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Short communication

Rare intracranial cholesterol deposition and a homozygous mutation of *LDLR* in a familial hypercholesterolemia patient

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ABSTRACT

Familial hypercholesterolemia (FH MIM# 143890) is one of the most common autosomal inherited diseases. FH is characterized by elevated plasma levels of total cholesterol and low-density lipoprotein-cholesterol. Mutation in the *LDLR* gene, which encodes the LDL receptor protein, is responsible for most of the morbidity of FH. The incidence of heterozygous FH is about 1/500, whereas the incidence of homozygous FH is only 1/1,000,000 in Caucasian population. In this study, we report a homozygous *LDLR* mutation (c.298G>A) in a familial hypercholesterolemia patient, who exhibited intracranial cholesterol deposition, which is a rare addition to the common FH phenotypes. The proband's consanguineous parents have the same heterozygous mutation with elevated concentrations of LDL-C but no xanthoma.

1. Introduction

Familial hypercholesterolemia (FH) is one of the most common autosomal genetic diseases, which is characterized by elevated plasma levels of total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C). To date, four causative genes of FH have been unraveled, including three autosomal dominant genes and one autosomal recessive gene (Muhidien et al., 2013). The major inheritance pattern of FH is autosomal dominant, of which the incidence is about 1/500 (Gerald et al., 2012). Low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*ApoB*), and pro-protein convertase subtilisin kexin 9 (*PCSK9*) are all well-known autosomal dominant genes involved in the pathogenesis of FH, while 85–90% of FH patients presenting the most serious phenotypes possess mutations in the *LDLR* gene (Goldberg et al., 2011). Up to January 14, 2011 (the latest update), 1741 *LDLR* allelic variants had been submitted to the *LDLR* mutation database of the British Heart Foundation (http://www.ucl.ac.uk/ldlr/Current/). Mutations in the *LDLR* gene lead to partial or complete loss of LDLR function, thereby causing elevated LDL-C level in the plasma. The TC and LDL-C levels are increased by over twofold, resulting in premature cardiovascular disease (CVD) as a common phenotype. FH is likewise a typical incomplete dominant disorder. Thus, phenotypes of homozygous patients are often more severe than that of heterozygotes (Robert et al., 2007). For example, xanthoma presents in most of the homozygous FH patients but only some of the heterozygous FH patients. It is same for the Chinese population, in which xanthoma becomes rare in heterozygous FH patients. Environmental factors may play a significant role in modulating the phenotype of heterozygous FH patients (Pimstone et al., 1998).

Treatments for FH include lifestyle improvement, drug, LDL-C apheresis and liver transplantation (Goldberg et al., 2011; Hovinqh et al., 2013). The target of treatment, formulated by the US National Lipid Association and the National Institute of Clinical Excellence in the UK, is to decrease the LDL-C concentration by approximately >50%. Some heterozygous FH patients can achieve this target by maintaining a healthy lifestyle and using lipid-lowering drugs, while homozygous FH patients can hardly meet this target via these methods. The best choices for homozygous FH patients would be LDL-C apheresis and liver transplantation.

In this study, we describe a Chinese patient with a pedigree of consanguineous familial hypercholesterolemia. The proband had high concentrations of LDL-C and CVD, together with whole-body multiple xanthoma and rare intracranial cholesterol deposition. Utilizing Sanger sequencing, a mutation (c.298G>A) was detected to be homozygous in the *LDLR* gene in the proband and heterozygous in his consanguineous parents who had elevated LDL-C concentration but no xanthoma.

Abbreviations: FH, familial hypercholesterolemia; LDL-R, low-density lipoprotein receptor; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; ApoB, apolipoprotein B; PCSK9, pro-protein convertase subtilisin kexin 9; CVD, cardiovascular disease; MRI, magnetic resonance imaging; DLCN, the Dutch Lipid Clinic Network; CCG, cerebral cholesterol granuloma; CTX, cerebrotendinous xanthomatosis.

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2. Materials and methods

2.1. Clinical evaluation and laboratory measurements

The proband and his consanguineous parents were identified at the Genetics Clinic of the State Key Laboratory of Medical Genetics (SKLMG) of China. Two-hundred randomly selected normal individuals were also included in this study. The study was approved by the Ethics Committee of SKLMG and informed consent was signed by each of the subjects.

We obtained comprehensive clinical history of the proband and conducted physical examination for xanthomas of whole body. We also performed biochemical tests to determine the TC level and LDL-C level, color Doppler ultrasound examination for pathological changes of heart and magnetic resonance imaging (MRI) for the brain.

2.2. Mutational analysis of the LDLR gene

Genomic DNA of all subjects was extracted from peripheral blood cells by phenol/chloroform method. The primers utilized to amplify the coding regions and intron/exon boundaries of *LDLR* were designed with PRIMER5 (PREMIER Biosoft International, Palo Alto, CA, USA). Primers and PCR conditions for the *LDLR* gene are supplied in the supplemental file. After identifying the *LDLR* mutation in the proband, PCR products of the consanguineous parents and controls were sequenced in order to validate the mutation.

