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Preventative cardiology

A case report of heterozygous familial hypercholesterolaemia with *LDLR* gene mutation complicated by premature coronary artery disease detected in primary care

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Background Familial hypercholesterolaemia (FH) is an autosomal dominant genetic condition predominantly caused by the low-density lipoprotein receptor (*LDLR*) gene mutation.

Case summary This is the case of a 54-year-old Malay woman with genetically confirmed FH complicated by premature coronary artery disease (PCAD). She was clinically diagnosed in primary care at 52 years old, fulfilling the Simon Broome Criteria (possible FH), Dutch Lipid Clinic Criteria (score of 8: probable FH), and Familial Hypercholesterolaemia Case Ascertainment Tool (relative risk score of 9.51). Subsequently, she was confirmed to have a heterozygous *LDLR* c.190+4A>T intron 2 pathogenic variant at the age of 53 years. She was known to have hypercholesterolaemia and was treated with statin since the age of 25. However, the lipid-lowering agent was not intensified to achieve the recommended treatment target. The delayed FH diagnosis has caused this patient to have PCAD and percutaneous coronary intervention (PCI) at the age of 29 years and a second PCI at the age of 49 years. She also has a very strong family history of hypercholesterolaemia and PCAD, where seven out of eight of her siblings were affected. Despite this, FH was not diagnosed early, and cascade screening of family members was not conducted, resulting in a missed opportunity to prevent PCAD.

Discussion Familial hypercholesterolaemia can be clinically diagnosed in primary care to identify those who may require genetic testing. Multidisciplinary care focuses on improving identification, cascade screening, and management of FH, which is vital to improving prognosis and ultimately preventing PCAD.

Keywords Familial hypercholesterolaemia • Heterozygous • *LDLR* gene mutation • Premature coronary artery disease • Case report • Multidisciplinary management • Primary care

ESC curriculum 3.1 Coronary artery disease • 8.3 Dyslipidaemia • 8.6 Secondary prevention

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Learning points

- This case highlights a missed opportunity to diagnose familial hypercholesterolaemia (FH) early in a patient with pre-existing premature coronary artery disease. FH should be clinically diagnosed in primary care to identify those who may require genetic testing.
- A multidisciplinary management of FH, including cascade screening of family members, is vital to prevent premature atherosclerotic cardiovascular disease in this extremely high-risk population.
- This case supports an urgent call for action to improve FH detection and multisectoral management in tandem with the global call to action to reduce the clinical and public health burden of FH.

