
Globin Gene Defects in Normal and Borderline Haemoglobin A₂ Levels: An IMR Experience

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The most common inherited monogenic disorders in the world are the haemoglobinopathies and thalassaemia. Thalassaemia is a heterogeneous group of genetic disorders of haemoglobin synthesis, characterised by a reduction in the production of one or more of the subunits of haemoglobin chains [1]. Haemoglobin A₂ (HbA₂) level is an important parameter in thalassaemia diagnosis. High HbA₂ level (≥ 4.0) detected in Hb analysis, points to the diagnosis of beta thalassaemia and other haemoglobinopathies. However, in some cases, the HbA₂ levels are apparently normal or borderline high despite abnormal haematological profile. In these cases, further testing is required to confirm the diagnosis. The aim of this study is to examine any abnormality at molecular level in cases of Hb analysis results with normal or borderline high HbA₂ level.

In the year 2015, 1890 samples were sent to Thalassaemia Molecular Genetic Lab, IMR for DNA analysis. Out of all samples, 299 has a normal (3.3-3.5%) and borderline (3.5-3.9%) HbA₂ levels. Subsequently, multiple molecular techniques which included but not limited to β -MARMS, β -MGAP, α -MARMS, α -MGAP, β -MLPA and β -sequencing were employed for detection of any gene defects. All data were tabulated and analysed using Microsoft Excel. Out of the samples analysed (n=299), 26% (77/299) has no globin gene defects. A majority of samples (58%; 174/299) has β -gene defects, and α -gene defects were detected in 5% (15/299 cases). The remaining 33 samples (11%) were detected to have co-existence of α - and β -gene defects. From the 222 cases with gene defects, 31% (69/222 cases) has normal HbA₂ level (3.3-3.5%) (Fig. 1).

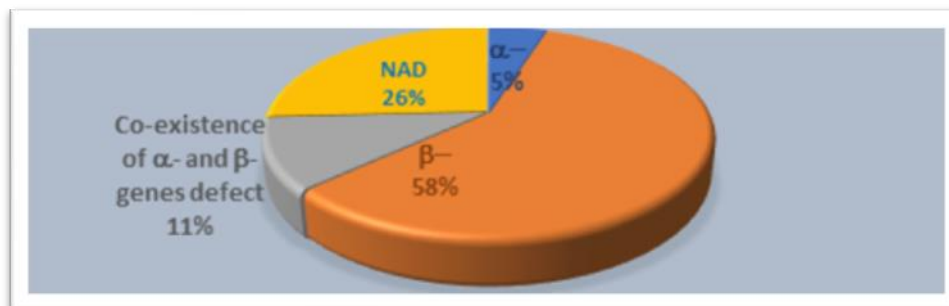


Fig. 1 – Detection of α^- and β^- , or co-existence of α^- and β^- genes defects in normal and borderline HbA₂ levels (3.3 – 3.9%)(n=299). NAD = no gene defect), α^- = alpha-gene defect, β^- = beta-gene defect

This study shows the importance of determining the range value for normal HbA₂ levels in Hb analysis, for Malaysian population, as this will contribute to the decision whether to proceed for molecular/DNA analysis and next to the diagnosis of thalassaemia. From our findings, β^- -gene defects hold the largest percentage: 58%, which shows that normal and borderline HbA₂ levels can still be present mostly in individuals having β^- -gene defects. From these results, we may suggest that individuals with borderline HbA₂, particularly when they marry a typical β^- -thalassaemia carrier, should be extensively investigated in order not to miss heterozygous β^- -thalassaemia [2]. This study shows that there are several cases with normal and borderline HbA₂ levels but with globin gene defects present. Hence, we conclude that HbA₂ range value which indicates further molecular testing should be revised for our population, to prevent missed diagnosis of thalassaemia and production of affected offspring among at risk couples.

Keywords: Thalassaemia, Borderline HbA₂ levels, α^- , β^-

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