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Case Report

A novel mutation in a young patient with familial hypercholesterolemia underwent coronary artery bypass grafting

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Abstract: Familial hypercholesterolemia (FH) is an autosomal dominant disorder that affects cholesterol metabolism and is an important risk factor for heart disease. We reported a novel mutation exon 9-10GC in low density lipoprotein receptor (LDLR) at an 18-years-old patient with FH. The chief complaint of the patient is effort angina. Laboratory evaluation and coronary angiography were performed to evaluate her heart disease. The results showed stenosis in coronary arteries, as well as significant higher levels of total cholesterol (TC) and low density lipoprotein cholesterol. Gene sequencing and mutation analysis in LDLR and apolipoprotein B genes revealed a novel mutation exon 9-10GC of LDLR in the proband and her mother. She was scheduled for coronary artery bypass graft (CABG) surgery and discharged after successful operation. We reported a new gene mutation exon 9-10 G > A in LDLR in a Chinese family with FH. CABG was an effective method in treating her coronary artery disease.

Keywords: Familial hypercholesterolemia, low density lipoprotein receptor, new mutation, exon 9-10GC

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disorder that affects cholesterol metabolism and is an important risk factor for heart disease [1]. It is clinically characterized by increased levels of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) and is a genetic disorder most commonly caused by mutation in LDL receptor (LDLR) gene [2]. Mutations have been identified in LDLR 4 [1], apolipoprotein B (APOB) gene mutation [3], and proprotein convertase subtilisin/kexin type 9 gene (PCSK9) [4]. Most cases of autosomal dominant hypercholesterolemia are caused by a mutation in LDLR, today more than 1100 mutations in LDLR are described (http://www.ucl.ac.uk/fh). There are several different systems used worldwide for the clinical diagnosis of FH, but genetic testing provides the possibility of making a definitive diagnosis based on pathogenic variations in LDLR, APOB and PCSK9 genes [5]. Herein we present an 18-year-old patient with FH, who had coronary artery disease. A novel mutation exon 9-10GC in LDLR was detected in the proband and her mother.

Clinical report

An 18 year-old female patient was hospitalized at Tianjin Medical University General Hospital because of effort angina. She had no family history to hypercholesterolemia or heart diseases.

Laboratory evaluation at the time of admission showed TC 11.6 mmol/L, LDL-C 10.07 mmol/L. The lipid levels of her family were: father: TC 5.68 mmol/L, LDL-C 3.49 mmol/L; mother: TC 7.30 mmol/L, LDL-C 6.10 mmol/L; younger brother: TC 5.01 mmol/L, LDL-C 2.49 mmol/L. We adopted Modified UK (Simon Broome) criteria for diagnosis [6], FH was diagnosed in the proband with the following criteria: TC > 7.8 mmol/L or LDL-C > 4.4 mmol/L (for adults). She was then prescribed atorvastatin 40 mg daily.

Physical examination showed a tendon xanthoma in dorsum of left elbow. Transthoracic echo-

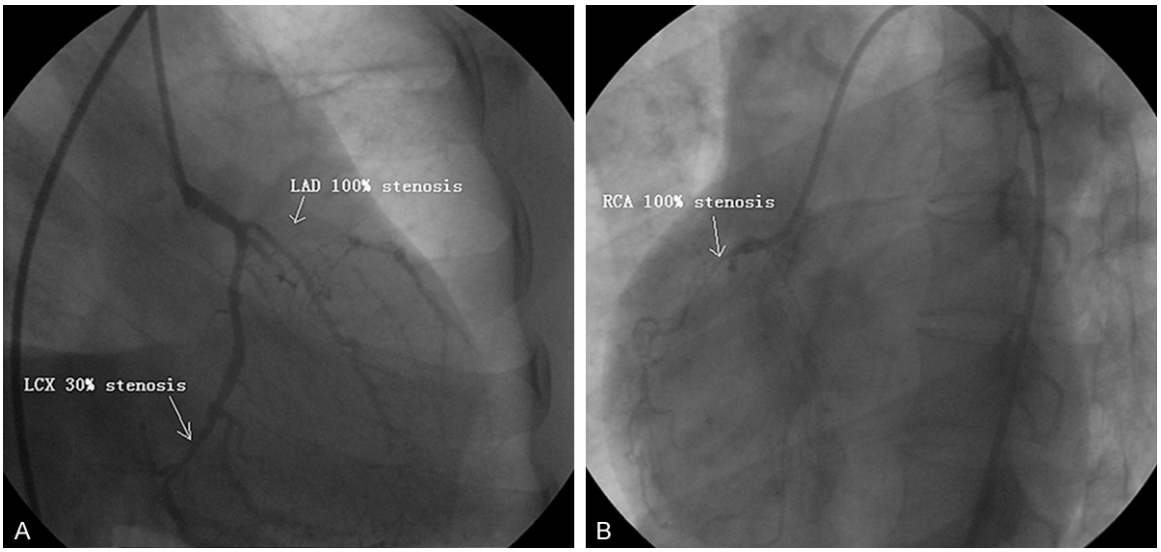

Figure 1. Coronary artery angiogram of the 18 year-old female patient. A. Proximal occlusions in the LAD and a 30% stenosis of the LCX; B. 100% stenosis of the RCA.

cardiography showed mild cardiomegaly with an ejection fraction of 50%. Coronary angiography revealed occlusions in the left anterior descending branch (LAD) (100%) and in the right coronary artery (RCA) (100%) as well as a stenosis of 30% in left circumflex coronary artery (LCX) (**Figure 1A** and **1B**).

