eMedical Research
Volume 3
Article ID: 100021

Case Report

Dyslipidemia due to Heterozygous Apolipoprotein E Mutation Compounded by Polygenic Risk Factors: A Family Case Series and Literature Review

Vishnu Priya Pulipati[1], Devin Loewenstein[2], Lauren S. Singer[3] and Michael H. Davidson[1*]

[1]Preventive Cardiology, Department of Cardiology, The University of Chicago Medicine, USA

[2]Division of Cardiology, Department of Internal Medicine, Rush University Medical Center, USA

[3]Department of Neurology, Rush University Medical Center, USA

***Corresponding author**: Michael H. Davidson, MD, FACC, FNLA, Professor, Director of the Lipid Clinic, The University of Chicago Medicine, 355 E Grand Ave, Second Floor, Chicago, Illinois, 60611, USA, Tel: +773-834-4150; Fax: +773-834-7260; E-mail: mdavidso@bsd.uchicago.edu

Received: June 04, 2021; **Accepted**: July 03, 2021; **Published**: July 10, 2021

Abstract

Dyslipidemia is a major risk factor for atherosclerosis and cardiovascular diseases. As genetic testing is increasingly available, clinicians now have an accessible tool for accurate diagnosis of an underlying disorder in patients suspected to have inherited dyslipidemia. Evaluation of genetic results facilitates patient-specific counseling, cascade screening, and proactive interventions to decrease cardiovascular disease risk.

A 51-year-old Caucasian male patient with a family history of heart disease presented with severe dyslipidemia and typical angina pectoris. ECG and exercise ECG stress test were negative for ischemic changes. Coronary CT angiography revealed extensive non-obstructive, predominately calcified plaque in the left anterior descending artery with more discrete plaques in the right coronary artery and left circumflex artery suggestive of premature atherosclerosis. He was started on lipid-lowering therapy. Due to suspicion for inherited dyslipidemia disorder, genetic testing was performed. Genetic testing reported a rare APOE mutation with polygenic risk factors for dyslipidemia. Cascade screening in his three daughters showed mixed hyperlipidemia with the same pathogenic APOE mutation and various polygenic risk factors for dyslipidemia, prompting early lipid-lowering intervention.

Keywords: *dyslipidemia, cardiovascular disease, genetics, screening, apolipoprotein, prevention*

Introduction

Dyslipidemia is an undisputed major risk factor for atherosclerosis and globally prevalent cardiovascular disease [1]. Lipid metabolism is regulated by several factors, including apolipoproteins, enzymes, transfer and signaling proteins, and cell receptors. Any disruption in this efficient process can cause dyslipidemia. Rare large-effect DNA mutations cause primary or genetic lipid disorders [2]. Monogenic mutation diseases run in families and can follow a multitude of genetic inheritance patterns, including dominant, recessive, autosomal, or sex-linked. Common small-effect genetic variants (SNPs) cause dyslipidemia due to polygenic inheritance [3]. The GWAS are used to identify whether a SNP is associated with a specific disease [4]. The polygenic risk scores that provide an overall estimate of genetic predisposition to a clinical manifestation at the individual level are derived from GWAS data [3]. Among patients with comparable lipid levels, monogenic hypercholesterolemia is associated with the greatest risk of cardiovascular disease, followed by polygenic hypercholesterolemia compared to those without an identified genetic cause [5]. The clinical signs and symptoms, family history, and pattern of lipid abnormalities are the initial clues available to clinicians to decipher the possible inherited dyslipidemia. As genetic testing is increasingly available,

clinicians now have an accessible tool for accurate diagnosis of an underlying disorder in patients suspected to have inherited dyslipidemia [6]. The use of genetic evidence is not new; previously rare familial genetic diseases or Mendelian randomization studies have provided a foundation for advances in lipid-lowering pharmacotherapy. Herein, we present a case series of a family with a rare genetic mutation in APOE compounded by various polygenic risk factors contributing to severe dyslipidemia and posing a risk for premature heart disease. Cascade screening in three first-degree relatives led to early diagnosis of dyslipidemia and proactive lipid-lowering intervention in family members to reduce cardiovascular disease risk.