Primary specialties involved other than cardiology

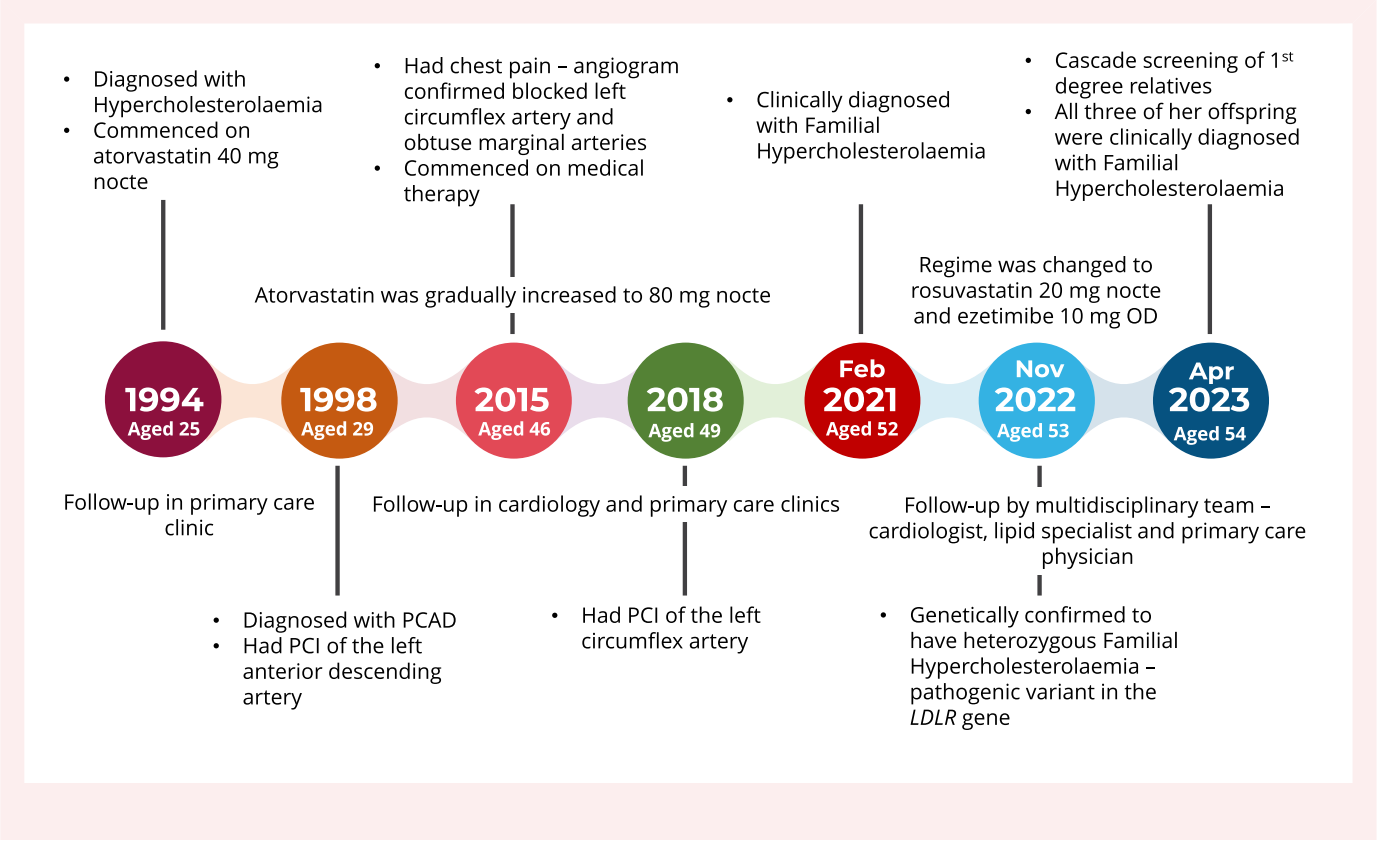
Primary care physicians and lipid specialists.

Introduction

Familial hypercholesterolaemia (FH) is an autosomal dominant genetic condition predominantly caused by low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*), or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene mutations.[1] An individual with FH has been exposed to a lifelong elevation of low-density lipoprotein cholesterol (LDL-c) since birth, leading to the development of atherosclerotic cardiovascular disease (ASCVD).[1] Heterozygous FH (HeFH) is common, with a global pooled prevalence of 1 in 303.[2]

Worldwide, FH is severely underdiagnosed and undertreated,[3,4] especially in primary care, mainly due to a lack of awareness and knowledge of this condition.[5,6] Clinically, FH can be diagnosed using the Simon Broome Criteria (SBC) or Dutch Lipid Clinic Network (DLCN) criteria based on a weighted combination of LDL-c level, the presence of premature corneal arcus (<45 years old) and/or tendon xanthomas, a personal or family history of hypercholesterolaemia, and early-onset ASCVD.[3,4] In primary care, FH can be clinically detected using the Familial Hypercholesterolemia Case Ascertainment Tool (FAMCAT), based on a risk prediction algorithm developed and validated from primary care databases.[7] These tools can identify those who may require genetic testing, especially when resources are limited.[3–5,7] In this case report, we present a Malay woman with pre-existing premature coronary artery disease (PCAD) since the age of 29, who was clinically diagnosed with FH at the age of 52 and was subsequently confirmed to have a heterozygous pathogenic mutation in the *LDLR* gene at the age of 53 years. The timeline of this case is summarized in the Summary figure.

