

# Association of Low-Density Lipoprotein Receptor (LDLR) Arg471Gly with Increased Homocysteine Level among the Iban Ethnic Group in the Sarawak Population

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## ABSTRACT

**Objective:** To determine the polymorphic allele and genotype frequencies of LDLR Arg471Gly. It is 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 Iban ethnic group in Sarawak.

**Material 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 for genotype frequencies and clinical profile was calculated using One Way ANOVA. As for the association of allele frequencies and clinical profile Independent Sample T test was used.

**Results:** Allele and genotype frequency association with homocysteine level showed statistically significant difference with p value less than 0.05. The wildtype and variant genotypes of LDLR Arg471Gly shows significant association with high homocysteine level with  $F(2,112) = 7.048, p < 0.05$ . Similarly, the variant allele of LDLR Arg471Gly is significantly associated with high level of homocysteine with  $t(2,267), p$  value of 0.024.

**Conclusion:** Our results showed that the genetic diversity of LDLR gene influences the susceptibility to increased level of homocysteine in the Malaysian population and support the involvement of LDLR mediated pathways in the process of familial hypercholesterolemia (FH).

## KEY WORDS

low-density lipoprotein receptor, homocysteine, Iban, Sarawak

## INTRODUCTION

The low-density lipoprotein receptor (LDLR) gene family consists of cell surface proteins involved in receptor-mediated endocytosis of specific ligands. LDLR gene is located on chromosome 19p13.1-13.3 with 18 exons and 17 introns that encodes 839 amino acid. Mutation can occur in the promoter, intron or in the exon of the LDLR gene. The LDLR gene encodes the functional structure of the LDL-receptors found on the liver cell surface. LDL-receptors function to remove the LDL particles from the serum (Goldstein & Brown, 1973).

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 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. On the other hand, 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 defective LDLR and other genes such as Apolipoprotein B 100 (APOB-100) and Proprotein convertase subtilisin kexin type 9 (PCSK9) gene (Rajih & Al-Talib, 2016). About 4% of FH patients were found to have mutation in the promoter region of the LDLR gene (Khuo, 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

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