Methods

Candidates to undergo genetic testing were selected by a clinical lipidologist. Genetic testing was primarily performed to screen for monogenic inherited dyslipidemias. Pre-testing counselling was provided by an experienced lipidologist. After the patient's consent, a genetic test was performed using GBinsight Comprehensive Dyslipidemia Panel (GB Lifesciences, San Diego, CA, USA). The participant's genomic DNA derived from saliva was sequenced using next-generation DNA sequencing at the regions targeted by GBinsight Panels on an Illumina HiSeq instrument. This panel is designed to analyze 127 genes known or suspected to be associated with dyslipidemia. Allele frequencies were estimated from the 1000 Genomics Phase 3 Database [7]. The polygenic risk score was calculated using a proprietary algorithm developed by GB HealthWatch. It included both risk-increasing and risk-decreasing variants and calculated on a relative scale between 1 and 100, with 1 being the lowest genetic risk and 100 being the highest genetic risk compared to the reference population for patient's ethnicity. The final genetic analysis report generated shows pathogenic and likely pathogenic variants with allele frequency, variants of uncertain significance, and variants likely high-impact to disease risk based on allele frequency, polygenic disease risk, and pharmacogenomic associations.

Case Presentations

Patient-1 (Index patient)

A 51-year-old Caucasian male presented to the lipid clinic with severe dyslipidemia and typical angina pectoris. ECG and exercise ECG stress test were negative for ischemic changes. Subsequent coronary CT angiography showed extensive non-obstructive, predominately calcified plaque in the LAD with more discrete plaques in the RCA and LCx (Figures 1 and 2). His baseline medical history included essential hypertension, prediabetes, metabolic syndrome, rheumatoid arthritis, and ankylosing spondylitis. He never smoked or used illicit drugs and endorsed drinking alcohol socially. He has a family history of hypertension, hyperlipidemia, sudden cardiac death at age 56 in his father and a history of smoking, hyperlipidemia, hypertension, and uncontrolled diabetes mellitus in his mother. Medications include guanfacine 2mg daily, spironolactone/hydrochlorothiazide 25-25mg daily, methotrexate 7.5mg once a week, and golimumab injection once a month. Physical exam was unremarkable except for BMI 26 kg/m^2 (overweight, Ref 18.5-24.9). Laboratory workup showed severe dyslipidemia without evidence of secondary etiologies (normal thyroid function test, liver function test, and renal function test), as shown in Table 1. Subsequent statin therapy, including alternate statin, low-dose, and intermittent dosing of statin, caused recurrent severe statin-associated muscle side-effects leading to discontinuation. Ezetimibe 10mg daily, Colesevelam 6 tablets of 625mg once daily, and patient-preferred over-the-counter supplements (including red yeast rice and omega-3 fish oil) led to suboptimal dyslipidemia control. At his age of 57, PCSK9i became available. With the use of subcutaneous injection evolocumab 140mg every two weeks, his LDL-C improved and to date continues to be maintained below 70 mg/dL, as shown in Table 1. Intensive lifestyle interventions, including a low carbohydrate diet accompanied by weight loss, improved his TGs. Severe hyperlipidemia, premature atherosclerosis, and family history of heart disease in his father raised suspicion for inherited lipid disorder; hence genetic testing was offered. The genetic results revealed a pathogenic mutation in APOE

compounded by polygenic risk factors for dyslipidemia, as shown in Table 2. Currently, at age 63, his dyslipidemia is well controlled while being adherent to lipid-lowering therapy (evolocumab and ezetimibe), and he has remained cardiac event-free for over ten years of follow up. Genetic findings prompted cascade screening in his three daughters (patient-2 aged 26, patient-3 & 4 are fraternal twins aged 21). Index patient's wife, who is the biological mother of his three daughters, is healthy without a history of hyperlipidemia or heart disease.

