Homozygous DNA variants in exon 9 of the LDL receptor gene in a Thai patient with primary hypercholesterolemia phenotype

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Abstract

Mutation in low density lipoprotein (LDL) receptor gene causes an inherited primary hypercholesterolemia namely familial hypercholesterolemia (FH). In this study, 46 Thai patients with primary hypercholesterolemia were screened for mutations in exon 9 of the LDL receptor gene by polymerase chain reaction - restriction fragment length polymorphism (PCR - RFLP). The analysed fragment was 224 bp in length. According to the published cDNA sequence, exon 9 of the LDL receptor gene contains several hypermutable CpG dinucleotides. Three of these sites are Hpa II recognition sites. PCR product of exon 9 obtained from amplification of wild-type DNA sample would yield four fragments after Hpa II digestion. The expected sizes of these restriction fragments were 15, 30, 40 and 139 bp. All normocholesterolemic subjects (n = 33) showed normal RFLP. However, in one patient (72 year old female), abnormal RFLP from Hpa II digestion of the amplified exon 9 was observed, i.e., a fragment of 70 bp and another one smaller than 139 bp. Such RFLP reflects that exon 9 of both alleles of the LDL receptor gene in this patient lost one and gained one Hpa II site. It is interesting that this patient, eventhough harbouring two mutations on both alleles of the LDL receptor gene (presumably homozygous genotype of FH), apparently revealed lipid levels of heterozygous phenotype of FH without symptoms of coronary artery disease. It has yet to be proved whether these genetic variations are disease-related mutations or presumably common DNA polymorphisms.

Keywords: CpG Dinucleotides; Gene Mutations; Hypercholesterolemia; LDL Receptor; PCR-RFLP

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