

REVIEW

Heterozygous familial hypercholesterolemia: an underrecognized cause of early cardiovascular disease

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ABSTRACT

Heterozygous familial hypercholesterolemia (HeFH) is a monogenic disorder that affects about 1 in 500 people, with a higher prevalence in certain subpopulations such as people of Quebecois, Christian Lebanese and Dutch South Afrikaner extraction. HeFH is characterized by cholesterol deposits affecting the corneas, eyelids and extensor tendons; elevated plasma concentrations of low-density lipoprotein (LDL) cholesterol; and accelerated vascular disease, especially coronary artery disease (CAD). Although HeFH is genetically heterogeneous, it is most often caused by heterozygous mutations in the *LDLR* gene encoding the LDL receptor. We describe a man who was diagnosed with HeFH after he had a myocardial infarction at 33 years of age. By DNA sequence analysis, he was found to have a heterozygous splicing mutation in his *LDLR* gene. This discovery expanded the growing mutational spectrum in patients with HeFH in Ontario.

Given that HeFH is a treatable cause of early vascular disease, it is important that this condition be recognized, diagnosed and treated in affected patients; but as yet, there is no consensus on the best approach. Diagnostic criteria based on family history and clinical presentation have been proposed for patients with suspected HeFH. Biochemical or molecular screening might be considered to detect new cases of HeFH in populations with a relatively high HeFH prevalence and a relatively small number of possible causative mutations. So far, however, the most cost-effective and efficient systematic strategy to detect previously undiagnosed cases of HeFH is still cascade testing: clinical and biochemical screening of close relatives of the proband patient diagnosed with HeFH. Pharmacologic treatment of HeFH is cost-effective.

CMAJ 2006;174(8):1124-9

Heterozygous familial hypercholesterolemia (HeFH) is an autosomal dominant disease characterized by markedly elevated plasma concentrations of low-density lipoprotein (LDL) cholesterol (LDL-C), typically well above the 95th percentile for age and sex.¹ Because HeFH is not only relatively common and associated with a high risk of early coronary artery disease (CAD) but is easily treatable with LDL-C-lowering strategies, this genetic disorder meets the World Health Organization (WHO) criteria for systematic screening.² WHO has estimated that HeFH is properly diag-

nosed in only about 15% of affected Canadians.² As many as 30% of patients do not survive their first myocardial infarction (MI); early detection of HeFH therefore has the potential to save many lives and prevent early morbidities related to CAD.^{3,4} To illustrate, we describe a patient whose HeFH was diagnosed subsequent to his early MI.

An illustrative case

A 34-year-old man of Irish ancestry was referred to the Lipid Genetics Clinic of the London Health Sciences Centre for dyslipidemia management. He had been in good general health until the age of 29 years, when routine blood tests returned a plasma total cholesterol (TC) result of 10 mmol/L and an LDL-C concentration of 8 mmol/L. The patient could not recall receiving specific medical advice at that time. His family history included premature CAD: his father and 2 paternal uncles each had elevated plasma levels of LDL-C and died of MI before 50 years of age.

At age 33, the patient experienced an acute MI. Angiography showed widespread CAD that required the placement of 3 stents. Daily oral drug therapy was initiated for secondary CAD prevention: atorvastatin (80 mg), ezetimibe (10 mg), ramipril (5 mg), clopidogrel (75 mg), bisoprolol (5 mg) and ASA (81 mg). At 6 months after his MI, his serum TC and LDL-C concentrations were 5.36 and 3.76 mmol/L, respectively; at 9 months after, 4.23 and 2.90 mmol/L. Rosuvastatin (40 mg) was substituted for atorvastatin at 9 months. At 12 months post-MI (i.e., 3 months later), his TC and LDL-C concentrations were 4.05 and 2.50 mmol/L, respectively; at 15 months, 4.28 and 2.46 mmol/L.

On examination, his weight was 110 kg, height 192 cm, body mass index 30 kg/m² and blood pressure 120/80 mm Hg. He had bilateral corneal arcus and bilateral xanthomas of his Achilles tendons and the extensor tendons of his hands (Fig. 1). These physical findings, together with his medical history of high plasma LDL-C concentrations and family history of premature CAD, led to a clinical diagnosis of HeFH. Sequence analysis of genomic DNA from leukocytes taken from the patient's peripheral blood revealed a splicing mutation at the splice donor site in intron 14 of the *LDLR* gene encoding the LDL receptor. This same mutation was previously reported in Utah among people of European descent with HeFH.⁵ The mutation alters the splicing of mRNA⁵ and produces a severely truncated LDL-receptor protein. The patient was a sim-

ple heterozygote; that no other mutations were found provided molecular confirmation of the clinical diagnosis of HeFH. The mutation expanded the spectrum of *LDLR* mutations that have been found among Ontarians with HeFH (see the online Appendix 1, available at www.cmaj.ca/cgi/content/full/174/8/1124/DC1).

