Letter to Editor

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A Rare Interactions Between Heterozygous --^{SEA} Deletion and Hb Ube-2 [α68 (E17) Asn →Asp]; First Reported Case from Malaysia

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ABSTRACT

To report a rare interaction between known pathogenic alpha variant (--^{SEA} deletion) with another rare alpha variant, Hb Ube-2 [α68 (E17) Asn →Asp] among our population. This finding may support the current classification of the rare variant as benign or likely benign variant. To date, limited data available in the literature describing this abnormal hemoglobin variant in compound heterozygous state with another pathogenic variant. Identification of the patient confirmed that the interaction of these rare Hb variants with α0-thalassemia does not lead to the Hb H disease.

Keywords: Hb Ube-2; Haemoglobin Variant; Benign and Likely Benign Variant

Introduction

Recently, we found a rare alpha variant thalassaemia in a Chinese patient from Kuala Lumpur, Malaysia. Haemoglobin Ube-2, a fast-moving haemoglobin variant (HBA2: c.205A>G) was first observed in a Japanese woman in 1960 [1] and subsequently reported in Turkish family [2] followed in Taiwanese [3]. To the best of our knowledge, this was first case encountered among Malaysian-Chinese population. 16 years old Female propositus, was found to have this rare alpha variant haemoglobinopathy during form four screening programme. She was asymptomatic with haemoglobin (Hb), MCV, MCH, RDW- CV and RBC of 11.6g/dL, 64.4 fL, 20.1 pg, 14.9% and RBC of 5.76 x 106/uL respectively. Haemoglobin analysis by high performance liquid chromatography (HPLC) showed reduced HbA2 of 1.7% and mildly raised Hb F level of 2.6% with haemoglobin variant at P3 window (38.2%). The haemoglobin variant located at zone 12 (45.2%) by capillary electrophoresis (CE). A fast-moving Hb was detected on alkaline cellulose acetate gel electrophoresis. Based on Hb analysis findings, the presumptive diagnosis of Hb J variant was made with possible interaction with alpha thalassaemia. Interestingly alpha sequencing and Gap-PCR showed mutation at codon 68 of HBA1 gene with two gene deletional alpha thalassaemia (--^{SEA}) (NG_000006.1: g.26264_45564del). As per date, very limited data available in the

literature describing this abnormal haemoglobin. Previous literature described three types of Hb Ube namely Ube-1, Ube-2 and Hb Ube-4 in mainland of China [4]. Both Hb Ube-2 and Ube-4 does not have any significant haematological and clinical manifestation in heterozygous. This variant has been classified as benign (B) or likely benign variant (LB) [5]. The percentage of the Hb Ube-2 variant reported by [4,3] was 26.16% and 25.1% with normal HbA2 level and the variant moved faster than Hb A in an alkaline gel electrophoresis but slower than Hb H band. These findings were consistent in all previous literatures with Hb variant level ranges from 22-35.2% from either capillary electrophoresis, alkaline gel electrophoresis or HPLC. [2-4,6] Interestingly, our case reported as first case of Hb Ube-2 with interaction between $-^{SEA}$ deletion causing mild thalassaemia phenotype. No history of transfusion or any significant organomegaly or chronic haemolytic features. In our case, the variant showed higher percentage (45.2%) as expected than usual heterozygous case with the presence of deletional mutation (Figure 1).

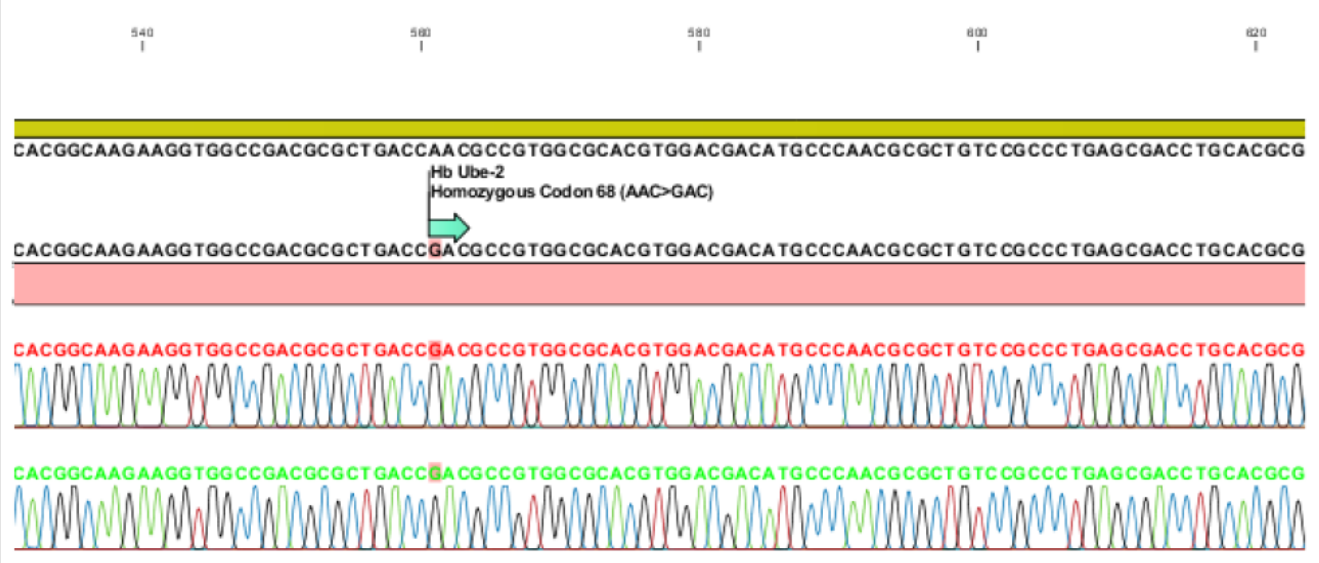

Figure 1: The results of direct sequencing of the α1-globin gene showed an A>G substitution at the first base of codon 68, indicated on the lower portion, and the reference sequence is shown on the upper portion (take note that the variant appears homozygous mutation from sequencing data in view of the presence of –SEA deletion in another allele).

Three types of Hb Ube described in literature, and the one with significant clinical phenotype is Hb Ube-1[β98 (FG5) Val→ Met] or Hb Köln as described by [4,7]. Hb Köln is one of the commonest unstable haemoglobin variants that cause Heinz bodies formation with significant anaemia. Predicting the percentage of an α chain variant is more complex as not only are there four α genes, but the α2 gene is transcribed at a higher rate than the α1 gene. An α chain variant would therefore be expected to comprise either about 37.5% or about 12.5% of total haemoglobin depending on which alpha globin gene were affected. The proportions may be differed in coexisting alpha thalassaemia that lead to relatively higher percentage of an alpha variant [8]. The co-existence of alpha zero thalassaemia in trans in our case lead to mark hypochromia and microcytosis. Compound heterozygous of $--^{SEA}$ deletion with Hb Ube-2 has never been described before. Based on our reported case, the interaction between pathogenic variant $--^{SEA}$ deletion with Hb Ube-2 does not cause significant disease phenotype, thus support the classification as benign or likely benign variant by [5]. This variant also has similar HPLC pattern and CE migration time with the more common Hb J variants which is a potential pitfall for misinterpretation. DNA sequence analysis is importance to provide a rapid, simple and accurate diagnostic procedure to identify this abnormal haemoglobin.

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Conflicts of Interest

The authors declare no conflict of interest.

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