Summary figure



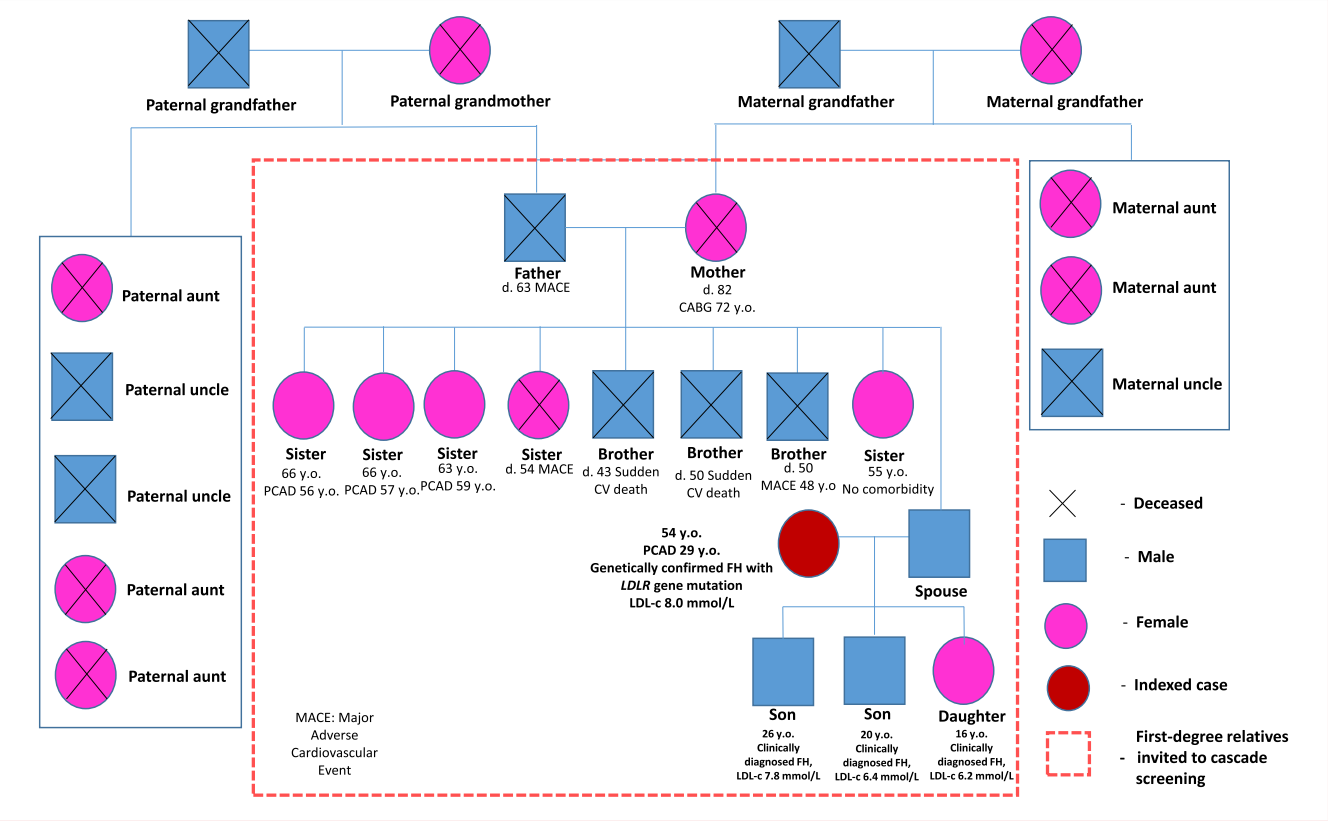


Figure 1 Family pedigree chart.

Figure 2 Grade 2 corneal arcus in both eyes.

Case presentation

This 54-year-old Malay woman, an insurance agent, was seen at a primary care clinic in February 2021 when she was 52 years old for a routine follow-up of hypercholesterolaemia. She had been on treatment for hypercholesterolaemia since the age of 25. Initially, atorvastatin 40 mg *nocte* was commenced, and the dose was gradually increased to 80 mg *nocte* at the time of presentation. There was no history of chronic kidney disease, diabetes, or hypothyroidism to suggest a secondary cause for hypercholesterolaemia. She was a non-smoker and did not drink alcohol. She had no history of hypertension or cerebrovascular disease. The Edinburgh Claudication Questionnaire was negative for peripheral vascular disease (PVD).[8] However, the WHO Rose Angina Questionnaire was positive.[9] She had retrosternal chest pain during exertion, relieved within 5 min of taking glyceryl trinitrate 0.5 mg. It occurred once or twice a month. There was no radiation, shortness of breath, or any other associated symptoms. Her resting electrocardiogram was normal.