Epidemiology

HeFH affects about 1 in 500 people, with higher rates because of genetic founder effects (i.e., the introduction of mutations by a few “pioneers” or population founders) among people of Quebecois, Christian Lebanese and Dutch South Afrikaner extraction.⁶ If undiagnosed and untreated, the cumulative risk of CAD by age 60 years is more than 60% among men and more than 30% among women with HeFH.⁷⁻⁹ Among people with HeFH in Quebec, CAD onset is generally at around 40 years of age in men and about 50 years in women.¹⁰ According to WHO, only some 15% of Canadian residents with HeFH have had it diagnosed.² About 10% of cardiologists and general practitioners screen their patients for HeFH.^{2,11} Because death immediately after MI is so frequent and because the medical management of HeFH is easy, the desirability of safe, effective and early diagnosis and institution of preventive treatments seem obvious. Less obvious is the most cost-effective approach to identify Canada’s estimated 60 000–80 000 people with HeFH.

Genetics

Familial clustering of tendon xanthomas, high serum cholesterol and early MIs was first noted by Müller in 1939.¹² Later, in a series of brilliant experiments that culminated in the 1985 Nobel Prize in Medicine and Physiology, Brown and Goldstein¹ discovered the LDL receptor, a cell-surface glycoprotein that binds the apolipoprotein (apo) B moiety on the LDL particle as part of the process of receptor-mediated endocytosis. HeFH patients were found to have one copy of a mutated *LDLR* gene, which normally is located on chromosome 19p13 and comprises 18 exons.¹ The catabolic defect in HeFH patients results in a doubling of plasma LDL-C concentration. Extremely rare patients — about 1 in a million people — have homozygous familial hypercholesterolemia (HoFH) because of mutations in both copies of their *LDLR* gene, with plasma LDL-C concentrations increased up to 10-fold and eye, skin, tendon and vascular atherosclerotic disease in childhood.¹

Genetic studies over the past 20 years have shown that various *LDLR* mutations

— of a total of about 800 — are found in most HeFH patients.¹³⁻¹⁶ Less commonly, the HeFH phenotype can result from a heterozygous mutation within the receptor-binding domain of *APOB* encoding apo B-100.¹⁴ Recently, 2 other genes called *ARH* and *PCSK9* were shown to cause a HoFH- and a HeFH-like phenotype, respectively,¹⁴ but these non-*LDLR* causes of familial hypercholesterolemia are very rare.

Clinical features

In patients with HeFH, the liver’s capacity to catabolize LDL-C in a regulated manner is impaired. LDL-C residence time in plasma is therefore prolonged, and the propensity of the cholesterol particles to undergo oxidation increased. The modified LDL particles are taken up by macrophages by means of an unregulated scavenger receptor, which causes cholesterol-laden foam cells to form. These can lead to clinical manifestations (Fig. 1). Cholesterol deposits within the