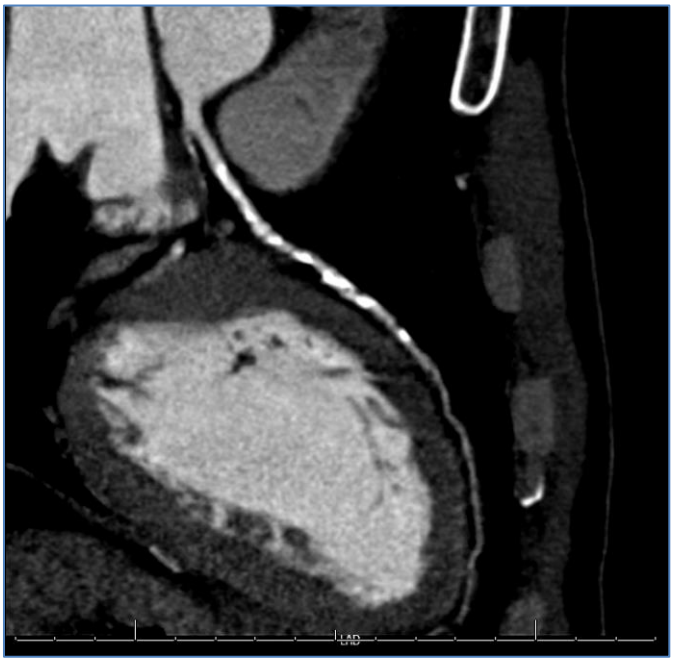

Figure 1. Coronary Computed Tomography Angiography Image of Patient 1. Extensive calcified plaque in the proximal and mid-left anterior descending artery

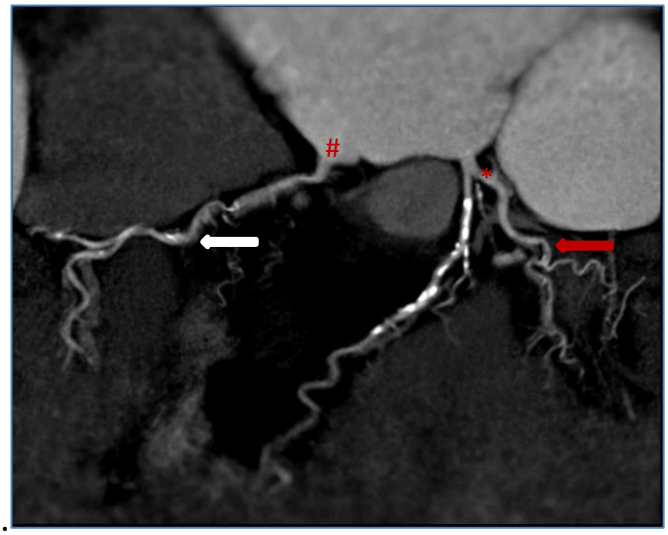

Figure 2. Coronary Computed Tomography Angiography Image of Patient 1. *Left circumflex artery: Red arrow showing calcified and non-calcified plaque with minimal stenosis (<30%). #Right Coronary artery: White arrow showing scattered calcified plaques in the mid and distal right coronary artery with minimal stenosis (<30%).

Patient 2

A 26-year-old Caucasian female underwent screening as a first-degree family member of the index patient. Her baseline medical history included migraines. She was a never-smoker with no history of alcohol or illicit drug use. She was not planning pregnancy and using an intrauterine device for contraception. Medications included occasional Botox

injections for migraines. Physical examination was unremarkable. Laboratory workup showed dyslipidemia without evidence of secondary etiologies (normal thyroid function test, liver function test, and renal function test), as shown in Table 1. The genetic results revealed a pathogenic mutation in APOE compounded by polygenic risk factors for dyslipidemia, as shown in Table 2. Due to severe dyslipidemia, genetic results, and strong family history of heart disease, she was started on a low-intensity statin, which was up-titrated to a high-intensity statin for better dyslipidemia control. Currently, at age 30, the patient remains healthy, and her dyslipidemia is well controlled while being adherent to lipid-lowering therapy (rosuvastatin 20mg once daily).

Table 1. Laboratory workup of patients

	TC Ref <200 mg/dL	**LDL-C Ref <100 mg/dL**	**TG Ref <150 mg/dL**	**HDL-C Ref >40-50 mg/dL**	**Non-HDL-C Ref <130 mg/dL**	**Other**
Patient 1 (age 52 years)						
Baseline (year 2009) • BMI 26 kg/m^2 • No lipid-lowering medications	288 (97.5-99th percentile)	192 (95-97.5th percentile)	217 (75-90th percentile)	53 (50-75th percentile)	235	• ApoB 125 (Ref <125 mg/dL) when non-HDL-C was 207 mg/dL • Lp(a) 9 mg/dl (Ref <30 mg/dL)
Recent labs (year 2021) • BMI 22.96 kg/m^2 • On ezetimibe 10mg once daily, evolocumab 140mg subcutaneous injection once every 2 weeks	100	28	142	44	56	
Patient 2 (age 26 years)						
Baseline (year 2015) • No lipid-lowering medications	254 (97.5-99th percentile)	174 (97.5-99th percentile)	174 (95-97.5th percentile)	56 (25-50th percentile)	198	
Recent labs (year 2021) • On rosuvastatin 20mg once daily	159	79	71	65	94	
Patient 3 (age 21 years)						
Baseline (year 2015) • No lipid-lowering medications	236 (97.5th percentile)	172 (>99th percentile)	92 (50-75th percentile)	59 (50-75th percentile)	177	
Recent labs (year 2020) • No lipid-lowering medications, started rosuvastatin 5mg once daily after this visit	227	145	95	63	164	
Patient 4 (age 21 years)						
Baseline (year 2015) • No lipid-lowering medications	240 (97.5-99th percentile)	175 (>99th percentile)	155 (95-97.5th percentile)	45 (10-25th percentile)	195	
Recent labs (year 2020) • On rosuvastatin 5mg once daily	186	97	105	68	118	
• All patients' secondary workup for dyslipidemia, including thyroid function test, liver function test, and renal function test, was normal. • Age and gender-specific baseline lipid values and percentile of TC, LDL-C, HDL-C, and TG [8].						

