection of deletions causing δ β thalassemia and hereditary persistence of fetal hemoglobin by enzymatic amplification. Blood. 1994; 83(6):1673-82.
7. Thein SL, Wood W. The molecular basis of beta thalassemia, delta β thalassemia, and HPFH Disorders of Hemoglobin (2nd ed.): Cambridge University Press; 2009:325-56.
8. Fucharoen S, Pengjam Y, Surapot S, Fucharoen G, Sanchaisuriya K. Molecular characterization of (δβ)(0)/β(0)-thalassemia and (δβ)(0)-thalassemia/hemoglobin E in Thai patients. Eur J Haematol. 2001; 67(4):258-62.