Genetic Variants in HBS1L-MYB rs9399137 and rs11759553 Associated with Elevated HbF Levels Among Filipino β°-deletion Carriers

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In Malaysia, Sabah population constitutes the most number of β-thalassaemia cases ranging from asymptomatic to transfusion dependent. Filipino β°-deletion has been reported as the predominant mutation in Sabah [1]. Despite having the same primary mutation, co-inheritance of genetic variants at HbF quantitative trait loci of HBS1L-MYB intergenic region may cause variability in clinical features by affecting the haemoglobin (Hb) subtypes level, especially HbF. Study suggested that MYB would activate γ-globin repressor gene directly and subsequently initiate the molecular HbF repression mechanisms. Polymorphisms within HBS1L-MYB intergenic region would inhibit binding of transcription factor on MYB and leading to elevation of HbF levels [2]. This can act as an ameliorating factor in the clinical presentation of β-thalassaemia patients [3]. This study aimed to elucidate the association of Hb subtypes levels with three HBS1L-MYB variants among 134 Filipino β°-deletion carriers. PCR-RFLP analysis was done for HBSIL-MYB rs4895441 (A→G) while tetra-primers ARMS PCR analysis was done for HBSIL-MYB rs9399137 (T→C) and rs11759553 (A→T) (Fig.1).

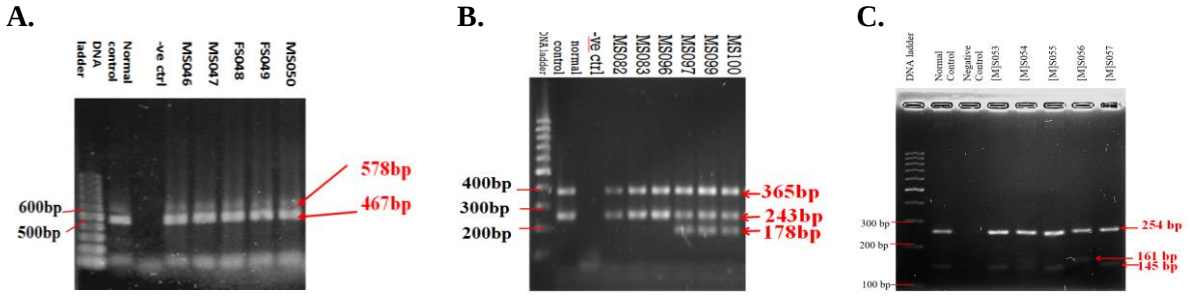

Fig. 1: Genotyping analysis for HBSIL-MYB rs4895441 (A→G) (A), rs9399137 (T→C) (B) and rs11759553 (A→T) (C). (A) For rs4895441, genotype A/A with 2 bands (578 & 467bp); genotype A/G with 2 bands (467 & 111bp) and genotype G/G with 2 bands (578 & 111bp). (B) For rs9399137, genotype T/T with 2 bands (365 & 243 bp); genotype T/C with 3 bands (365, 243 & 178 bp) and genotype C/C with 2 bands (365 & 178 bp).(C). For rs11759553, genotype A/A with 2 bands (254 & 145 bp); genotype A/T with 3 bands (254, 161 & 145 bp) and genotype T/T with 2 bands (254 & 161 bp).

Through the genotyping analysis, two HBS1L-MYB variants (rs9399137, MAF = 0.18 and rs11759553, MAF = 0.190) were found with significant minor allele frequency (MAF) which is greater than .05. HBS1L-MYB rs4895441 showed no influential effect on Hb subtypes level. However, rs9399137 and rs11759553 showed significant different in HbF level. HbF level was elevated when Filipino β°-deletion carriers co-inherited with HBS1L-MYB rs9399137 or rs11759553 (Fig.2).

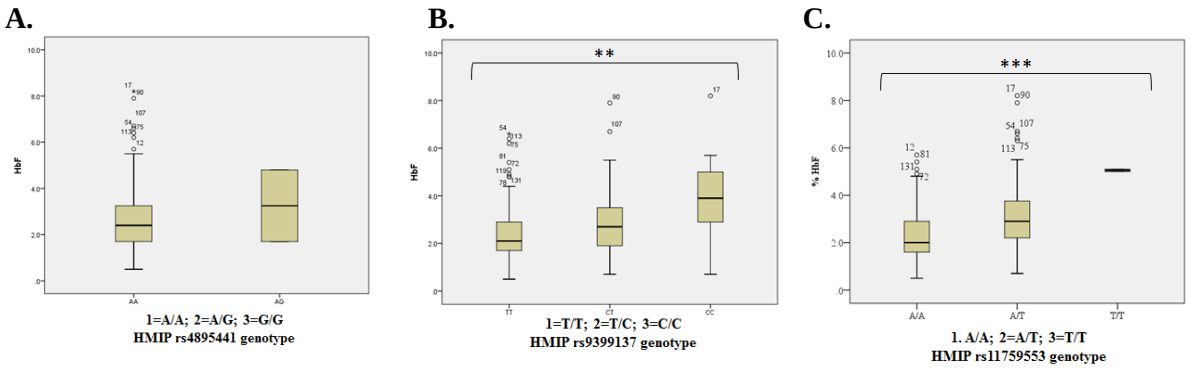

Fig. 2: Association of HBS1L-MYB (A) rs4895441 (*p-value*: 0.590), (B) rs9399137 (*p-value:* 0.007**) and (C) rs11759553 (*p-value:* 0.000***) genotypes with percentage of HbF level.

In conclusion, HBS1L-MYB rs9399137 and rs11759553 are significantly in elevating HbF levels which are not seen in rs4895441, making it a potent therapeutic target for gene therapy. The significant difference in Hb subtypes levels across the genotype variants had suggested the importance to include the detection of HBS1L-MYB rs9399137 and rs11759553 among Filipino β°-deletion patients in order to provide proper patient management.

Keywords: HBS1L-MYB variants, Filipino β°-deletion, rs9399137, rs11759553, rs4895441

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Acknowledgements

This study was funded by UTAR Research Fund (UTARRF) 2016 Cycle 1 by Universiti Tunku Abdul Rahman (IPSR/RMC/UTARRF/2016-C1/T6).

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