GENETICS

Association of Upstream Transcription Factor 1 Gene (*USF1*) 306 G > A with Increased Homocysteine Level among Iban Ethnic Groups in Sarawak Population

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ABSTRACT

Objective: **to determine the polymorphic allele and genotype frequencies of *USF1* 306 G > A. It aimed to elucidate the association of the polymorphic allele and genotypes with clinical profiles such as total cholesterol (TC), high- density lipoprotein (HDL), low- density lipoprotein (LDL) and homocysteine level in Iban ethnic group in Sarawak.**

Materials and methods: **One hundred and fourteen (114) individuals of the Iban ethnic group were recruited as the study subjects. The Allele Specific PCR (AS-PCR) was used in the genotyping. Association of genotype frequencies and clinical profile was assessed using One Way ANOVA. As for the association of allele frequencies and clinical profile, Independent Sample T test was used.**

Results: **Genotype frequency showed statistical significant difference with homocysteine level with p value less than 0.05. The heterozygous and variant genotypes of Upstream Transcription Factor 1 (*USF 1*) 306 G > A is significantly associated with high level of homocysteine with F (2,112) = 7.048, p < 0.05. The variant allele of *USF 1* 306 G > A is also significantly associated with high level of triglycerides with t (-2.116), p value of 0.035.**

Conclusion: **Our results show that the genetic diversity of USF1 gene influences the susceptibility to increased level of homocysteine in the Iban ethnic group of the Malaysian population. This results support the involvement of *USF1* mediated pathways in the process of familial hypercholesterolemia (FH).**

KEY WORDS

Upstream Transcription Factor 1, Homocysteine, Iban, Sarawak

INTRODUCTION

The upstream transcription factors 1 (*USF 1*) and USF 2 are members of the basic helix-loop-helix/leucine zipper transcription factor family (Yamanaka *et al*., 2016). In addition, USFs have been shown to regulate the expression of genes for fatty acid synthesis and insulin signaling, suggesting their involvement in glucide/lipid metabolism (Corre & Galibert, 2005). The USF1 gene is located at chromosome 1q22-q23. It consists of 11 exons and extends to 6.73 kb. It was found to be genetically associated with Coronary artery disease (CAD) in Finnish families (Pajukanta *et al*., 2004). USF1 was also found can manifest as hypercholesterolemia and have been shown to predispose to premature cardiovascular diseases (Meng *et al*., 2010).

Familial Hypercholesterolemia (FH) is a genetic disease that is characterized by high levels of low density lipoprotein cholesterol (LDLC) and early cardiovascular disease (CVD). Defects in the Low-Density Lipoprotein (*LDLR*) gene was found to be associated with Familial Hypercholesterolemia (FH) which gave rise to a well-characterized clinical phenotype (Scriver, 2001). The same study suggested that FH is strongly influenced by the genetic background whereby the lipid profile, frequencies of xanthomas and onset as well as severity of cardiovascular disease exhibit great variability in their phenotypic expression. FH was found to be associated with increased risk of coronary disease and premature death (Shivraj & Lye, 2011). Monogenic FH was found to attribute to the defect of LDLR and other genes such as Apolipoprotein B 100 (APOB-100) and Proprotien convertase subtilisin kexin type 9 (PCSK9) gene (Rajih & Al-Talib, 2016). About 4% of FH patients was found to have mutation in the promoter region of *LDLR* gene (Khoo, Van Acker, Tan, & Deslypere, 2000).

Homocysteine is an intermediate product of amino acid methionine and cysteine. It is produced via demethylation of dietary methionine that is found abundantly in animal protein (Faeh, Chiolero, & Paccaud, 2006). Hyperhomocysteinemia is a medical condition whereby higher level of homocysteine (more than 15 micromolar per liter) is detected in the blood (Guo, Chi, Xing, & Wang, 2009). Hyperhomocysteinemia may be influenced by genetic mutation on enzymes that are involved in homocysteine metabolism. Prevalence of hyperhomocystienemia varies between population and is dependant on age, diet and genetic background.

Sarawak is the largest state of Malaysia. The indigenous groups make up about 50% of the total population of 2.6 million people. Iban is the largest indigenous group which comprise of 38% and Bidayuh, second largest after the Iban, make up about 10% of the population (Vasudevan, Fathihah, & Patimah, 2011). The incidence of Iban and Bidayuh with Coronary Vascular Disease (CVD) was higher compared to other ethnic groups in Borneo (Sabah & Sarawak) (Fong *et al*., 2014).

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