

# Maternally inherited diabetes and deafness coexists with lipoprotein lipase gene mutation-associated severe hyperlipidemia that was resistant to fenofibrate and atorvastatin, but sensitive to bezafibrate: A case report

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## Keywords

Hypertriglyceridemia, Lipoprotein lipase, Maternally inherited diabetes and deafness

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## ABSTRACT

Maternally inherited diabetes and deafness is a rare genetic disease mainly caused by a point mutation in mitochondrial deoxyribonucleic acid. Lipoprotein lipase gene mutations are associated with familial dyslipidemias, which are difficult to manage. We reported for the first time a case that had both maternally inherited diabetes and severe hyperlipidemia caused by lipoprotein lipase gene mutation (C.347(exon3)G>C) that was resistant to fenofibrate and atorvastatin. We were able to manage the patient's hyperlipidemia with bezafibrate, and her diabetes was well controlled with insulin. In conclusion, genetic testing is helpful in identifying rare and interesting cases when clinicians suspect inheritable diseases. Additionally, when one fibrate drug is ineffective in treating hyperlipidemia, it might be worthwhile trying another fibrate.

## INTRODUCTION

Maternally inherited diabetes and deafness is a rare genetic disease mainly caused by a point mutation in mitochondrial deoxyribonucleic acid (tRNA3243A>G). It is extremely rare when it coexists with another genetic disease. Lipoprotein lipase (LPL) is a rate-limiting enzyme that hydrolyzes cleavage of the triglyceride core of lipoproteins, which is essential for TG clearance and modulation of lipid metabolism. LPL gene mutations result in disturbance in TG clearance and disorders in lipid metabolism. They are associated with several types of familial dyslipidemias<sup>1–3</sup>. Here, we report a case with severe hyperlipidemia who carries a point mutation in the LPL gene

(heterozygous, C.347(exon3)G>C) (rs775728208) and a point mutation in mitochondrial deoxyribonucleic acid (tRNA3243A>G).

## CASE REPORT

A 31-year old female patient with low body mass index (14.5 kg/m<sup>2</sup>) was found to have elevated blood glucose 5 years earlier in a medical checkup. Her blood glucose was not well controlled until insulin was started 3 years earlier. Several of her family members from her mother's descent had diabetes and hyperlipidemia (Figure 1). The patient's grandmother died from diabetic ketoacidosis at the age of 33 years. Her aunt died from diabetic nephropathy at the age of 47 years. The patient's mother, her aunt and cousin had mild hyperlipidemia that was

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being well managed with statins. The patient's blood lipid profile on admission was 16.8 mmol/L (1486.73 mg/dL) for triglycerides (TG) and 9.91 mmol/L (382.53 mg/dL) for total cholesterol (TC). Abdominal ultrasonography showed splenomegaly. Her visual and auditory acuities were within the normal limits. The results of C-peptide release test are shown in Table 1. Insulin autoantibody, protein tyrosine phosphatase antibody, islet cell antibody and glutamic acid decarboxylase antibody were negative.

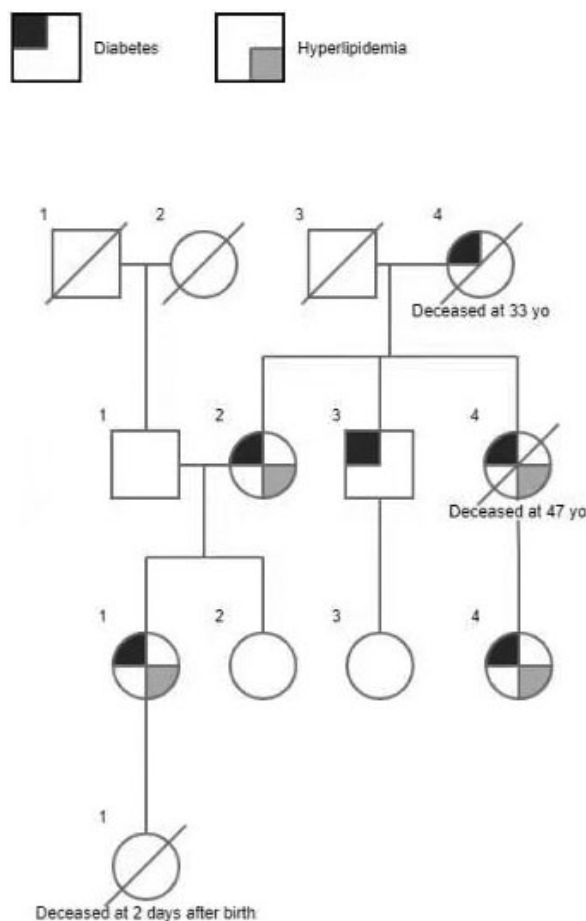
As a matter of fact, severe hyperlipidemia was identified in the patient 2.5 years earlier in a medical checkup. She was put on a low-fat diet and was additionally treated with fenofibrate. However, minimal effects were observed. Two years earlier, she stopped taking lipid-lowering medications during the fourth week of pregnancy and suffered from acute pancreatitis as a result of chylomicronemia, an extremely high TG level (>33.3 mmol/L; 2,946.92 mg/dL) and a TC level of 16.94 mmol/L (653.88 mg/dL) at the 26th week of her pregnancy. During hospitalization, her baby was delivered spontaneously at week 26<sup>+3</sup>, but died 2 days after birth. Daily fenofibrate combined with atorvastatin was prescribed to her

after delivery. Although her blood TC level was reduced to 3.94 mmol/L (152.08 mg/dL) with combined treatment, her blood TG stayed >10 mmol/L (884.96 mg/dL).

