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Familial lecithin-cholesterol acyltransferase deficiency: Biochemical characteristics and molecular analysis of a new LCAT mutation in a Polish family

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Abstract

Familial LCAT deficiency (FLD) is a rare genetic disorder associated with corneal opacities, anaemia and proteinuria with renal failure. Here we report detailed analyses on plasma lipids, lipoproteins, and the molecular defect in two siblings from a Polish family presenting classical symptoms of FLD and their family members with newly discovered Val309Met mutation in exon 6 of LCAT gene. Both patients displayed low total (2.19 and 2.94 mmol/l) and HDL-cholesterol concentrations (0.52 and 0.48 mmol/l), low percentage of cholesteryl esters (CE) (11.1 and 12%), and decreased apo AI and apo AII serum levels. Low LDL-cholesterol, apo B and Lp(a) levels, and increased oleate/linoleate ratios in CE could be of importance in the development of atherosclerosis in these patients with low HDL-cholesterol.

LCAT activity was 10% of normal, α-LCAT activity was 0, and LCAT concentration was undetectable by immunoassay. Plasma CETP activity was at lower limits of normal.

PCR and sequence analysis of DNA from the proband and affected brother revealed a novel G → A mutation in exon 6 of LCAT gene, which resulted in an amino acid substitution of valine for methionine (Val309Met). The proband and affected brother were both homozygous carriers, while the mother, siblings and children of patients were heterozygous carriers of a newly discovered mutation. This is the first LCAT mutation described in the Slavic population.

Keywords: Familial LCAT deficiency; Hypo-alphalipoproteinemia; LCAT gene mutation

1. Introduction

The human LCAT enzyme is a monomeric glycoprotein (molecular weight 63 kDa), synthesised by the liver and secreted into the circulation. LCAT catalyses the transfer of an acyl group from the *sn*–2 position of phosphatidylcholine (PC) to esterify free cholesterol [1]. There is evidence that human LCAT prefers phosphatidylcholines, which have 16:0–18:2 in position 2 and synthesises predominantly 18:2 cholesteryl ester (CE) [2]. Cholesteryl ester transfer protein (CETP), like LCAT, has been found to be associated with HDL particles. CETP plays a critical role in plasma levels and intravascular remodeling of HDL particles and is a new therapeutic target in atherogenic dyslipidemia [3,4].

The mature LCAT protein is comprised of 416 aminoacids and a leader sequence of 24 residues. The gene encoding

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the LCAT protein has been cloned, sequenced, and mapped to chromosome 16q 22. It spans 4.2 kb and consists of six coding exons [1]. Several mutations have been described in the LCAT gene and classified as familial LCAT deficiency (FLD) or as fish eye disease (FED). The underlying mechanism which discriminates FLD from FED has not been clarified. In humans, mutations in the LCAT gene associated with partial LCAT deficiency lead to FED, whereas complete absence, or very low plasma LCAT activity, leads to FLD [5]. In FED, LCAT is unable to esterify cholesterol in the HDL molecule, while it retains its activity in VLDL and LDL, resulting in near normal levels of plasma cholesteryl esters. In FLD, plasma LCAT activity is nearly absent, and plasma HDL and cholesteryl esters levels are very low, with most plasma cholesterol present in the free form. Patients with FLD often present normochromic haemolytic anaemia with target cells, corneal opacities, and proteinuria, leading to renal failure in the 4–5th decade of life. Heterozygotes exhibit approximately 50% of normal plasma LCAT activity and some of them also have low HDL-cholesterol and apo A-I levels [1,6,7].

Here we describe the clinical and biochemical characteristics of a three-generation Polish family with FLD caused by a novel Val to Met mutation in nucleotide GTG/ATG in codon 309.

