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LETTER TO EDITOR

An insight of -50 (G>A) mutation in the direct repeat element of the β-globin gene: From Malaysian perspective

Norafiza MOHD YASIN*, Faidatul Syazlin ABDUL HAMID, Syahzuwan HASSAN, Yuslina MAT YUSOFF, Ermi Neiza MOHD SAHID, Ezalia ESA

Haematology Unit, Cancer Research Centre, Institute for Medical Research, Jalan Pahang, 50588 Kuala Lumpur, Malaysia

Dear Editor,

As per date, there is only one publication was found to report the -50 (G>A) mutation as a pathogenic variant.[1] Therefore, we would like to support their findings and classify this pathogenic variant as a β^+ thalassaemia. Five cases were found among Malaysian and all of the cases were asymptomatic. The first reported case with the occurrence of compound heterozygous for -50 (G>A) and CD41/42 (-TTCT) in a Chinese family presented as severe thalassaemia major.[1] Interestingly in Malaysia, we discovered 4 unrelated cases among Malay ethnicity. Our findings revealed that this promoter mutation has a mild β^+ phenotype as in their clinical phenotype and complete blood count (CBC) (Table 1). One case presented as silent beta thalassaemia with normal Hb A_2 level not explained by co-inheritance with alpha or delta thalassaemia.

Table 1: Summary of haematological findings for 5 cases carrier for -50 (G>A) mutation

Case	Age (years)	Ethnic	Hb (g/dL)	MCV (fL)	MCH (pg)	RBC (10^9/L)	RDW (%)	Hb A_2 (%)	HbF (%)	Alpha genotype
1	31	Malay	12.5	84.4	29.0	4.31	12.5	2.7	-	αα/αα
2	16	Malay	13.0	79.0	24.5	5.31	13.0	3.4	-	αα/αα
3	19	Malay	15.3	77.9	24.5	6.25	14.6	3.8	-	αα/αα
4	16	Chinese	13.2	79.1	24.6	5.37	12.3	3.4	0.3	$\alpha\alpha^{QS}/\alpha\alpha$
5	25	Malay	11.1	73.4	24.8	4.47	11.0	3.7	0.3	$-\alpha^{3.7}/\alpha\alpha$

MCHC Mean corpuscular haemoglobin concentration, *RDW* red blood cell distribution width, QZ Quang Sze (HbQS) mutation, *HPLC* high performance liquid chromatography

Majority of our cases presented with borderline Hb A_2 value ranging from 3.4-3.8% as compared to heterozygous case of -50 (G>A) that previously reported with classical Hb A_2 range of beta thalassaemia carrier.[1] Currently, there are up to 900 mutations of beta thalassaemia have been reported in *Hb Var* database.[2] Based on IMR experience (unpublished data), the commonest beta thalassaemia mutations are IVS 1-5 (G>C), CD41/42 (-TCTT), IVS 1-1 (G>T), CD 19 (AAC>AGC) (Hb Malay) and Poly A (AATAAA>AATAGA) mutation (unpublished data). From this data, the potential occurrence of compound heterozygous with other severe beta mutations are high as IVS 1-5 (G>C), IVS 1-1 (G>T), and CD41/42 (-TTCT) mutation are common in our population.

The promoter of β-globin gene contains sequence motifs that are highly conserved during evolution, including two CACCC boxes at nt –105 to –101 and –90 to –86 from the cap site, the CCAAT box at –76 to –72, and the TATA box at –30 to –26.[3] Mutation of the β-globin gene promoter within the CCAAT box cause mild β-thalassaemia phenotypes. Few studies have evaluated the functional effect of these promoter mutations by quantification of messenger RNA (mRNA) level by using real-time quantitative reverse transcript polymerase chain reaction analysis (RT-PCR) and the result showed a slightly reduced β-globin mRNA level as compared to healthy individuals.[1,4] As previously described, -50 (G>A) mutation occurs in direct repeat element (DRE) that consists

**Address for correspondence*: Norafiza Mohd Yasin, MD DrPath; Hematology Unit, Cancer Research Centre, Institute for Medical Research, Jalan Pahang, 50588 Kuala Lumpur, Malaysia. Tel 03- 26162666 Fax 03-26162566; email: *norafizayasin@gmail.com*

of an imperfect direct repeat of a 10-bp sequence, AGGGCAGGAGCCAGGGCTGGGC, located between the CCAAT and TATA elements in the human β- globin promoter (between positions –53 and –32).[1,3]

Case of -42 (C>G) mutation was reported as thalassaemia intermedia in compound heterozygous with CD30 (G>A) mutation.[5] Another case reported the classical beta-thalassaemia phenotype in cases with -32 (C>A) mutation with Hb A_2 level range (6.0-8.7%) with significant microcytic red blood cell indices.[6] There were almost 40 mutations were reported to be at the promoter region of the β-globin gene and these mutations have variable clinical phenotype.[2] Based on these findings, we conclude that, promoter gene mutations should be highlighted even though the HbA2 level could be in a borderline level like mild or silent beta thalassaemia trait, it could possibly cause beta thalassaemia major or intermedia in compound heterozygous with other pathogenic beta variants.

Conflict of interest: The authors declare no conflict of interest.

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