Table 2. Genetic test results of patients. Reference for clinical variants [9]

	Patient 1	Patient 2	Patient 3	Patient 4
Pathogenic and Likely Pathogenic Variants	Heterozygous APOE E4-(c.137T>C(p.Leu46Pro)) rs769452 haplotype	Heterozygous APOE E4-(c.137T>C(p.Leu46Pro)) rs769452 haplotype	Heterozygous APOE E4-(c.137T>C(p.Leu46Pro)) rs769452 haplotype	Heterozygous APOE E4-(c.137T>C(p.Leu46Pro)) rs769452 haplotype
Variants of Uncertain Significance and large effect size variants	-- Heterozygous ABCA7 (c.2966G>A(p.Arg989His)) rs139214131 -- Heterozygous LMF1 (c.1052G>A(p.Arg351Gln)) rs192520307 -- Homozygous MC4R (g.60183864T>C) rs17782313	-- Heterozygous ABCA7 (c.2966G>A(p.Arg989His)) rs139214131 -- Heterozygous LMF1 (c.1052G>A(p.Arg351Gln)) rs192520307 -- Heterozygous CREB3L3 (c.700C>G(p.Leu234Val)) rs199855279	-- Homozygous FTO (c.46-43098T>C) rs1421085	-- Heterozygous ABCA7 (c.2966G>A(p.Arg989His)) rs139214131 -- Heterozygous LMF1 (c.1052G>A(p.Arg351Gln)) rs192520307 -- Homozygous PNPLA3 (c.444C>G(p.Ile148Met)) rs738409 -- Homozygous FTO (c.46-43098T>C) rs1421085
Polygenic Disease Risk for Combined Hyperlipidemias	92 (High risk)	97 (High risk)	88 (High risk)	92 (High risk)
Polygenic Disease Risk for Hypercholesterolemia	99 (High risk)	99 (High risk)	92 (High risk)	99 (High risk)
Polygenic Disease Risk for Hypertriglyceridemia	86 (High risk)	54 (Moderately high risk)	77 (High risk)	80 (High risk)
Polygenic Disease Risk for Low HDL levels	31 (Not identified)	14 (Not identified)	1 (Not identified)	2 (Not identified)
Polygenic Disease Risk for High lipoprotein (a) levels	12 (Not identified)	22 (Not identified)	30 (Not identified)	17 (Not identified)
Polygenic Disease Risk for Defective reverse cholesterol transport	Not identified	Not identified	Not identified	Not identified
Pharmacogenomic Associations	None	None	None	None

Patient 3

A 21-year-old Caucasian fraternal-twin female underwent screening as a first-degree family member of the index patient. Her baseline medical history included treated anorexia nervosa. She was a never-smoker with no history of alcohol or illicit drug use. She was not planning for pregnancy, using an etonogestrel/Ethinyl estradiol vaginal ring for contraception. Medications included escitalopram 10mg daily. Physical examination was unremarkable with a normal BMI. Laboratory workup showed dyslipidemia without evidence of secondary etiologies (normal thyroid function test, liver function test, and renal function test), as shown in Table 1. The genetic results revealed a pathogenic mutation in APOE compounded by polygenic risk factors for dyslipidemia, as shown in Table 2. She was monitored with a regular lipid panel once a year per patient preference. Currently, at age 25, due to persistent hyperlipidemia, genetic results, and strong family history of heart disease, she was started on a low-intensity statin (rosuvastatin 5mg once daily).