This patient was diagnosed with PCAD in 1998 at 29 years of age when she presented to a cardiology clinic complaining of exertional angina and reduced effort tolerance. She subsequently underwent percutaneous coronary intervention (PCI) of the left anterior descending artery. After the intervention, she received follow-up care at a primary care clinic. Unfortunately, she developed another episode of chest pain in 2015 at the age of 46. An angiogram revealed an 80% blocked left circumflex artery and obtuse marginal arteries. She was initially treated with medical therapy due to financial constraints but eventually underwent another PCI in 2018 at the age of 49 years. She then continued her follow-up concurrently in the cardiology and primary care clinics.

This patient had a strong family history of hypercholesterolaemia and PCAD. Both of her parents were treated for hypercholesterolaemia. Her father passed away at 63 due to a major adverse cardiovascular event (MACE). Her mother had coronary artery bypass grafting at 72 years old. Among her eight siblings, seven were treated for hypercholesterolaemia and had either MACE or sudden cardiac death between the ages of 43 and 56 at the time of diagnosis. She has three children who are being investigated for high cholesterol. None of her family members have had genetic testing for suspected FH. Her family pedigree chart is shown in *Figure 1*.

On examination, she was obese, with a body mass index of 38.4 kg/m^2. Her blood pressure was 104/74 mmHg. Other vital signs were normal. Bilateral grade 2 corneal arcus were observed (*Figure 2*), but the patient only noticed them at 52 years old. There was no tendon xanthoma.

The SBC, DLCN score, and FAMCAT relative risk score for this patient were deduced based on the clinical history and laboratory

investigations that were extracted from her electronic medical record. The highest LDL-c level was 8.0 mmol/L, and the highest total cholesterol (TC) level was 10.7 mmol/L, recorded in October 2020. Therefore, this patient fulfilled the SBC (possible FH), DLCN (score of 8 – probable FH), and FAMCAT (relative risk score of 9.51) criteria. She was then offered and counselled for genetic testing, the gold standard for diagnosing FH.[10] Targeted next-generation sequencing of the three FH candidate genes (*LDLR*, *APOB*, and *PCSK9*) was conducted.[10] Subsequently, she was confirmed to carry a heterozygous pathogenic variant in the *LDLR* gene (rs769446356) located in intron 2 (noncoding area), in keeping with the American College of Medical Genetics and Genomics (ACMG) recommendation.[11] This patient was then counselled by the primary care physician regarding the genetic diagnosis, the need to intensify her lipid-lowering medication (LLM), and to screen her first-degree relatives. The importance of adherence to lifestyle modification and pharmacotherapy was also emphasized.

This patient received long-term follow-up care from a multidisciplinary team of primary care physician, cardiologist, and lipid specialist. Despite being on atorvastatin 80 mg *nocte*, her LDL-c level was still high at 8.0 mmol/L, and her TC level was also high at 10.7 mmol/L. The cardiology team changed the LLM regime to a combination therapy of rosuvastatin 20 mg *nocte* and ezetimibe 10 mg daily. The lower rosuvastatin dose of 20 mg was chosen instead of 40 mg to minimize the potential side effects of high-intensity statin in this patient. She responded well to the combination treatment, where her LDL-c level decreased to 5.0 mmol/L, and her TC level decreased to 7.6 mmol/L. However, she still failed to achieve the ≥50% reduction in LDL-c or the target LDL-c of <1.8 mmol/L as recommended by the international guidelines.[12,13] Her LLM will be further intensified by the lipid specialist in the subsequent follow-ups to achieve the recommended LDL-c target of <1.8 mmol/L by maximizing rosuvastatin from 20 to 40 mg *nocte* before adding an injectable LLM, such as the PCSK9 inhibitors. The possibility that lipoprotein apheresis may be needed in the future was also discussed with the patient if there is an inadequate response to the maximum tolerated dose of LLM.[13,14] The cost of treatment with PCSK9 inhibitors and lipoprotein apheresis was also discussed, as these treatments are not currently reimbursed by the government health financing system in Malaysia.