We suspected the patient had genetic diseases related to glucose and lipid metabolism. Therefore, blood samples from the patient and her mother were collected for genetic testing. Her diabetes continued to be treated with insulin, but we changed her lipid-lowering drug to bezafibrate. The patient's TC level was successfully reduced to 2.5 mmol/L (96.5 mg/dL), and her TG level dropped to 2.3 mmol/L (203.54 mg/dL) after bezafibrate treatment for 3 months. The genetic testing results showed that the patient had a point mutation in the LPL gene (heterozygous, C.347(exon3)G>C; rs775728208; Figure 2) and a point mutation in the mitochondrial gene (TRNL1, tRNA3243A>G; Figure 3). Her mother was reported to have the same heterozygous point mutation in the LPL gene (Figure 2).

**DISCUSSION**

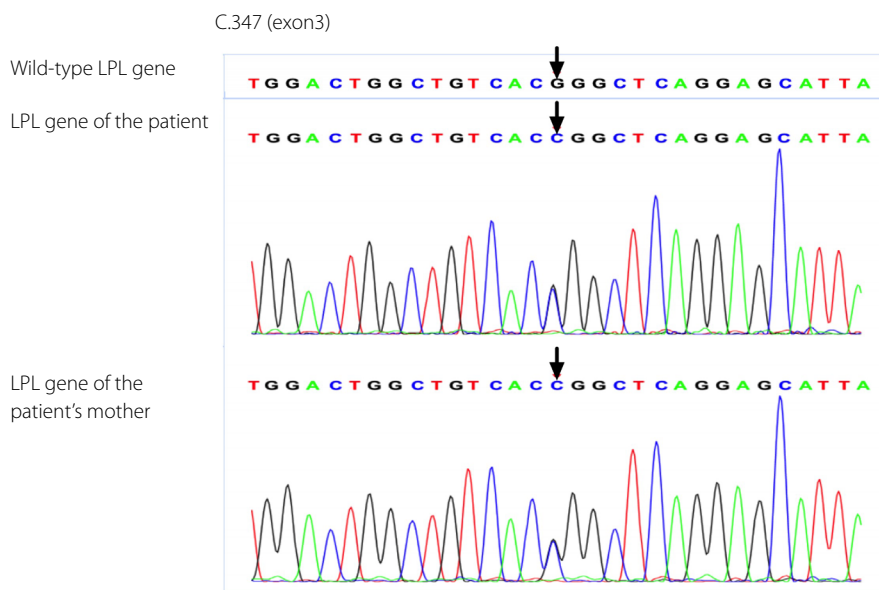
The clinical manifestations of maternally inherited diabetes and deafness and its severity are different from patient-to-patient, because different amounts of mutated mitochondrial



**Figure 1** | Pedigree chart of the patient's family. The arrow denotes proband (the patient). LPL, lipoprotein lipase gene.

**Table 1** | 75-g glucose load oral glucose tolerance test and C-peptide release test

	0 min	30 min	60 min	120 min
Glucose (mmol/L)	9.51	13.97	19.18	21.73
Glucose (mg/dL)	171.18	251.46	345.24	391.14
C-peptide (nmol/L)	0.413 (0.48–0.78)	1.157 (2.01–3.23)	1.68 (3.52–4.76)	1.27 (1.34–2.50)