Patient 4

A 21-year-old Caucasian fraternal-twin female underwent screening as a first-degree family member of the index patient. Her baseline medical history included symptomatic sinus tachycardia. She was a never-smoker with no history of alcohol or illicit drug use. She was not planning for pregnancy, using an etonogestrel/Ethinyl estradiol vaginal ring for contraception. Medications included escitalopram 10mg daily, propranolol 20mg twice daily. Physical examination was unremarkable. Laboratory workup showed dyslipidemia without evidence of secondary etiologies (normal thyroid function test, liver function test, and renal function test), as shown in Table 1. The genetic results revealed a pathogenic mutation in APOE compounded by polygenic risk factors for dyslipidemia, as shown in Table 2. She was subsequently

monitored with a regular lipid panel once a year per patient preference. At age 22, due to persistent hyperlipidemia, genetic results, and strong family history of heart disease, she was started on a low-intensity statin (rosuvastatin 5mg once daily). Currently, at age 25, the patient remains healthy, and her dyslipidemia is well controlled while being adherent to lipid-lowering therapy (rosuvastatin 5mg once daily).

Discussion

In our case series, four first-degree relatives from two subsequent generations show mixed dyslipidemia (elevations in TG and LDL-C) with genetic testing notable for the same pathogenic mutation in APOE. The index patient marks the first generation diagnosed in this family (see family pedigree chart shown in Figure 3). While the index patient already developed symptomatic CAD with extensive atherosclerosis at a young age of 51, his daughters in their early adulthood were screened and managed before the onset of atherosclerotic cardiovascular disease. The clinical presentation of mixed dyslipidemia of varying severity in our cohort, premature CAD in the index patient, and family history of fatal premature CAD in prior generations prompts the differential of FH, FCH, familial dysbetalipoproteinemia, rare mutations with or without SNPs for dyslipidemia. In our case series, after further understanding of the physiologic and pathophysiologic role of ApoE, we suspect that the APOE mutation compounded by polygenic risk factors is the likely etiology for the familial clinical manifestations.

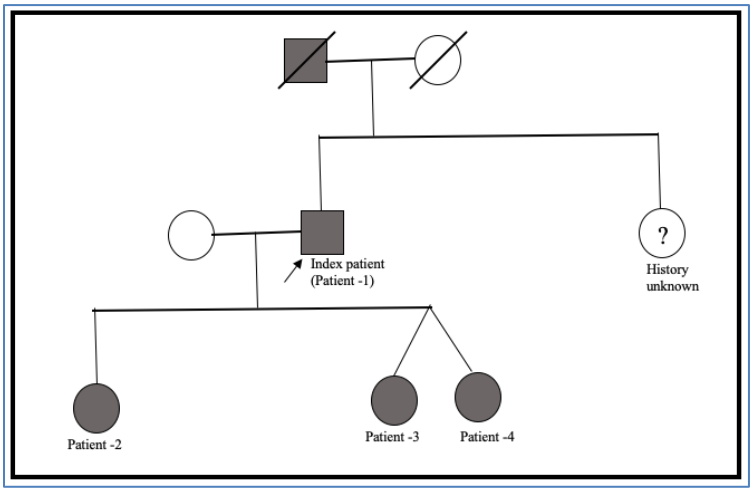

Figure 3. Pedigree chart of the family

The APOE gene is located on chromosome 19q13.2 [10]. ApoE is a multifunctional protein, primarily produced by the liver, with a crucial role in lipid metabolism, neurobiology, and neurodegenerative diseases [11]. It is one of the major apolipoprotein of VLDL, IDL, and a minor apolipoprotein of chylomicrons and HDL [10]. ApoE plays a crucial role in the clearance of remnant lipoprotein particles (IDL) by serving as a ligand for binding to hepatic LDL and LRP receptors. There are three major isoforms of ApoE (ApoE2, ApoE3, ApoE4), each encoded by three codominant alleles with varying properties. The major difference in properties being receptor binding capacity; while ApoE3 and ApoE4 have 100% receptor binding capacity, ApoE2 has <2% [11]. In addition to the common ApoE isoforms, several rare ApoE variants have been identified. One such variant is ApoE4Freiburg [12]. All the patients in our case series have heterozygous ApoE4Freiburg variant. This variant occurs due to p.Leu46Pro sequence change that replaces leucine with proline at codon 46 of the immature ApoE protein. The structural perturbations due to the mutation interfere with key folding pathways of the ApoE protein and appear to lead to important functional changes [13]. The mutant protein can interact with lipids, but the kinetics and final products are altered. ApoE4Freiburg is biochemically more acidic than ApoE4. According to the gnomAD (largest database for cataloguing genetic variants), this variant is found in nearly 1 in 130 people of Finnish European ancestry followed by 1 in 300 people of Ashkenazi Jewish ancestry, and in 1 in 400