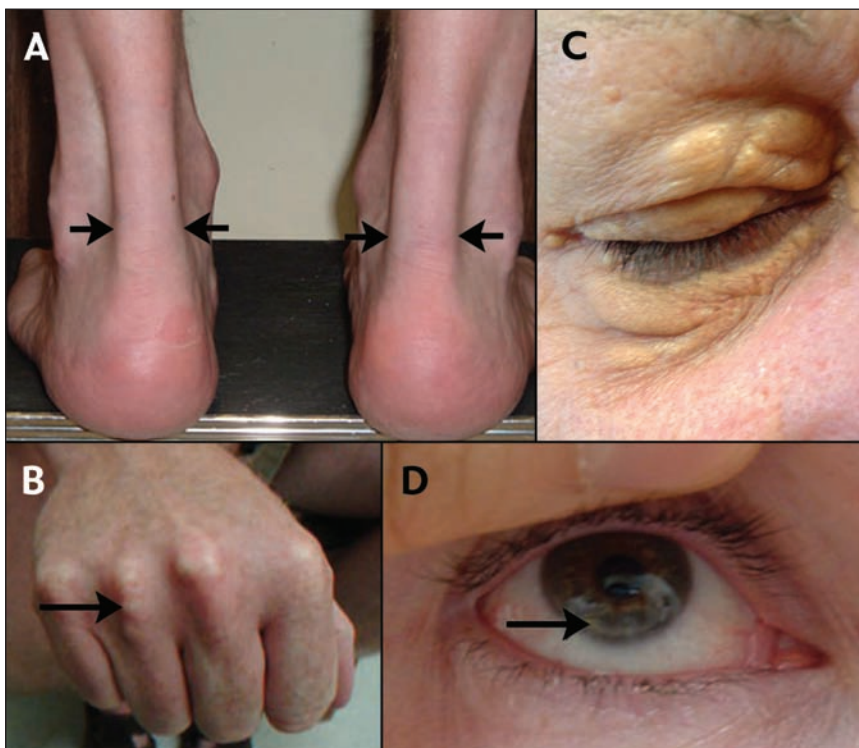


Fig. 1: Physical signs of heterozygous familial hypercholesterolemia (HeFH), which result from cholesterol deposited within macrophages in specific sites. Tendonous xanthomas, for example, manifest first as thickening of, and later as deposits within, extensor tendons. A: Lateral borders of thickened Achilles’ tendons are shown with arrows. B: Tendonous xanthomas can also occur in the extensor tendons of the hands (shown), feet, elbows and knees. C: Xanthelasma are cholesterol deposits in the eyelids. D: Arcus cornealis results from cholesterol infiltration around the corneal rim (arrow). Deposits in and around the eye tend to be more specific for HeFH in people younger than 45 years; in elderly people, they are less likely to be associated with blood lipoprotein abnormalities, for instance in the case of arcus senilis.

Some patients may report having observed cutaneous cholesterol deposition in response to a functional enquiry. People with HeFH have been known to undergo cosmetic eyelid surgery to remove xanthelasma — even repeatedly, for lesions that continued to recur — without ever having had their plasma lipoprotein profiles determined.

Box 1: Dutch Lipid Network clinical criteria for diagnosis of heterozygous familial hypercholesterolemia (HeFH)

Criteria	Points
1. Family history: a first-degree relative (a parent, offspring or sibling of the patient) with known	
a) Premature* coronary and vascular disease	1
b) Plasma LDL-C concentration > 95th percentile for age and sex	
i) In an adult relative	1
ii) In a relative < 18 years of age	2
c) Tendon xanthomata or arcus cornealis	2
2. Clinical history: patient has premature*	
a) Coronary artery disease	2
b) Cerebral or peripheral vascular disease	1
3. Physical examination of the patient	
a) Tendon xanthomata	6
b) Arcus cornealis in a patient < 45 years of age	4
4. LDL-C levels in patient's blood, mmol/L	
a) ≥ 8.5	8
b) 6.5-8.4	5
c) 5.0-6.4	3
d) 4.0-4.9	1
5. DNA analysis showing a functional mutation in the <i>LDLR</i> or other HeFH-related gene	8

Diagnosis	Total points
Definite HeFH	> 8
Probable HeFH	6-8
Possible HeFH	3-5

Note: LDL-C = low-density lipoprotein cholesterol.
*If a male relative, < 55 years of age; if a female relative, < 60 years.

Box 2: Simon Broome Register criteria for diagnosis of heterozygous familial hypercholesterolemia (HeFH)

Criteria
A A plasma cholesterol measurement of either: <ul style="list-style-type: none"> • Total cholesterol > 7.5 mmol/L (adult patient) or > 6.7 mmol/L (child aged < 16 yr) • Low-density lipoprotein > 4.9 mmol/L (adult patient) or > 4.0 mmol/L (child aged < 16 yr)
B Tendon xanthomas in the patient or any of the patient's first- or second-degree relatives*
C DNA-based evidence in the patient of mutation in <i>LDLR</i> or any other HeFH-related gene
D Family history of myocardial infarction before the age of <ul style="list-style-type: none"> • 50 yr, in any first- or second-degree relative* • 60 yr, in any first-degree relative*
E Family history of plasma total cholesterol measurements > 7.5 mmol/L in any first- or second-degree relative*

Diagnosis	Criteria required
Definite HeFH	A + B or C
Probable HeFH	A + D or A + E

*First-degree relation = parent, offspring or sibling; second-degree relation = grandparent, grandchild, nephew, niece or half-sibling.

