GENETICS

Association of *PCSK9* g.24382G > A with Increased Homocysteine Level among Bidayuh Ethnic Group in Sarawak Population

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ABSTRACT

Objective: **To determine the polymorphic allele and genotype frequencies of Proprotein Convertase Subtilisin/Kexin type 9 PCSK9 g.24382G > 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 the Bidayuh ethnic group in Sarawak.**

Material and Methods: **One hundred and thirty-nine (139) individuals from the Bidayuh ethnic group in Sarawak participated as study subjects. The Allele Specific PCR (AS-PCR) was used in the genotyping of PCSK9 g.24382G > A to detect the selected SNPs variant (Polymorphisms). Association of genotype frequencies with clinical profile was calculated using One Way ANOVA. As for the association of allele frequencies with clinical profile, Independent Sample T test was used.**

Results: **Heterozygous genotype was statistically higher in normal level of total cholesterol level, LDL and homocysteine level whereas high level of total cholesterol and HDL ratio was statistically higher in variant genotype compared to homozygous genotype ($p < 0.05$). Heterozygous and variant genotypes of PCSK9 g.24382G > A show that it is significantly associated with high homocysteine level, $F(1,137) = 5.018$ ($p = 0.027$).**

Conclusion: **Our results showed that the genetic diversity of PCSK9 gene influences the susceptibility to increased level of homocysteine in the Malaysian population and also support the involvement of LDLR mediated pathways in the process of Familial Hypercholesterolemia.**

KEY WORDS

Proprotein Convertase Subtilisin/Kexin type 9, homocysteine, Bidayuh, Sarawak

INTRODUCTION

The low-density lipoprotein (LDL) receptors pathway could be regulated by several enzymes in cholesterol homeostasis. One of the enzymes is proprotein convertase subtilisin/kexin type 9 (PCSK9), as it has major influence in decreasing the hepatic LDL receptors in two separate routes shown by mechanistic studies (Grefhorst, McNutt, Lagace, & Horton, 2008; McNutt, Lagace, & Horton, 2007). By inhibiting PCSK9 activity, LDL receptors would bind to the LDL lipoprotein and lower the cholesterol level in the blood. PCSK9 was found to be involved in intracellular and extracellular LDL receptors pathway (Poirier *et al*., 2009). PCSK9 was originally known as neural apoptosis regulated convertase (NARC-1) and is mainly expressed in liver and intestines (Seidah *et al*., 2003). The gene is located on 1p32.3 and spans approximately 22-kb. It contains 12 exons and 11 introns (Seidah & Prat, 2007).

Majority of developed countries showed hyperlipidemia, the elevation of lipid (both triglycerides and cholesterol) levels that eventually lead to atherosclerosis (Goldstein, Hazzard, Schrott, Bierman, & Motulsky, 1973). Hyperlipidemia (hyperlipoproteinemia) is defined as either high cholesterol level (hypercholesterolemia) or high triglyceride level (hypertriglyceridemia) or high level in both. The progression of atherosclerosis leads to the development of cardiovascular disease (CVD) comprising of all diseases related to the heart and its circulation. Example of CVD are coronary heart disease (CHD), angina, myocardial infarction, congenital heart disease and stroke. Familial Hypercholesterolemia (FH) is a genetic disease that is characterized by high levels of low-density lipoprotein cholesterol (LDLC) and early cardiovascular disease (CVD). It is already known that FH was originally caused by LDLR mutation. However, most of the variation found in lipid profiles were caused by several common alleles in other genes

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