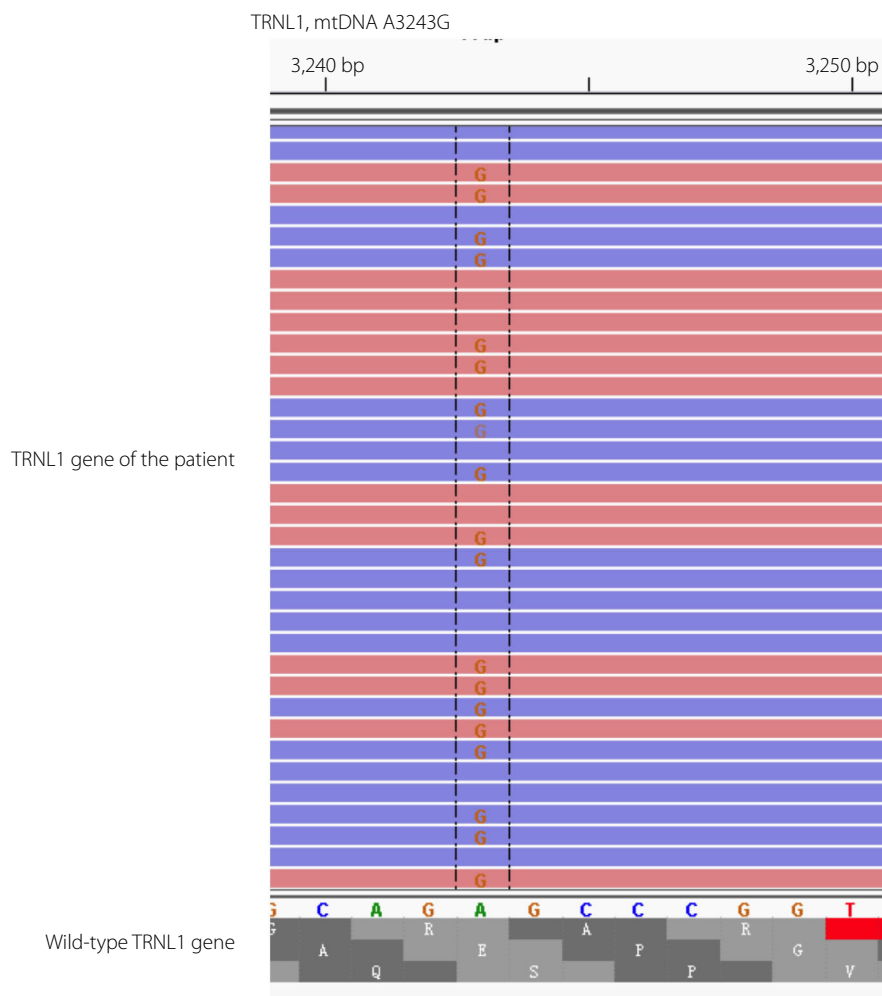
**Figure 2** | Lipoprotein lipase gene (LPL) gene analysis of the patient and her mother. The arrow denotes the variation site.

deoxyribonucleic acid are inherited<sup>4</sup>. The patient had insulin-dependent diabetes, low body mass index and splenomegaly, but no impairments in visual and auditory acuities. Several of her family members developed severe diabetes complications and died at an early age, some of them had hyperlipidemia that was easy to control. It is not clear whether maternally inherited diabetes and deafness could affect lipid metabolism. Given the patient presented with severe hyperlipidemia that was resistant to fenofibrate and atorvastatin, her clinical manifestations and her family history, a suspicion of genetic disease involving both glucose and lipid metabolism was raised. There is evidence showing that fibrates are not effective enough in familial dyslipidemia because of LPL gene mutations<sup>5</sup>. Interestingly, although fenofibrate failed to reduce blood TG levels in this patient, bezafibrate dramatically decreased her blood TG level to near normal. Brisson *et al.*<sup>6</sup> reported that LPL-P207L mutation attenuated the effects of fenofibrate in reducing TG levels. Likewise, Gao *et al.*<sup>7</sup> showed that some rare synonymous LPL gene variants could decrease the TG reduction effects of fenofibrate. In contrast, some LPL gene mutations, such as LPL D9N and LPL N291S, did not show a significant influence on the lipid-lowering effect of bezafibrate<sup>8</sup>. Therefore, it is possible that

the LPL gene mutation seen in this patient attenuated fenofibrate effects, but preserved the role of bezafibrate in reducing blood TG.

Fibrates are known to activate peroxisome proliferator-activated receptor (PPAR)  $\alpha$  to modulate lipoprotein gene expression, and upregulate LPL protein expression and activity, therefore promoting TG clearance. Bezafibrate is a non-selective PPAR activator, whereas fenofibrate only activates PPAR $\alpha$ <sup>9</sup>. PPAR $\beta$  is associated with fatty acid oxidation and energy consumption<sup>9</sup>. A previous case report showed that pioglitazone, a PPAR $\gamma$  agonist, greatly augmented the TG-lowering effects of fenofibrate and atorvastatin<sup>10</sup>, which suggests the augmentation effects of PPAR $\gamma$  agonists on reducing TG. The effect of bezafibrate on PPAR $\beta$  and PPAR $\gamma$  might contribute to the lipid-lowering action of bezafibrate.

This is the first case reporting a patient carrying a mutation in the LPL gene (heterozygous, C.347(exon3)G>C)(rs775728208) and a mutation in the mitochondrial gene (TRNL1, tRNA3243A>G). The patient's hypertriglyceridemia was resistant to fenofibrate and atorvastatin, but sensitive to bezafibrate, which gives clinicians a clue that when one fibrate drug is ineffective, it might be worthwhile trying another one.



**Figure 3** | Mitochondrial gene analysis of the patient. TRNL, mitochondrially encoded transfer ribonucleic acid leucine; mtDNA, mitochondrial deoxyribonucleic acid.

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### DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: N/A.

Informed Consent: Written informed consent was obtained from all the participants.

Approval date of Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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