The primary care physician conducted a cascade screening of her first-degree relatives. All three of her children were found to have elevated LDL-c levels and were clinically diagnosed with FH. They were started on statin monotherapy by the primary care physician and were referred to the lipid specialist for further management and intensification of LLM.[13] The cardiology team was informed of the FH diagnosis in these children. *Table 1* summarizes the important key features of this case, and *Table 2* summarizes the clinical histories of her three children.

Discussion

Familial hypercholesterolaemia is rarely detected in primary care due to suboptimal awareness and knowledge among primary care physicians[5,6]; therefore, it is often underdiagnosed and undertreated.[3,15] In this case, the patient was clinically diagnosed in primary care and was subsequently confirmed to have a heterozygous *LDLR* pathogenic variant. *LDLR* gene mutations were responsible for 85–90% of genetically confirmed FH in the Asian population, followed by *APOB* and *PCSK9*.[4] Lifelong exposure to elevated LDL-c predisposed this patient to PCAD, as she was diagnosed at the age of 29 years old and subsequently had PCI. Unfortunately, FH was not identified at that stage, and her LLM was not intensified to achieve the recommended treatment target,[12,13] leading to the second PCI at the age of 49 years old. Despite having a very strong family history of PCAD, FH was not diagnosed earlier, and cascade screening of family members was not conducted, resulting in a missed opportunity to prevent premature ASCVD.[3] When left untreated, affected men have a 30% chance of a fatal or nonfatal cardiac event by the age of 50, while affected women have a 50% chance of this event by the age of 60.[1]

Early diagnosis and intensive treatment significantly improve the prognosis of individuals with FH.[3,16] The established clinical criteria, such as SBC and DLCN, and the FAMCAT primary care screening tool can be used as a first step to identify those who may require genetic testing, especially when resources are limited.[3,16,17] In contrast to developed nations like the UK, genetic testing is not frequently available or covered by Malaysia's health financing system.[17] Clinically diagnosed individuals with or without a molecular diagnosis should be treated following the guidelines' recommendations.[12,13]

This patient was on a combination treatment of rosuvastatin and ezetimibe. Her LDL-c decreased by 37.5% from the highest recorded reading of 8.0–5.0 mmol/L. The initial goal is to achieve at least a 50% reduction in LDL-c, followed by further reductions to achieve the recommended target of <1.8 mmol/L.[12,13] The LLM combinations should be increased to the maximum tolerated dose, e.g. rosuvastatin 40 mg and ezetimibe 10 mg, as the majority of HeFH patients can achieve the guideline-recommended LDL-c target with these combinations.[13] If the target is still not achieved, novel non-statin therapies such as inclisiran injection (a PCSK9-interfering mRNA) or bempedoic acid (an adenosine triphosphate-citrate lyase inhibitor) can be considered.[12,13] Lipoprotein apheresis, lomitapide, and evinacumab are indicated for patients with homozygous FH and those with a severe form of HeFH.[12,13] However, it is worth noting that bempedoic acid is currently unavailable in Malaysia, and the government health financing system does not currently reimburse other new treatments such as PCSK9 inhibitors and lipoprotein apheresis. Patients have to pay out of pocket for these treatments, and many private health insurance companies charge exorbitant fees to cover such treatments. Failure to achieve the recommended LDL-c target has been widely reported due to undertreatment of FH,[3,15] which may be attributable to drug costs and availability issues.