people in the general population [14]. The ApoE4Freiburg variant was identified and studied in white subjects residing in the region surrounding Freiburg in southwestern Germany. One study analyzed three groups with this variant – the control subject group, patient group, and family study group [12]. The ApoE4Freiburg allele was significantly more common in the CAD patient group than control (1:137 *vs*. 1:426; p=0.0004). In this study, the age- and sex-adjusted OR for CAD was 3.09 (95% CI, 1.20 to 7.97) in carriers of ApoE4Freiburg than non-carriers. Analysis in patients with angiographic evidence of CAD revealed an allelic frequency similar to all CAD patients [12]. The ApoE4Freiburg variant was also noted to exert atherogenic properties by modulating the metabolism of TG-rich lipoproteins and HDL with varying phenotypic presentation [12]. In a study characterizing the genetic background associated with autosomal dominant hypercholesterolemia (n=120 children and 109 adults), APOE variants were found in four patients (1.7%) with one patient suffering from mixed hyperlipidemia and three with isolated hypercholesterolemia [15]. In this study, one patient with the ApoE4Freiburg variant had a severe form of hypercholesterolemia [15]. Another study by Wieland et al. identified a similar ApoE4 variant in German-Caucasian subjects that was not associated with hyperlipidemia [16]. The ApoE4Freiburg variant is also implicated in increased risk for late-onset Alzheimer's disease [13].

Clinical genetic testing identified heterozygosity for ApoE4Freiburg haplotype consisting of p.Cys130Arg (E4) and p.Leu46Pro genetic variants in the germline be associated with FH [17]. Recently some variants in APOE were observed to present with clinical features of autosomal dominant FH, prompting interest in screening the APOE gene as a potential etiology for autosomal dominant FH [18]. Despite not having the common monogenic mutation, FH-phenotype due to other underlying genetic variants can be a risk for CAD. Patients with FH-phenotype (defined by untreated LDL-C >230 mg/dL for ages 18-29, >238 mg/dL for ages 30-39, >260 mg/dL for ages 40-49, and >255 mg/dL for >ages 49) have notably increased risk for atherosclerotic cardiovascular disease compared to the normolipidemic population [19]. Patients younger than 35 years with FH-phenotype have a 16-fold risk for CAD [17]. The polygenic risk factors for dyslipidemia can contribute to polygenic FH or worsen the risk of underlying monogenic FH [20].

As mentioned, in cases of mixed dyslipidemia and premature CAD, it is prudent to assess for the more commonly occurring genetic dyslipidemias such as FCH and familial dysbetalipoproteinemia before considering rare variants as potential etiologies. FCH is the most common autosomal dominant hyperlipidemia in the general population with a high risk of premature CAD [21]. The underlying pathophysiology is believed to be hepatic overproduction of ApoB-100 containing lipoprotein particles from the liver, resulting in increased plasma TC, TG, ApoB, small dense LDL, and low HDL-C [22]. The plasma ApoB level >125 or 130 mg/dL is considered an important diagnostic criterion for diagnosis of FCH [1,23]. In our family case series, primary hyperlipoproteinemia and familial predisposition do raise suspicion for the diagnosis of FCH, but the index patient near-normal ApoB level (as shown in Table 1) makes it less likely. Rare APOE mutations were identified in patients diagnosed with FCH [18]. However, ApoE4Freiburg is not among the variants found to be associated with FCH, overall making this diagnosis less likely in our cohort.