2. Material and methods

2.1. Subjects

The proband, WX, a 36-year-old woman, was referred to the Lipid Clinic with suspected FLD. At the age of 31 years, the proband presented proteinuria and ankle oedema during her 3rd pregnancy. The initial diagnosis of FLD was based on a renal biopsy, performed 3 years later to diagnose proteinuria, which revealed characteristic serpiginous fibrillar deposits under electron microscopy. On physical examination the proband presented ankle oedema and corneal opacities. Laboratory analyses revealed classical features of FLD: proteinuria (0.72 g/l), haemolytic anaemia with target cells (Hb 10.2 g/l, bilirubin 24.5 μmol/l, Fe 25.4 μmol/l), and markedly decreased esterified cholesterol and low HDL-cholesterol with typical "stacked coin" picture of HDL under electron microscopy. The diagnosis was finally confirmed by a marked decrease in LCAT activity. After 3 years, her proteinuria was 1.9 g/24 h and the patient received an ACE inhibitor to which she responded with a decrease in urine protein to 1.4 and then 0.9 g/24 h. The patient reported that her father died at age 72, her mother at 75, and had arterial hypertension, obesity, and coronary artery disease. The cause of death was heart failure and pneumonia complicating hospitalisation with severe

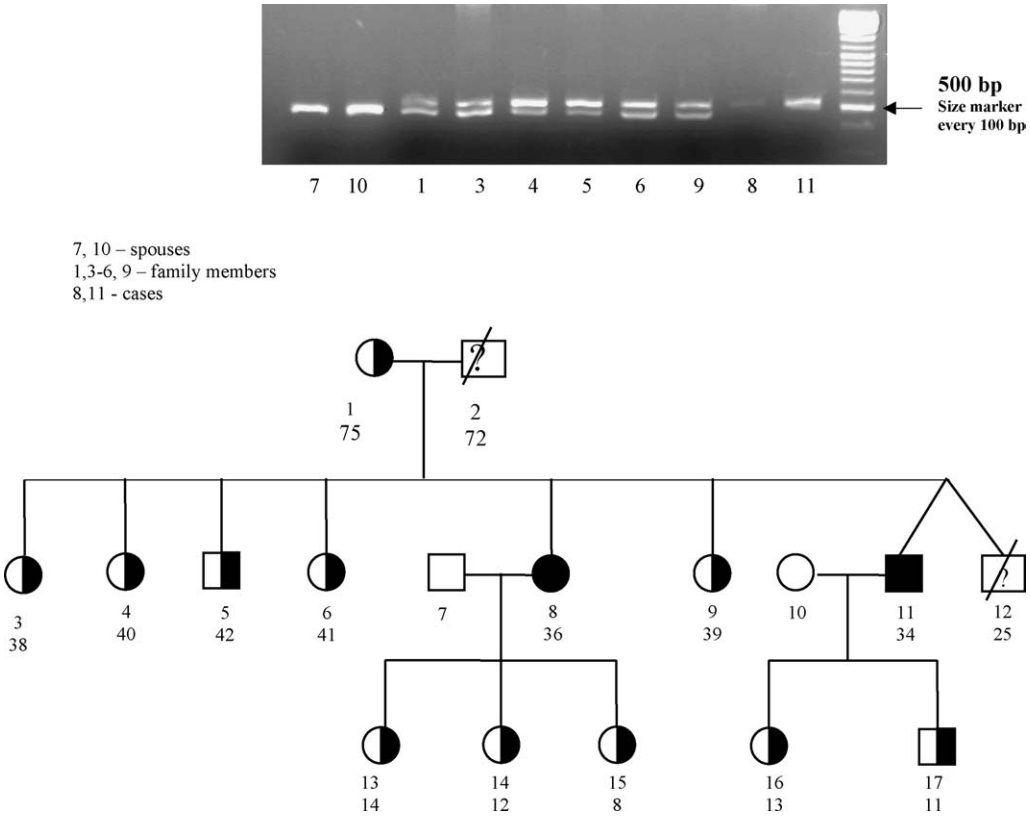

Fig. 1. Pedigree of the LCAT deficient family and agarose gel of the RFLP analysis. Shaded and half-filled shaded circle area represent homozygous and heterozygous carriers of Val309Met mutation. The first line is the identification number, the second is the age at the examination.