Heterozygous Null *LDLR* Mutation in a Familial Hypercholesterolemia Patient With an Atypical Presentation Because of Alcohol Abuse

Kamaldeep Panach, MD; Abhimanyu Garg, MD; Zahid Ahmad, MD

Patients with familial hypercholesterolemia (FH; Online Mendelian Inheritance in Man #143890) have lifelong elevations in low-density lipoprotein cholesterol (LDL-C) that result in deposition of cholesterol in tendons— referred to as tendon xanthomas and occurring in ≈19% of heterozygous FH patients[1]—and an increased risk of premature cardiovascular disease. FH is an autosomal dominant disorder resulting from mutations in the LDL receptor (*LDLR*), *APOB* (apolipoprotein B), or *PCSK9* (proprotein convertase subtilisin-like kexin type 9) genes.[2]

Heterozygous mutations in *LDLR* are the most common cause of FH. In addition to elevated LDL-C, patients harboring *LDLR* mutations may have lower levels of high-density lipoprotein cholesterol and only mild, if any, elevations in triglycerides.[3–5] Severe hypertriglyceridemia is rarely seen in FH patients.[5] We report an alcoholic patient who presented with severely elevated serum triglycerides and both tuberous and tendon xanthomas in whom the diagnosis of FH was confirmed by genetic testing.

Clinical Case

A 75-year-old Hispanic man was referred to us for genetic testing as part of a larger research protocol.[6] His medical history included 3-vessel coronary artery bypass graft at age 47 and a myocardial infarction at age 60, hypothyroidism, osteoporosis, gastro-esophageal reflux, hypertension, recurrent major depressive disorder with a history of a suicide attempt, heavy alcohol and tobacco abuse, and Alzheimer dementia (initially diagnosed at age 72 with superimposed frontal lobe damage from prior alcohol use).

Hyperlipidemia was first diagnosed at age 34, although his wife noted that he had Achilles tendon xanthomas and arcus senilis since age 22 (when they first met). He had been tried on multiple medications (he could not recall exact names) and ultimately underwent ileal bypass surgery at age 41 for treatment. The ileal bypass was reversed at age 60 because of multiple episodes of intestinal obstruction. At age 66, he was hospitalized for rhabdomyolysis. His serum creatine kinase level was found to be >40 000 U/L (reference range, 52–336 U/L) while taking simvastatin 40 mg BID, gemfibrozil 600 mg BID and niacin 500 mg TID. He had been on simvastatin for 15 years, gemfibrozil for 4 years, and niacin for 18 months before this hospitalization. After this hospitalization, he was referred to a specialty lipid clinic for further evaluation and treatment.

His mother experienced a lethal myocardial infarction at age 34 and several maternal uncles had hypercholesterolemia. His sister had a history of a coronary artery bypass graft and also had a lethal myocardial infarction at age 55, and his brother committed suicide at age 19. He had 4 daughters, one of whom was known to have hypercholesterolemia.

The patient smoked 1.5 packs of cigarettes per day for >30 years and consumed 4 to 8 glasses of wine per day. His wife reported a memory disturbance after the reversal of the ileal bypass, which was progressive and worse when he drank alcohol.

After hospitalization for rhabdomyolysis, his lipid medications had been adjusted to atorvastatin 20 mg QD per day, fish oil 5 capsules TID, colesevelam 1875 mg BID, and sitostanol margarine 2 tablespoons daily. He had extreme elevations in both serum total cholesterol of 611 mg/dL (reference range, <200 mg/dL) and triglycerides 725 mg/dL (reference range, 50–150 mg/dL). High-density lipoprotein cholesterol was 42 mg/dL (reference range, 40–60 mg/dL). A few available lipid panels before admission showed serum total cholesterol ranging from 239 to 461 mg/dL, triglycerides ranging from 192 to 499 mg/dL, high-density lipoprotein cholesterol 43 to 62 mg/dL, and LDL-C 157 to 240 mg/dL. His serum Thyroid Stimulation Hormone level was normal (3.77 µIU/mL; reference range, 0.35–5.5 µIU/mL).

