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CASE REPORT

A Familial Analysis of Familial Hyperlipidemia Attributed to the Y2184C Mutation of the APOB Gene

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SUMMARY

Background: **Familial hyperlipidemia (familial hypercholesterolemia, FH) is an autosomal genetic disorder. It includes type heterozygous familial hyperlipidemia (heterozygous familial hypercholesterolemia). HeFH is mainly caused by mutations in the LDLR, APOB, and PCSK9 genes and is characterized by elevated plasma low-density lipoprotein cholesterol levels.**

Methods: **We present a case of HeFH attributed to an APOB gene mutation. The whole-genome DNA of peripheral blood was extracted from the blood of the proband and their parents, and the exons of peripheral blood were sequenced through high-throughput sequencing. The selected mutation sites were verified by sequencing using the Sanger method.**

Results: **A heterozygous mutation, c.6551A>G (p.Y2184C), in exon 26 of the APOB gene (Chr2-21233189) was identified in both the proband and the mother. Combined with the clinical features, HeFH caused by this mutation was initially considered.**

Conclusions: **For patients with a high degree of clinical suspicion of FH, a definitive diagnosis should be established through genetic testing, enabling patients to receive early treatment and effectively prevent the occurrence of cardiovascular events.**

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KEYWORDS

familial hypercholesterolemia, APOB, heterozygous familial hypercholesterolemia, LDL-C

INTRODUCTION

Familial hypercholesterolemia (FH) is a prevalent autosomal genetic disorder, which is characterized by elevated levels of plasma low density lipoprotein cholesterol (LDL-C). Arteriosclerotic cardiovascular diseases, such as coronary heart disease, ischemic stroke, and peripheral artery disease, occur prematurely and progress rapidly [1]. In two meta-analyses conducted in 2020, the prevalence of heterozygous familial hypercholesterolemia (HeFH) in the general population was 1/311 and 1/313, respectively [2,3]. The genes of HeFH mainly encompass LDLR, APOB, and PCSK9. Currently, over 2,000 mutant genes of LDLR have been reported [4], but only a limited number of mutations have been iden-

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tified in APOB and PCSK9 [5-8]. In this paper, a family analysis of HeFH caused by an APOB gene mutation is reported to provide evidence for the clinical diagnosis and treatment of the patient.

CASE PRESENTATION

The proband, a 27-year-old male, visited the outpatient department of Endocrinology at Shaoxing Central Hospital on December 30, 2023, due to "discovery of elevated blood lipids for 3 years". The patient's physical examination three years ago revealed elevated blood lipids, with total cholesterol at 6.22 mmol/L, low density lipoprotein at 4.07 mmol/L, high density lipoprotein at 1.77 mmol/L, triglyceride at 0.78 mmol/L, and normal thyroid function. He has been on a controlled diet without medication. On the day of re-examination for treatment, it was shown that total cholesterol was 7.28 mmol/L, low density lipoprotein was 4.97 mmol/L, triglyceride was 0.77 mmol/L, and thyroid function was normal. Atorvastatin 10 mg tablet was prescribed for oral lipid-lowering treatment once before bedtime. After 1 month of treatment, total cholesterol was 5.17 mmol/L, low density lipoprotein was 2.68 mmol/L, high density lipoprotein was 1.45 mmol/L, and triglyceride was 0.83 mmol/L. Physical examination: height 180 cm, body weight 80 kg, body mass index 24.7 kg/m^2, blood pressure 125/72 mmHg (1 mmHg = 0.133 kPa), body shape was normal, no physical appearance of Cushing was observed, and heart, lung, and abdominal examinations were normal. No edema was found in both lower limbs.

The mother of the patient had a family history of hyperlipidemia (Figure 1). Her total cholesterol was as high as 5.57 mmol/L and low density lipoprotein was up to 3.38 mmol/L. Arterial B-ultrasonography indicated plaque formation, and blood lipid returned to normal after diet and exercise control. None of the patient's father, grandparents or maternal grandparents had a history of hyperlipidemia.