Once an index case is identified, cascade screening of close relatives should be performed using a combined phenotypic and genotypic strategy to identify affected individuals.[18] In this case, all three of her children were found to have elevated LDL-c levels and were clinically diagnosed with FH, including her 16-year-old daughter. However, genetic testing could not be conducted due to financial constraints. They were referred to the lipid specialist for further management and intensification of the LLM. In her daughter's case, pre-pregnancy counselling should be conducted if she decides to have children in the future. Fertile women with FH require risk reduction, with particular emphasis on safe therapy during pre-conception, pregnancy, childbirth, and lactation.[19] Once conception occurs, early referral to the obstetrician is required for close monitoring to ensure a successful pregnancy outcome.[19]

This patient and her three children receive multidisciplinary management and long-term follow-up care from a primary care physician, lipid specialist, and cardiologist. All three of her children were started on statin monotherapy by the primary care physician because ezetimibe is unavailable in government primary care clinics. They were referred to the lipid specialist for intensification of the LLM, which includes a combination of high-dose potent statins with either ezetimibe or PCSK9 inhibitors.[12,13] Current evidence showed that a combination of high-dose potent statin with ezetimibe outperformed statin monotherapy in reducing the LDL-c, and patients were more likely to achieve their LDL-c target.[13] Therefore, ezetimibe should be made available in the government primary care clinics so as not to delay the intensification of LLM using combination therapy in patients with high ASCVD risk.

This case highlights a delay in FH diagnosis in patients with preexisting PCAD, which may be due to the lack of awareness and knowledge of this condition among doctors. Molecular diagnosis was also delayed as genetic testing is not routinely available or covered by Malaysia's national health financing system. The intensification of LLM

Table 1 Clinical summary of the indexed case

Details			
Age (year)		54 (born in April 1969)	
Gender		Female	
Personal history			
Premature coronary artery disease		Yes CAD Had PCI at the age of 29 and 49 years old	
ROSE Angina Questionnaire		Positive	
Premature cerebrovascular disease		No	
Edinburgh Claudication Questionnaire		Negative	
Chronic kidney disease		No	
Diabetes		No	
Hypothyroidism		No	
Family history			
Premature coronary artery disease (male <55 years; female <60 years)		Yes Seven out of eight siblings had either an adverse cardiovascular event or sudden cardiac death at the age of 43–56 years old	
Premature cerebrovascular or peripheral vascular disease (male <55 years; female <60 years)		No	
Hypercholesterolaemia		Yes Both parents and seven out of eight siblings	
First-degree relatives with corneal arcus		No	
First-degree relatives with tendon xanthoma		No	
Physical examinations			
Blood pressure (mmHg)		104/74	
Body mass index (kg/m^2)		38.4	
Waist circumference (cm)		115	
Xanthomas		No	
Premature corneal arcus (<45 years old)		No The patient noticed at the age of 52 years old	
Fasting serum lipid	Normal range	14 October 2020—the highest TC and LDL-c ever recorded	14 November 2022
TC (mmol/L)	<5.2	10.7	7.6
LDL-c (mmol/L)	<1.8	8.0	5.0
HDL-c (mmol/L)	>1.0	1.8	1.7
TG (mmol/L)	<1.7	1.9	1.8
Lipid-lowering medications		Atorvastatin 80 mg *nocte*	Rosuvastatin 20 mg *nocte*, ezetimibe 10 mg once daily
Other medications		Valsartan 40 mg once daily Acetylsalicylic acid 100 mg + glycine 45 mg once daily Bisoprolol 7.5 mg once daily Isosorbide mononitrate 90 mg once daily Glyceryl trinitrate 0.5 mg as needed	
Clinical diagnostic criteria			
SB Criteria		Possible FH	
DLCN score		8 (probable FH)	
FAMCAT relative risk score		9.51	
Mutation			
Gene		*LDLR* (NM_000527.4)	
Intron		2	
Nucleotide change		c.190+4A>T	
Chromosome position		chr19:11211025 (GRCh37)	

Continued

Table 1 *Continued*

Details	
dbSNP ID	rs769446356
Type of mutation	Intronic (non-coding area)
Pathogenicity of variants based on the ACMG guidelines[8]	Likely pathogenic Global MAF: 0.00001773 (gnomAD v2.1.1) East Asia MAF: 0.0002005 (gnomAD v2.1.1)

PCAD, premature coronary artery disease; PCI, percutaneous coronary intervention; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; SB, Simon Broome; DLCN, Dutch Lipid Clinic Network; FAMCAT, Familial Hypercholesterolemia Case Ascertainment Tool; ACMG, American College of Medical Genetics and Genomics.