Other medications included aspirin 325 mg daily, folic acid 1 mg daily, isosorbide mononitrate 20 mg BID, calcium carbonate 500 mg daily, donepezil 10 mg daily, duloxetine 60 mg daily, ergocalciferol 50 000 international units monthly, esomeprazole 40 mg daily, levothyroxine 25 micrograms daily, ramipril 5 mg daily, and risedronate 10 mg weekly.

On physical examination, he had normal body mass index (24 kg/m^2). He had bilateral arcus senilis, calcified appearing tuberous xanthomas over his knees, and large xanthomas over his Achilles tendons (Figure 1A).

His initial and repeated lipid panels demonstrated high triglycerides and total cholesterol. He was tried on multiple lipid-lowering regimens and was counseled on the need to abstain from alcohol. Of note, when he abstained from alcohol on 2 occasions (Figure 2), his serum triglycerides improved to 164 mg/dL. However, he resumed alcohol, often drinking

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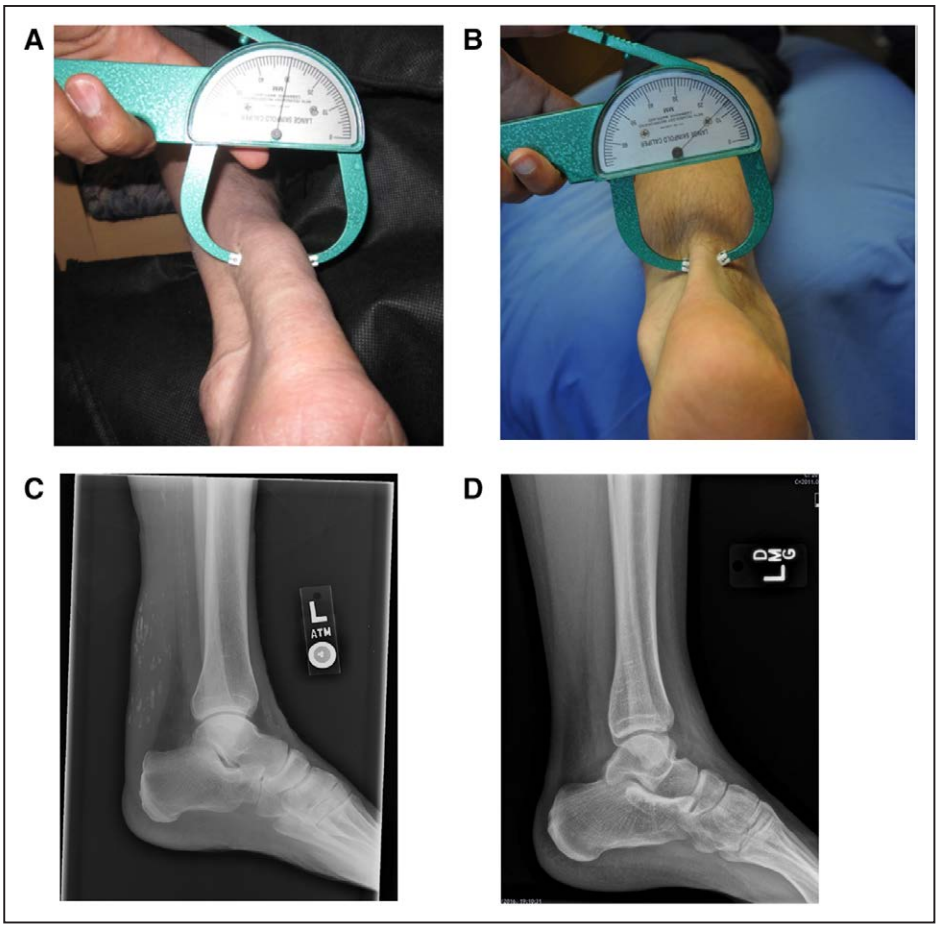

Figure 1. Achilles tendon xanthomas. **A**, Image of patient's Achilles tendon with caliper measuring thickness of 30 mm. **B**, Image of a normal Achilles tendon with width of 13 mm. **C**, Lateral plain radiograph demonstrating thickness of the patient's Achilles tendon with scattered calcifications. **D**, Lateral plain radiograph with normal Achilles tendon (courtesy of Dr Ian Bickle[28]).

