Ala519Thr Mutation in Exon 11 of LDL Receptor Gene in Members of a Malaysian Family with Hypercholesterolaemia

Sarni Mat Junitt*, Shatrah Othman†, Rohana Yusof‡, Michael A. Billett§ and Fatimah Harun∥

1 Department of Molecular Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.
2 Department of Paediatrics, University Malaya Medical Centre, 50603, Kuala Lumpur, Malaysia.
3 School of Biomedical Sciences, Nottingham University Medical School, Queens Medical Centre, Nottingham NG7 2UH, UK.

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Abstract. We report a case of a Familial Hypercholesterolaemic (FH) patient (FH1) and her family members. They are Malaysian of Indian origin with evidence of consanguinity in the parents. We characterised the LDL receptor gene mutation in FH1, her brother (S1) and their mother, P2. The father (P1) died of coronary heart disease (CHD) in his early 40s. Our investigation reveals that FH1 and her family do not carry the two of the major known Familial Defective ApoB mutations, Arg3500Gln and Arg3531Cys. Sequencing analysis of the LDL receptor gene demonstrated that FH1 is homozygous for a G to A substitution at nucleotide position 1618, which causes the amino acid to change from alanine to threonine at position 519 (A519T). Both the mother and the eldest brother (S1) of FH1 are heterozygous for the A519T mutation. The A519T mutation had been previously reported in Western ethnicity of the United Kingdom, German and Icelandic origin but this is the first to be identified in the Asian region.

Keywords. Familial Hypercholesterolaemia, LDL Receptor, RT-PCR, Gene sequencing

INTRODUCTION

Mutations in the low-density lipoprotein (LDL) receptor gene on chromosome 19 result in an autosomal dominant disorder, familial hypercholesterolaemia (FH) (Brown et al., 1986). This disorder of defective LDL clearance gives rise to increased plasma cholesterol 2 to 5 times higher than normal and an increased risk of premature coronary heart disease. The genetic mutation in this inherited disease may occur in one (heterozygous FH) or both (homozygous FH) LDL receptor alleles with frequencies of about 1 in 500 and 1 in a million respectively (Bertolini et al., 1992). Despite conventional diet and drug therapy, most FH heterozygotes acquire CHD by the age of 35 while FH homozygotes normally die of myocardial infarction (MI) within their first 2 decades of life (Brown et al., 1986; Hobbs et al., 1990). Early detection of such patients is therefore necessary in order to delay the onset of clinical symptoms.

Familial defective apoB (FDB), another inherited disease that causes hypercholesterolaemia and premature development of CHD (Goldstein et al., 1983), is clinically indistinguishable from FH. Genetically, it is caused by mutation(s) in the apo B-100 gene, specifically in the 3' end that is not present in the apo B-48 gene. Two major mutations in the apo B gene have been associated with FDB: i) Arg3500Gln (Gaffney et al., 1995); and ii) Arg3531Cys (Pullinger et al., 1995) that can both be detected by PCR assays of the genomic DNA. A variety of different mutations in the LDL receptor gene that result in FH have been characterized that include gross deletions, major gene rearrangements, small deletions and point mutations. A database of LDL receptor gene mutations (http://www.ncbi.nlm.nih.gov/htbin Entrez?db=OMIM) indicates that there are over 600 different mutations characterized worldwide demonstrating a high degree of allelic heterogeneity at this locus (Varret et al., 1997). The majority of the LDL receptor mutations characterized are among the European, American and African populations. In this study, we attempted to characterize the LDL receptor gene mutation(s) in a Malaysian familial hypercholesterolaemia patient and her family members.

*Author for Correspondence.
Mailing address: Department of Molecular Medicine, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia. Tel: 603-7967 4718; Fax: 603-7967 4957; Email: sarni@um.edu.my.