Type III hyperlipoproteinemia (also known as familial dysbetalipoproteinemia) is another possible etiology of mixed hyperlipidemia with premature CAD. It occurs due to 2 copies of ApoE2 (one from each parent) with reduced ability to clear atherogenic remnant lipoprotein particles. Of the individuals with two copies of ApoE2, only 15% develop significant clinical disease characterized by severe mixed hyperlipidemia, tuberous xanthomas, and premature CAD [21]. Typically, secondary factors (obesity, insulin resistance) that inhibit remnant clearance by degradation of hepatic receptors must be present to trigger clinical presentation. In the remaining 80-90% of individuals with two copies of ApoE2, mixed hyperlipidemia is the most common phenotype. Most commonly, this disorder is autosomal recessive or polygenic; only in rare 10% of the cases, it is caused by autosomal dominant mutation [24]. Clinically the ratio of non-HDL-C/ApoB (cut-off ≥ 1.43) is the best predictor and is used as a screening test for diagnosis of familial

dysbetalipoproteinemia [25]. Our index patient had primary hyperlipoproteinemia, premature CAD, non-HDL-C/ApoB ratio 1.65 (abnormal), and familial predisposition that would support the diagnosis of familial dysbetalipoproteinemia, but the absence of obesity, insulin resistance, tuberous xanthomas, or ApoE2 isoforms on genetic analysis makes the diagnosis less likely.

After a detailed assessment of the clinical information, family history, genetic results, and evaluating differential diagnosis, we suspect heterozygous ApoE4Freiburg to be the primary driver of the observed phenotypes. The varying severity of dyslipidemia in the cohort with the same APOE mutation suggests that we cannot attribute the clinical manifestation solely to APOE mutation. The patient-specific polygenic variants compounding the APOE mutation might be playing a role in these observed differences. During evaluation for inherited dyslipidemias in our patients, overlapping clinical features posed a significant diagnostic challenge. Genetic testing played a crucial role in identifying and ruling out possible etiologies. The accurate diagnosis of underlying disorder facilitated patient-specific counseling, cascade screening, and proactive intervention to reduce future cardiovascular events. As evidence expands, the potential classification of this variant as a pathogenic etiology for familial dyslipidemia will have a significant impact on patient care. However, there are limitations to genetic testing, including high cost, poor availability of the resource, and in some cases, limited information on specific mutations or variants. As preventive lipidology is evolving, these challenges are being highlighted and addressed.

Conclusion

Genetic testing for inherited dyslipidemias is an important diagnostic tool that is increasingly available. It facilitates accurate diagnosis of inherited dyslipidemias, especially when patients have overlapping features, and assists in identifying polygenic risk factors. Evaluation of genetic results allows patient-specific counseling, cascade screening, and proactive intervention for cardiovascular disease risk reduction. Our family case series is one of the few reported with heterozygous ApoE4Freiburg pathogenic variant compounded by polygenic risk factors resulting in familial mixed dyslipidemia and premature CAD.

Conflict of Interests

Michael H. Davidson, MD, FACC, FNLA is a Consultant and Speaker for Amgen, Esperion, New Amsterdam, Novo Nordisk, Piper Biosciences, Regeneron, Sanofi.

Abbreviations

Apo: Apolipoprotein; BMI: Body Mass index; CAD: Coronary Artery Disease; CI: Confidence Interval; CT: Computed Tomography; DNA: Deoxyribonucleic Acid; ECG: Electrocardiogram; FCH: Familial Combined Hyperlipidemia; FH: Familial Hypercholesterolemia; GWAS: Genome-wide Association Studies; HDL-C: High-density Lipoprotein Cholesterol; IDL: Intermediate-density Lipoprotein; LAD: Left Anterior Descending Artery; LCx: Left Circumflex Artery; LDL: Low-density Lipoprotein; LDL-C: Low-density Lipoprotein Cholesterol; Lp(a): Lipoprotein (a); LRP: Low-density Lipoprotein Receptor related Protein; OR: Odds Ratio; PCSK9i: Proprotein Convertase Subtilisin/kexin type 9 inhibitors; Ref: Reference; RCA: Right Coronary Artery; SNPs: Single Nucleotide Polymorphisms; TC: Total Cholesterol; TG: Triglyceride; VLDL: Very Low-density Lipoprotein.

References

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, et al. (2019) AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 73: 3168-3209.