6 to 8 cups of wine per day and was intoxicated every day per his wife.

His best lipid panel during follow-up has been total cholesterol of 181 mg/dL, triglycerides 125 mg/dL, high-density lipoprotein cholesterol 49 mg/dL, and LDL-C 107 mg/dL, while adherent to ezetimibe 10 mg daily, fish oil 5 capsules BID, colesevelam 1875 mg BID, and rosuvastatin 20 mg daily (Figure 2).

Materials and Methods

The protocol was approved by the Institutional Review Board of UT Southwestern, and the patient provided written informed consent. Genomic DNA was isolated from whole blood. All 18 exons and the flanking intronic regions of *LDLR* were amplified and sequenced using Applied Biosystems 3730xl DNA Analyzer (Applied Biosystems, Carlsbad, CA) as described previously.[7] Apolipoprotein E genotyping was done as described previously.[7]

Results

LDLR sequencing revealed the patient harbored a heterozygous p.(Q448*);c.1342C>T mutation on exon 9. The patient also was heterozygous for a single nucleotide polymorphism in *LDLR* intron 16 (rs2738460; c.2389+46C>T with a minor allele frequency of 0.23 in subjects of European origin; from dbSNP—accessed May 2017). Apolipoprotein E genotyping revealed he was wild type (E3/E3).

Discussion

Our case demonstrates that patients with FH can develop a unique lipid phenotype—because of chronic alcoholism—causing a diagnostic conundrum and highlighting the use of a detailed social history, physical examination, and confirmatory genetic testing. Although the presence of tendon xanthomas, arcus senilis, and a strong family history suggested FH, severe hypertriglyceridemia and tuberous xanthomas on the knees suggested an alternative diagnosis of dysbetalipoproteinemia (type 3 hyperlipoproteinemia, Online Mendelian Inheritance in Man #107741). In light of genetic testing confirming the diagnosis of FH, heavy alcohol intake likely changed his phenotype from a classical FH phenotype to one consistent with dysbetalipoproteinemia (increased cholesterol and triglycerides).[8] Alcohol ingestion is known to increase plasma triglyceride concentrations by increasing triglyceride synthesis and production of very LDL particles in the liver.[9]

Typically, plasma triglyceride levels in heterozygous FH patients are not significantly elevated. In a US registry of FH patients (mostly diagnosed clinically without genetic confirmation), the median (interquartile range) plasma triglyceride level was 116 mg/dL (82–170 mg/dL; n=1867).[10] Furthermore, patients with mutation-confirmed FH—like our patient—have slightly lower triglycerides than mutation-negative FH