Her lipid level was TC 3.44 mmol/L and LDL-C 2.37 mmol/L after therapy. She was scheduled for CABG surgery. The LAD received a left internal mammary artery graft, and two saphenous vein grafts were used to bypass the left diagonal branch and right posterior descending artery. In the operation, coronary arteries were diffused with multiple atheromatous plaques along LCX. No atheromatous plaque was detected on aorta. After operation, atorvastatin was continued (40 mg per day), and accompanied with beta-blocker and aspirin.

Gene sequencing and mutation analysis revealed a novel mutation, exon 9-10GA in LDLR in the proband. The proband's mother had the same genotype with her, but that for her father and younger brother were different (**Figure 2**). This is the first time that exon 9-10 G > A in LDLR was reported in a family with FH.

Discussion

The LDLR mediates the removal of LDL and remnant lipoproteins from circulation, LDLR plays a major role in the regulation of plasma cholesterol levels in humans [7]. Previous studies in Chinese patients have found many mutations in LDLR, which were different from Western populations [8]. In this report, a novel mutation exon 9-10 G > A in LDLR in a familial hypercholesterolemia was detected, which locates in the upstream of exon 9, this mutation may cause a decrease in LDLR mRNA levels. We hypothesized that this mutation may lead to either zero expression of related protein product or related protein defective in function. Defective LDLR causes disturbance of LDL metabolism with excessive accumulation of cholesterol in the tissues, leading to the formation of tendon xanthomas as well as severe premature coronary heart disease.

Disease is attributed to mutations in LDLR gene, which encodes LDLR protein and whose deficiency results in decreased uptake of apoB-containing cholesterol particles by the liver and elevated serum LDL-C levels. Heterozygous FH is inherited in an autosomal-dominant pattern with incidence of 1:500 in the general population. These patients usually present with premature cardiovascular disease at 30-40 years and have baseline LDL-C levels ranging from 4.92 to 5.96 mmol/L [9]. Homozygous FH, however, is much rarer, occurring in one in a million births; those afflicted present with severe cardiovascular disease in childhood and have baseline LDL-C levels greater than 7.77

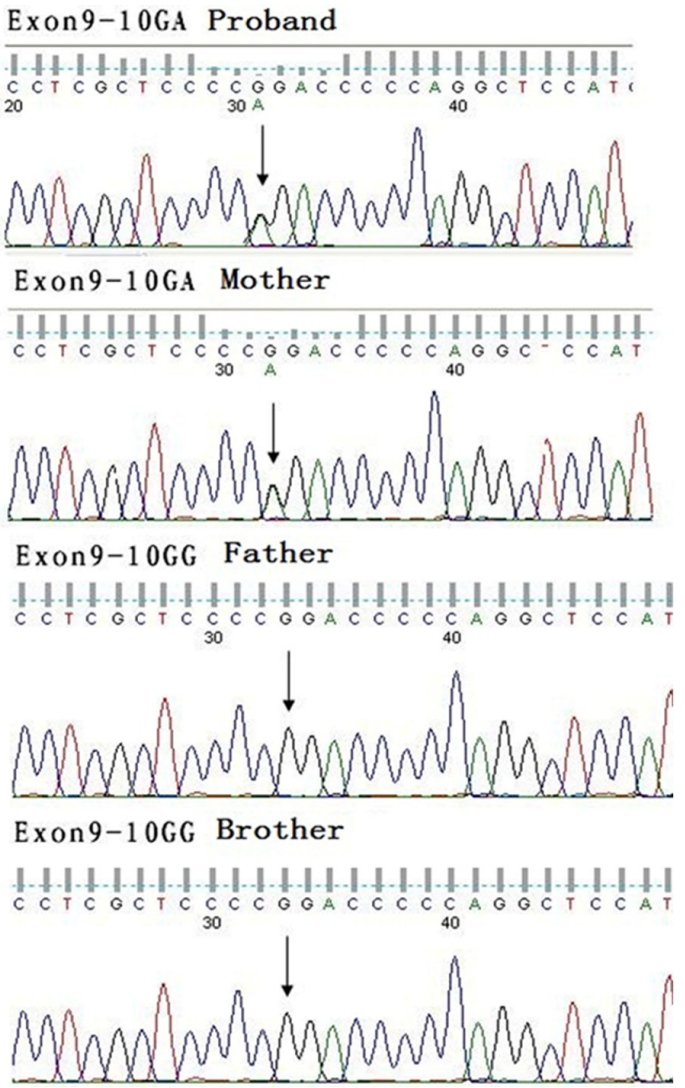

Figure 2. Gene sequences illustrated the proband and her mother had exon 9-10GA mutations in LDL receptor gene while her father and younger brother did not have.

mmol/L. Often FH patients do not reach their target LDL-C levels on conventional therapies such as statins. Even with combination therapy, the percent of FH patients reaching target cholesterol levels is less than 30% and while apheresis is a therapeutic option for those with the most severe disease, many FH patients seek less invasive therapeutic strategies.

During the therapeutic progress, aggressive lipid-lowering medications should be continued. A risk of new lesion formation in patients with a higher TC level has been reported [10]. As to our patient, the atorvastatin was stopped because of cardiac surgery. The TC increased from 3.44 to 5.22 mmol/L, and LDL-C increased from 2.37 to 3.76 mmol/L. The atorvastatin was prescribed again 3 days after CABG.

Conclusion

We reported a new gene mutation exon 9-10 G > A in LDLR in a Chinese family with FH. CABG is an effective method in treating her coronary artery disease.

Disclosure of conflict of interest

None.

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