Table 2 Clinical summary for the three offspring of the indexed case

Details		Offspring 1	Offspring 2	Offspring 3
Age (year)		26 (born in March 1996)	20 (born in April 2002)	16 (born in December 2006)
Gender		Male	Male	Female
Personal history				
Premature coronary artery disease		No	No	No
ROSE Angina Questionnaire		Negative	Negative	Negative
Premature cerebrovascular disease		No	No	No
Edinburgh Claudication Questionnaire		Negative	Negative	Negative
Chronic kidney disease		No	No	No
Diabetes		No	No	No
Hypothyroidism		No	No	No
Family history				
Premature coronary artery disease (male <55 years; female <60 years)		Mother had PCAD PCI at the age of 29 and 49 years old		
Premature cerebrovascular or peripheral vascular disease (male <55 years; female <60 years)		No		
Hypercholesterolaemia		Yes Mother is genetically confirmed to have HeFH—*LDLR* gene mutation		
First-degree relatives with corneal arcus		Yes Mother noticed at the age of 52 years old		
First-degree relatives with tendon xanthoma		No		
Physical examinations				
Blood pressure (mmHg)		138/74	109/70	112/58
Body mass index (kg/m^2)		31.4	20.5	21.6
Waist circumference (cm)		89	77	67
Xanthomas		No	No	No
Premature corneal arcus (<45 years old)		No	No	No
Fasting serum lipid	Normal range	7 April 2023	17 April 2023	7 April 2023
TC (mmol/L)	<5.2	10.1	8.5	8.5
LDL-c (mmol/L)	<1.8	7.8	6.4	6.2
HDL-c (mmol/L)	>1.0	1.6	1.6	1.7
TG (mmol/L)	<1.7	1.5	1.1	0.9
Lipid-lowering medications		Atorvastatin 20 mg *nocte*	Atorvastatin 20 mg *nocte*	Atorvastatin 20 mg *nocte*
Other medications		Nil	Nil	Nil
Clinical diagnostic criteria				
SB Criteria		Possible FH	Possible FH	Possible FH
DLCN score		8 (probable FH)	6 (probable FH)	6 (probable FH)

PCAD, premature coronary artery disease; PCI, percutaneous coronary intervention; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; SB, Simon Broome; DLCN, Dutch Lipid Clinic Network.

using combination therapy was also delayed due to the issues of limited drug availability in primary care. Although this patient and her children are currently receiving multidisciplinary management by a primary care physician, lipid specialist, and cardiologist, communication between the multidisciplinary teams can be further improved. In conclusion, an urgent call for action to improve FH detection and management in Malaysia is highly needed. This aligns with the global call to action to reduce the clinical and public health burden of FH by adopting public policy recommendations, including awareness, advocacy, screening, testing, diagnosis, treatment, family-based care, registries, research, cost, and value.[20] This multisectoral approach is pivotal to prevent premature ASCVD in this extremely high-risk population.[20]

Lead author biography

Professor Dr Anis Safura Ramli is a Consultant Family Physician and Deputy Dean for Research & Innovation at the Faculty of Medicine, Universiti Teknologi MARA (UiTM), Malaysia. Her research niche area is in CVD prevention and cardiometabolic risk factor management. She has published numerous scientific research papers in international high-impact journals and has vast experience in leading research team as a principal investigator of national and international grants. She has won several research and innovation awards at the national and international levels, including Best Researcher Award at AAU 2020 and Gold Medal Award at ITEX 2021 for the EMPOWER-SUSTAIN Mobile App for patients with CVD risk factors.

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Consent: This patient participated in a study titled 'Reducing Premature Coronary Artery Disease by Early Identification of Familial Hypercholesterolaemia'. Written informed consent was obtained from this patient upon recruitment into the study. The authors also confirmed that written informed consent for submission and publication of this case report, including images and associated text, has been obtained from the patient in line with the COPE guidance.

Conflict of interest: None declared.

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Data availability

Data are kept at the Department of Primary Care Medicine, Universiti Teknologi MARA, Selangor, Malaysia. Anonymous data will be shared upon request, and it is subjected to the data protection regulations.

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