Deletional Haemoglobin H Disease Diagnosed with Compound Heterozygous of (--^{SEA}) and A New Single Gene Deletion Involving the *HBA1*

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Haemoglobin H (Hb H) disease presented as moderate to severe anaemia and commonly occurs in the form of deletional Hb H. An eleven years old, Chinese girl and her mother's (a Papua New Guinea ethnicity) samples were referred to Institute for Medical Research for further alpha thalassaemia molecular analysis. She presented at two years old with severe hypochromic microcytic anemia (haemoglobin, MCV, MCH, RBC of 3.8g/dL, 65fl, 16.8 pg and 2.28 x 106/µL respectively). Her Hb analysis findings revealed low Hb A2 of 1.6% and Hb F value of 0.3% with presence of fast band in the H region. Presumptive diagnosis of Hb H disease was made based on haemoglobin analysis. At the age of 8 years old, her transfusion requirement increased with evidence of extramedullary haematopoiesis and large splenomegaly; thus, TDT regiment was initiated. She was currently 11 years old, pre-transfusion Hb level was 9-10 g/dl and growing well with spleen shrunk to 1-2cm. No history of recurrent infection to explain her transfusion requirement. Common *alpha-globin* gene deletions and point mutations were ruled out using the Multiplex Gap and ARMS PCR methods. Further investigation was done using Multiplex Ligation-dependent Probe Amplification (MLPA) method. Heterozygous (--^{SEA}) deletion was detected using Multiplex Gap and Amplification-Refractory Mutation System (ARMS) PCR methods. MLPA findings of the index patient revealed a compound heterozygous state for (--^{SEA}) and uncharacterized deletion spanning from *HBA1* intron 2 until *HBQ1* exon 3 region. The same uncharacterized deletion was found in the mother's DNA. Based on the MLPA findings, the deletion size is estimated about ~29.6Kb, which involves *HBA1* and leaving the *HBA2* gene intact. This finding gives rise to a single gene deletion in the *HBA1*. Thus, a combination of any two genes deletion with this uncharacterized deletion may result in deletional Hb H. Based on the method performed, a new spectrum of alpha thalassaemia deletion had been discovered. Further characterization of the deletion breakpoint shall be done to identify the actual size of the deletion for better genotype-phenotype correlation.

Keywords: α-thalassaemia, *HBA1* deletion, Hb H disease, deletional Hb H, new deletion

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References:

1. Ahmad R et.al (2013) Distribution of alpha thal gene variants in diverse ethnic population in Malaysia: Data from Institute for Medical Research. DOI:10.3390/ijms140918599
2. Phylipsen M et.al (2010) Thalassemia in Western Australia: 11 novel deletions characterized by Multiplex Ligation-dependent Probe Amplification. DOI:10.1016/j.bcmd.2009.12.011
3. Hamid FSA et.al (2015) A novel single gene deletion (-α3.5MAL) giving rise to silent alpha thal carrier removing the entire HBA2 gene observed in two chinese patients with Hb H disease: case report of two probands. DOI: 10.4081/thal.2015.4675
4. Eng B et.al (2005) Characterization of a rare single a-globin gene deletion in a chinese woman with Hb H disease DOI: 10.1080/03630260500312618