3. Results

The 21-year-old proband was the son of consanguineous parents from China. Xanthoma first appeared at the ulnar side of his right forearm when he was 5 years old, and then expanded all over the body (Fig. 1A, B). When he was 15 years old, the TC and LDL-C concentrations were 11.55 mmol/L (normal range: 3.0–5.7 mmol/L) and 10.25 mmol/L (normal range: 2.1–3.1 mmol/L), respectively. After Ezetimibe and Simvastatin tablet treatment at the dose of 10/40 mg per day, the TC and LDL-C levels decreased, but did not reach the treatment target. When he was 20 years old, the TC and LDL-C concentrations were 6.23 mmol/L and 8.30 mmol/L. They increased to 14.37 mmol/L and 10.55 mmol/L one year later, after the statin treatment ceased because the proband could not tolerate such large doses with obviously elevated transaminase level. Color Doppler ultrasound examination of the heart was first performed when the proband was 15 years old, by which we detected mild prolapse of the anterior mitral valve with regurgitation, supravalvular aortic stenosis, and aortic regurgitation, as well as a neoplasm on the ascending aorta and aortic sinus junction. The second ultrasound examination was performed 6 years later, detecting no further deterioration of CVD. In the early months of the same year, brain MRI was performed for intermittent headache, which revealed big occupying lesions on the left posterior cranial fossa, petrous bone, mastoid, and right petrous tip region (Fig. 1C–E). These lesions had clear borders and hyperintense changes were shown by both T1 weighted and T2 weighted images. The MRI features of the lesions indicated one kind of cholesterol deposition. In addition, the compressions of the surrounding brain parenchyma, the fourth ventricle narrowing, supratentorial ventricle expansion, a shift in the midline, and cerebellar tonsillar descent were also detected. In the end of that year, the proband's headache became continuous, and he lost partial vision and partial hearing. After 5 months, he had lost entire vision and almost entire hearing.

The proband's parents are first-cousins, which means the marriage is between the older sister's son and the younger sister's daughter, i.e., a third degree relationship (Fig. 2). Xanthoma did not appear in the 58-year-old father and the 55-year-old mother. They declined the color Doppler ultrasound examination of the heart and statin treatment for

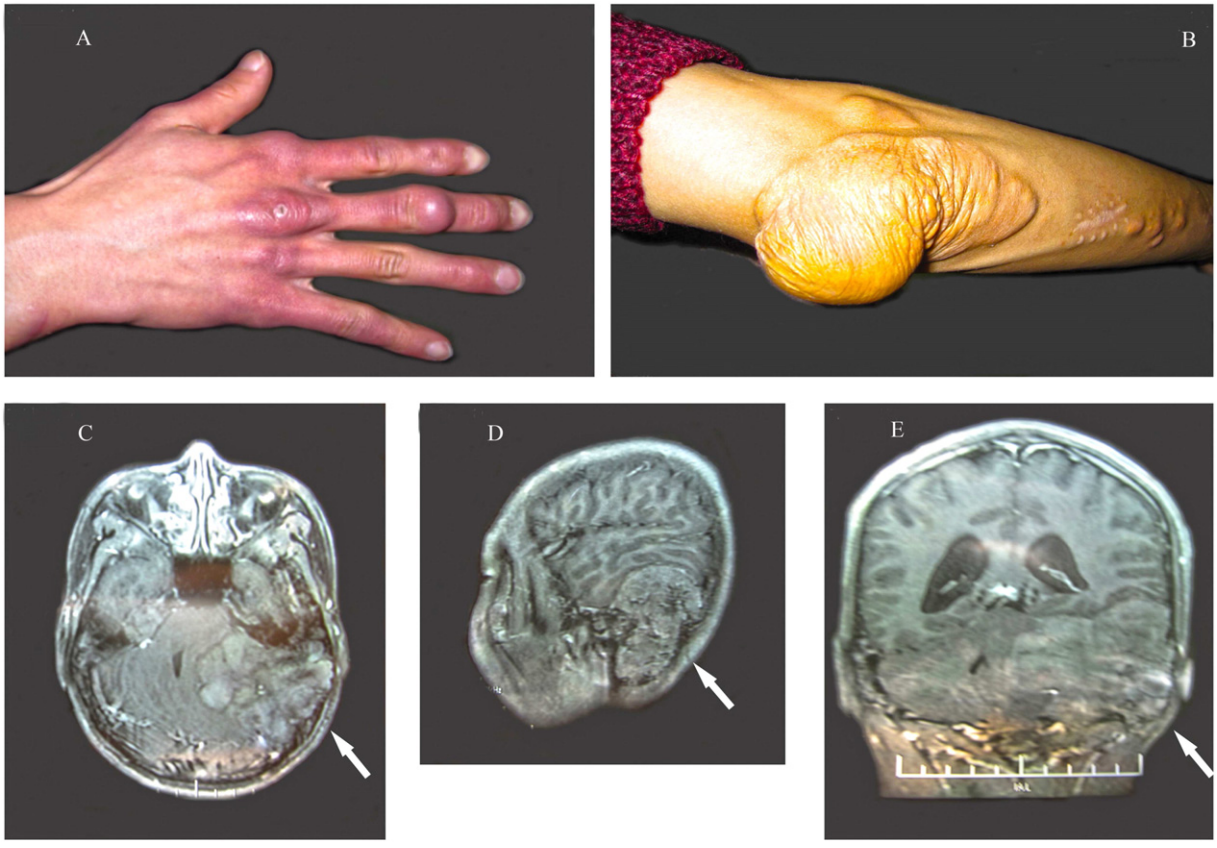

Fig. 1. A, B: Photographs of the proband showing the xanthomas located in the hand and elbow. C, D, E: MRI images of the proband showing the cholesterol deposits located in the left posterior cranial fossa, petrous bone and mastoid, and the right petrous tip region with a clear border, respectively.