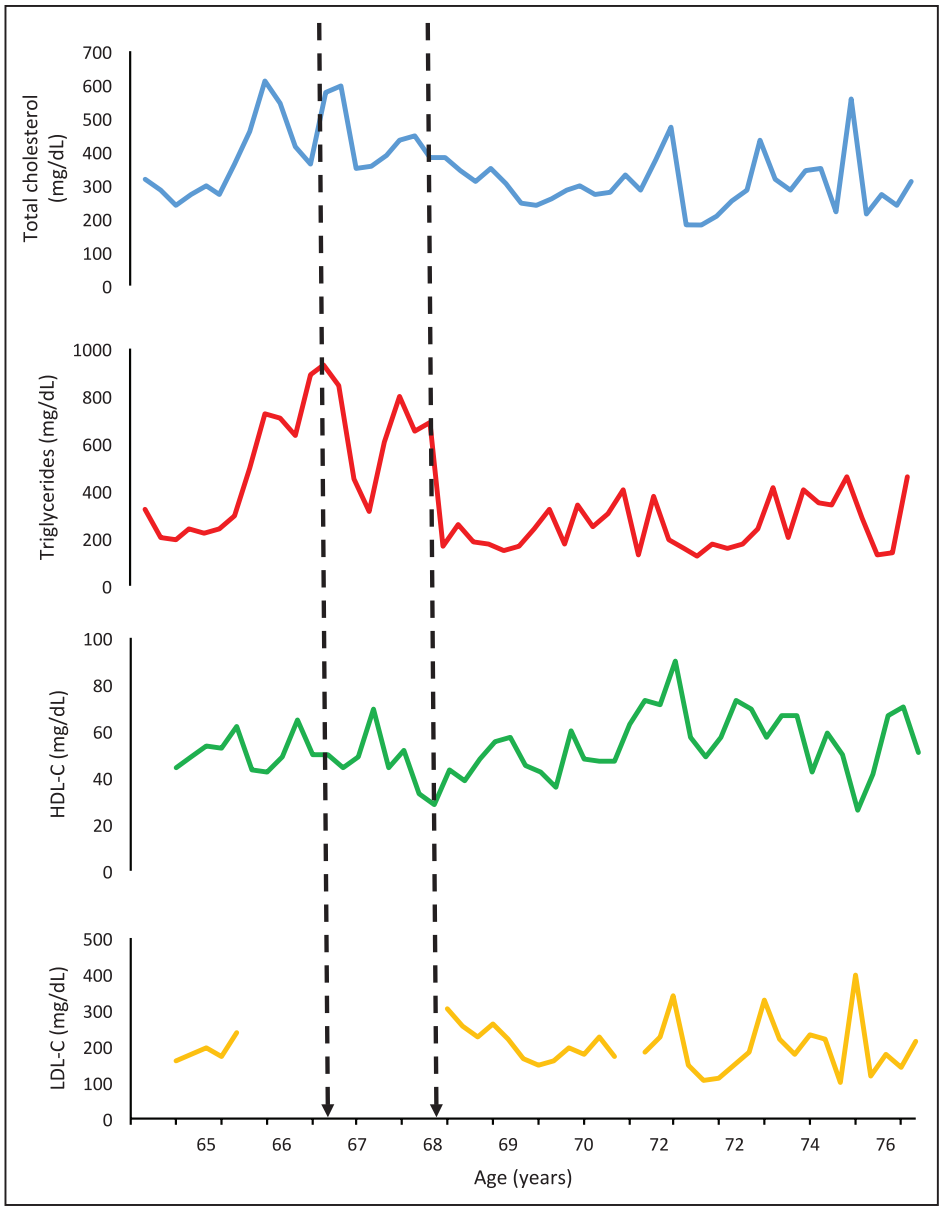

Figure 2. Graphs depicting lipid levels during 10 y of follow-up. Dashed arrows indicate time points where the patient had stopped drinking alcohol but with resumption during time points in between. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

patients: in a Spanish population of FH patients, the median (interquartile range) triglyceride level was 97 mg/dL (68–139 mg/dL; n=459) in those with *LDLR* or *APOB* mutations, whereas the median (interquartile range) triglyceride level was 122 mg/dL (86–189 mg/dL, n=366) in those without an identifiable mutation.[11]

Influence from incidental genes may lead to severe hypertriglyceridemia in FH patients. Recently, a mutation-confirmed FH patient—similar to our case—was reported with triglycerides of 951 mg/dL and tendon xanthomas on physical examination.[12] Targeted next-generation DNA sequencing was done, and although it failed to identify any disease-causing mutations in hypertriglyceridemia-associated genes (eg, lipoprotein lipase, apolipoprotein c2), the patient did harbor a high polygenic burden of single nucleotide polymorphisms that raise serum triglyceride levels.

Based on our patient's lipid profile, FH may not be on the differential diagnosis unless a thorough physical examination was done and a detailed medical history was obtained. Once FH was suspected, diagnostic criteria for FH (Simon-Broome, MedPed, and the Dutch Lipid Clinic Network) could have been used to give a diagnosis. However, these criteria have been called into question in recent articles as having poor sensitivity and specificity to predict pathogenic *LDLR* mutations.[13]

For FH, genetic testing has an unclear role in clinical care. In this case, the patient participated in a larger research study that involved genetic testing. Although the results may not benefit him directly (other than to provide a definitive diagnosis), they may be useful for his daughters and grandchildren. Recent data indicates that a positive genetic test has prognostic implications for cardiovascular risk beyond just LDL-C levels,[6,14,15] for which his relatives should be counseled.