2. Hegele RA (2001) Monogenic dyslipidemias: window on determinants of plasma lipoprotein metabolism. Am J Hum Genet 69: 1161-1177.
3. Crouch DJM, Bodmer WF (2020) Polygenic inheritance, GWAS, polygenic risk scores, and the search for functional variants. Proc Natl Acad Sci U S A 117: 18924-18933.
4. GWAS Catalog. [Available at: https://www.ebi.ac.uk/gwas/]
5. Trinder M, Francis GA, Brunham LR (2020) Association of Monogenic vs Polygenic Hypercholesterolemia With Risk of Atherosclerotic Cardiovascular Disease. JAMA Cardiol 5: 390-399.
6. Brown EE, Sturm AC, Cuchel M, Braun LT, Duell PB, et al. (2020) Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. J Clin Lipidol 14: 398-413.
7. 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, Garrison EP, et al. (2015) A global reference for human genetic variation. Nature 526: 68-74.
8. Balder JW, de Vries JK, Nolte IM, Lansberg PJ, Kuivenhoven JA, et al. (2017) Lipid and lipoprotein reference values from 133,450 Dutch Lifelines participants: Age- and gender-specific baseline lipid values and percentiles. J Clin Lipidol 11: 1055-1064.e6.
9. ClinVar. [Available at: https://www.ncbi.nlm.nih.gov/clinvar/]
10. Giau VV, Bagyinszky E, An SS, Kim SY (2015) Role of apolipoprotein E in neurodegenerative diseases. Neuropsychiatr Dis Treat 11: 1723-1737.
11. Huang Y, Mahley RW (2014) Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. Neurobiol Dis 72 Pt A: 3-12.
12. Orth M, Weng W, Funke H, Steinmetz A, Assmann G, et al. (1999) Effects of a frequent apolipoprotein E isoform, ApoE4Freiburg (Leu28-->Pro), on lipoproteins and the prevalence of coronary artery disease in whites. Arterioscler Thromb Vasc Biol 19: 1306-1315.
13. Argyri L, Dafnis I, Theodossiou TA, Gantz D, Stratikos E, et al. (2014) Molecular basis for increased risk for late-onset Alzheimer disease due to the naturally occurring L28P mutation in apolipoprotein E4. J Biol Chem 289: 12931-12945.
14. gnomAD. [Available at: https://gnomad.broadinstitute.org/].
15. Wintjens R, Bozon D, Belabbas K, MBou F, Girardet JP, et al. (2016) Global molecular analysis and APOE mutations in a cohort of autosomal dominant hypercholesterolemia patients in France. J Lipid Res 57: 482-491.
16. Wieland, H., Funke, H., Krieg, J., Luley, C., 1991. ApoE3-Freiburg and apoE4-Freiburg are two genetic apoE variants which are caused by exchanges of uncharged amino acids and do not appear to be associated with lipid disorders or heart disease. pp.164.
17. National Center for Biotechnology Information. ClinVar; [VCV000441268.2]. [Available at: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000441268.2].
18. Khalil YA, Rabès JP, Boileau C, Varret M (2021) APOE gene variants in primary dyslipidemia. Atherosclerosis 328: 11-22.
19. Masana L, Zamora A, Plana N, Comas-Cufí M, Garcia-Gil M, et al. (2019) Incidence of Cardiovascular Disease in Patients with Familial Hypercholesterolemia Phenotype: Analysis of 5 Years Follow-Up of Real-World Data from More than 1.5 Million Patients. J Clin Med 8: 1080.
20. Sarraju A, Knowles JW (2019) Genetic Testing and Risk Scores: Impact on Familial Hypercholesterolemia. Front Cardiovasc Med 6: 5.

21. Gaddi A, Galetti C, Pauciullo P, Arca M (1999) Familial combined hyperlipoproteinemia: experts panel position on diagnostic criteria for clinical practice. Committee of experts of the Atherosclerosis and Dysmetabolic Disorders Study Group. Nutr Metab Cardiovasc Dis 9: 304-311.
22. van Himbergen TM, Otokozawa S, Matthan NR, Schaefer EJ, Buchsbaum A, et al. (2010) Familial combined hyperlipidemia is associated with alterations in the cholesterol synthesis pathway. Arterioscler Thromb Vasc Biol 30: 113-120.
23. Gaddi A, Cicero AF, Odoo FO, Poli AA, Paoletti R (2007) Atherosclerosis and Metabolic Diseases Study Group. Practical guidelines for familial combined hyperlipidemia diagnosis: an up-date. Vasc Health Risk Manag 3: 877-886.
24. Koopal C, Marais AD, Visseren FL (2017) Familial dysbetalipoproteinemia: an underdiagnosed lipid disorder. Curr Opin Endocrinol Diabetes Obes 24: 133-139.
25. Paquette M, Bernard S, Blank D, Paré G, Baass A (2020) A simplified diagnosis algorithm for dysbetalipoproteinemia. J Clin Lipidol 14: 431-437.