With the informed consent of the patient and his family, the blood of the proband and his parents was extracted for peripheral blood whole genome DNA extraction, and peripheral blood whole genome exon high-throughput sequencing was carried out. The selected mutation sites were sequenced by Sanger method (Taizhou Angpu Medical Laboratory). The results showed that the proband was a heterozygous mutation c.6551A>G (p.Y2184C) in exon 26 of the APOB gene (Chr2-21233189), resulting in the change from amino acid tyrosine to cysteine (Figure 2), which was a missense mutation. There have been reports of hyperlipidemia caused by this site in HGMD database [9]. The frequency of this locus variation in the normal population database shows low-frequency variation. The proband's mother showed a heterozygous variation at this site, while the proband's father did not.

DISCUSSION

FH is one of the most common inherited metabolic disorders and is primarily associated with mutations in genes related to LDL-C clearance. Based on the type of gene mutation, it can be classified into Homozygous Familial Hypercholesterolemia (HoFH) and Heterozygous Familial Hypercholesterolemia (HeFH), among which HeFH is the most prevalent, but its awareness rate and diagnosis and treatment rates are extremely low. Studies have revealed that only 10 - 25% of patients diagnosed with FH receive appropriate treatment [10]. The diagnosis of FH requires a combination of clinical manifestations and genetic testing. The clinical manifestations of FH are mainly characterized by elevated levels of LDL-C, which can significantly enhance the risk of coronary heart disease and atherosclerotic cardiovascular disease (ASCVD). The risk of coronary heart disease in FH patients without statin treatment is 13 times higher than that in the general population [11]. Cholesterol-lowering therapy should be initiated immediately after the diagnosis of FH, and statins are the first-line treatment for FH. Among patients with FH, the incidence of cardiovascular events in patients treated with statins was reduced by 75% compared with untreated patients [12]. Therefore, early diagnosis and treatment of FH can improve the prognosis of FH and reduce the risk of cardiovascular events.

The APOB gene is one of the mutant genes of HeFH, and its mutation can reduce the binding degree of the APOB protein to LDLR, thereby influencing the transport and metabolism of LDL-C [13]. It is situated on the short arm of human chromosome 2 (2p24.1) and comprises 29 exons and 28 introns, ultimately encoding a protein consisting of 4,563 amino acids. Its mutation sites are relatively prevalent in exon 26 and 29 fragments [14], but only a few APOB mutations have been demonstrated to be pathogenic. It was discovered that the mutations in the related sequences of the ApoB gene were only associated with 8 diseases, most of which occurred in exon 26, the hotspot of mutation. Since the APOB gene is a polypeptide gene, and its mutation resulted in the clinical phenotype of HeFH patients being milder than that of LDLR mutation, further functional assessment of these mutations was necessary to determine the pathogenicity [15].

In this FH family, the level of LDL-C in the proband was significantly elevated, and the blood lipids returned to normal following treatment with statins. By sequencing the entire exon gene of the proband, it was discovered that exon 26 of the APOB gene had a c.6551A>G heterozygous missense mutation. Through the corresponding point mutation verification of the parents, it was found that hyperlipidemia in this family might be associated with the APOB (c.6551A>G; p.Y2184C) gene mutation in an autosomal dominant inheritance pattern. Both the proband and his mother are heterozygous carriers of this mutation, and both have hyperlipidemia, but the clinical phenotype is mild and can be