Our patient's mutation—the stop mutation p.(Q448*)—has been reported previously in a homozygous FH patient from Spain and a heterozygous FH patient from Mexico.[16,17] However, phenotype data on lipid and lipoprotein values was not reported for these subjects. This mutation is not in the ExAC database[18] or in ClinVar (accessed March 2017).[19]

Although, our patient's baseline and postsurgical serum lipids and lipoprotein values were not available, he may have benefited from the intestinal bypass surgery with regards to not just LDL-C lowering but improving his lifespan. Before US Food and Drug Administration approval of statins in 1987,[20] only bile acid sequestrants, niacin, and fibrates were available for lipid lowering. For those FH patients who were unresponsive to these therapies, partial ileal bypass was recommended. Partial ileal bypass is effective at reducing LDL-C and death because of coronary heart disease: Buchwald et al[21] showed that the procedure reduced LDL cholesterol by 38% at 5 years compared with controls, and death because of coronary heart disease and confirmed nonfatal myocardial infarction was 35% lower in those undergoing partial ileal bypass surgery (n=421) compared with controls (n=417; 125 versus 82 events, respectively; $P<0.001$). Common side effects of partial ileal bypass include diarrhea, kidney stones, gallstones, and intestinal obstruction.[21] Our patient had multiple episodes of intestinal obstruction and, thus, had the procedure reversed.

Our patient had remarkable Achilles tendon xanthomas. Tendinous xanthomas form movable hard nodules that can infiltrate tendons, tendon attachments, ligaments, fascia, and the periosteum.[22] These are suggestive of FH but can also be seen in other rare genetic disorders, such as cerebrotendinous xanthomatosis and sitosterolemia. To distinguish between these other genetic disorders, the clinical history, genetic testing, and serum sterol profiles are important because the xanthomas may seem similar.[22] In cerebrotendinous xanthomatosis, individuals may have neurological or cognitive symptoms, normal cholesterol levels, and high plasma levels of cholestenol.[23] In sitosterolemia, individuals have premature cardiovascular disease associated with high plasma cholesterol levels (≤1000 mg/dL) and increased plasma concentrations of plant sterols.[24] Other lesions can appear similarly but can be differentiated based on lipid levels. In FH, lesions are commonly found on the Achilles tendons, dorsum of the hands, and extensor surfaces of the knees and elbows. On lateral plain radiographs, xanthomas on the Achilles tendon appear as abnormal thickening of the tendon or as noncalcified soft-tissue masses.[25,26] Our patient had rare atypical xanthomata involving the bilateral Achilles tendons that appeared calcified on radiographs (Figure 1B). Our patient also had tuberous xanthomas over his knees. Tuberous xanthomas are flat or slightly elevated yellow-appearing nodules in the dermis and subcutaneous tissue.[22] These lesions are commonly found in the skin over the joints or on the buttocks. They are most often described in patients with dysbetalipoproteinemia but can also occur in patients with FH, cerebrotendinous xanthomatosis, or sitosterolemia.[22]

Our patient was on a high dose of simvastatin in addition to gemfibrozil at the time of his episode of rhabdomyolysis. Because FH patients present with severe hypercholesterolemia, they usually do not require fibrates. However, because of this patient's presentation with severe hypertriglyceridemia, he was initiated on a combination of simvastatin and gemfibrozil, which resulted in rhabdomyolysis. Rhabdomyolysis is a known rare side-effect of statin use, exacerbated by interactions with concomitant medications, such as gemfibrozil.[27] The US Food and Drug Administration has now classified the drug interaction between simvastatin and gemfibrozil as risk rating X with the recommendation to avoid the combination. The reported time course for the development of rhabdomyolysis with this drug combination varies widely, ranging from 5 to 900 days.[27] Our patient was reportedly on this combination for ≈4 years; however, he was known to be poorly adherent to his medications. So the exact number of days he was compliant with this therapy remains unknown.

Conclusions

The diagnosis of FH is made clinically; however, laboratory findings are not always as expected and other medical conditions may cause secondary changes in the lipid profile. Genetic testing may play a role in cases such as ours, where the clinical course and physical examination findings suggest FH but lipid levels may not be consistent.

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