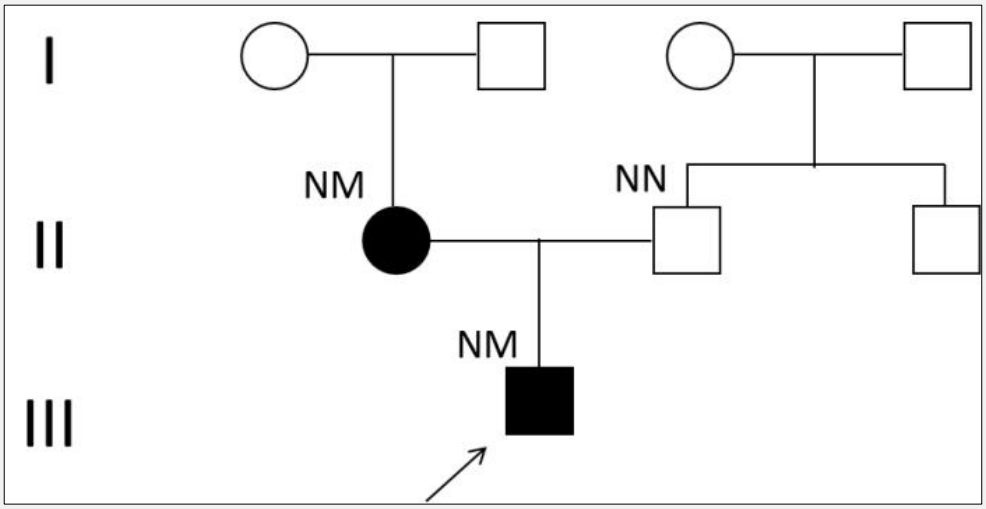

Figure 1. A heterozygous mutation of APOB gene (c.6651A >G; p.Y2184C), Family diagram of the patient.

The black arrow indicates the progenitor. The square symbolizes the male, while the circle symbolizes the female. The solid graph represents the individual with hyperlipidemia, and the hollow graph represents the individual with normal lipid levels. NN stands for no detected mutation, and NM represents the detection of heterozygous mutation.

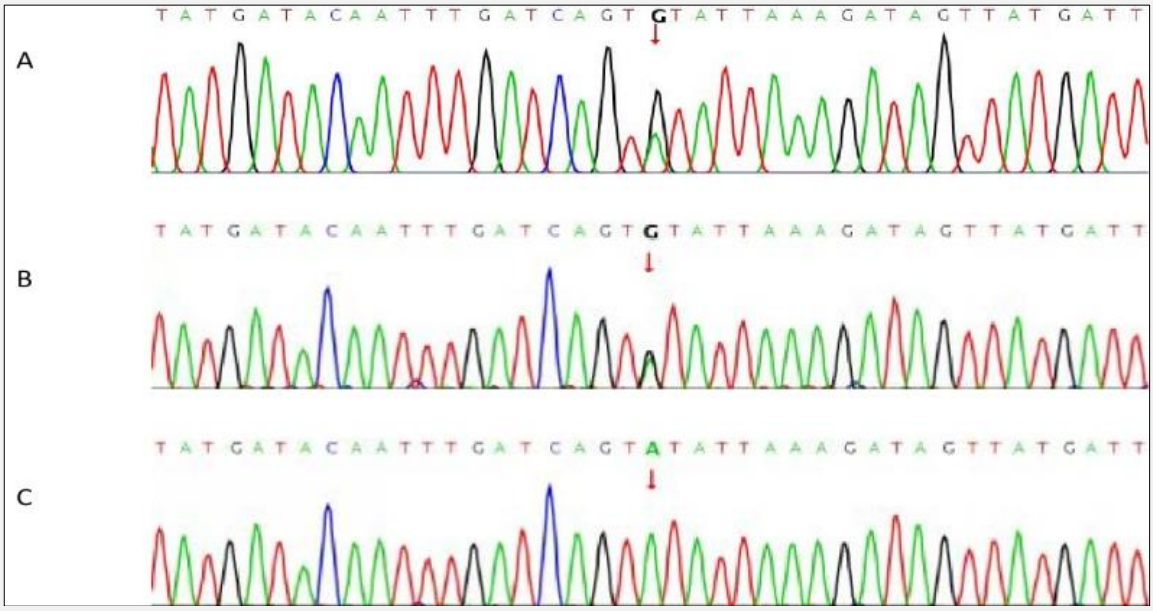

Figure 2. Heterozygous mutation of exon 26 of the APOB gene in this family (c.6651A > G; Sequencing diagram of p.Y2184C).

A and B represent sequences of heterozygous mutations of the proband and his mother, respectively, with arrows indicating the heterozygous mutation sites; C is the sequence diagram of the proband's father, where no variation is observed at the -location of the arrow.

controlled by diet, exercise, and low-dose statins. Although this site mutation has been reported, further functional tests are necessary for its confirmation.
In conclusion, for patients with a high clinical suspicion of FH, a definite diagnosis and early identification of FH should be accomplished through genetic testing. This not only offers individualized treatment to patients but also is of great significance for the prognosis of patients.

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Declaration of Interest:
All authors declare that they have no competing interests.

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