Diagnosis

In the context of primary CAD prevention, HeFH should be suspected by an incidental discovery of elevated plasma concentrations of TC or LDL-C; a family history of premature onset of symptomatic CAD (i.e., in a first-degree male relative under the age of 55 or a first-degree female relative under the age of 60 years) or even very high test results for TC or LDL-C; and suggestive physical findings (Fig. 1). For secondary CAD prevention, patients in whom atherosclerotic disease developed at a young age should be carefully evaluated for HeFH.

The clinical diagnosis of HeFH typically requires a combination of evidence from family history, clinical history, physical signs and biochemical markers (Box 1, Box 2). Diagnostic guidelines for HeFH diagnosis in patients who either are¹⁸ or are not¹⁹ part of a family with known HeFH members are shown in Box 1, Box 2 and Table 1. Because of Mendel's laws, a plasma LDL-C level above a critical threshold becomes a highly specific diagnostic marker when one family member has been diagnosed with HeFH (Table 1). The diagnostic value of newer biochemical analytes, such as apo B, is promising but not yet established.

HeFH is most effectively diagnosed when a family member is already known to have HeFH. With use of molecular diagnosis as the "gold standard," the Utah Medical Pedigrees project to Make Early Diagnoses and Prevent Early Deaths (MEDPED) for people with familial hypercholesterolemia showed that a screening test that uses plasma LDL-C limits to attain 98% specificity would detect HeFH in the general population with only 54% sensitivity.¹⁸ In contrast, the greater likelihood of a positive diagnosis with use of the same

skin of the eyelids, for instance, are called xanthelasmas; those in connective tissues within and surrounding extensor tendons, especially the Achilles and extensor tendons of the hands, are called xanthomas; and deposits along the corneal margin are called arcus cornealis or corneal arcus. The most dangerous deposits occur within arteries, where they have potential to cause premature CAD, stroke and peripheral vascular disease.¹

The medical history of the proband patient highlights the marked risk of early CAD associated with HeFH. For instance, findings from a prospective evaluation in 1980-1989 (i.e., in the pre-statin era) of 526 patients with HeFH (2234 person-years) through the Simon Broome Register essentially reflected the natural history of HeFH.¹⁷ Excess rates of death from CAD in people with HeFH were highest between the ages of 20 and 39 years (standardized mortality ratio [SMR] 9686, 95% confidence interval [CI] 3670-21 800). SMR for all causes was 183 (95% CI 117-273) and was highest between the ages of 20 and 39 years (SMR 902, 95% CI 329-1950). Thus, HeFH was associated with a markedly increased risk of death, especially among young adults.

Table 1: Low-density lipoprotein (LDL) cholesterol thresholds to diagnose heterozygous familial hypercholesterolemia (HeFH) with 98% specificity in a patient, by degree of relatedness to his or her closest relative with known HeFH

Patient's age, yr	LDL cholesterol concentration, mmol/L			Average in general population
	Degree of relatedness to patient			
	First*	Second†	Third‡	
< 18	4.0	4.3	4.4	5.2
18-29	4.4	4.6	4.8	5.7
30-39	4.9	5.2	5.4	6.2
≥ 40	5.3	5.6	5.8	6.7

*Parent, offspring or sibling.

†Grandparent, grandchild, nephew, niece or half-sibling.

‡Great-grandparent, first cousin, great-grandchild.

screening method (but with relatively low plasma LDL-C thresholds, compared with the diagnostic levels used for screening of the general population) in relatives of patients already known to have HeFH was highly effective:¹⁸ while specificity remained high at 98%, sensitivity improved to 88% for first-degree relatives, 85% for second- and 81% for third-degree relatives because of the greater likelihood of a positive diagnosis. The authors¹⁸ strongly recommended biochemical screening of relatives of patients found to have HeFH (an approach that has been called cascade testing)²⁰ over other detection strategies such as population-wide LDL-C testing.

Most often, a diagnosis of HeFH in a family member has not already been made, so standard diagnostic criteria are required. The Dutch Lipid Network (DLN)^{2,19} (Box 1) and the United Kingdom Simon Broome Register (SBR)¹⁷ (Box 2) have suggested diagnostic criteria for HeFH that use various clinical, biochemical and molecular genetic attributes. More than 80% of people with a DLN score above 8 had genetic mutations; this threshold was therefore used to specify individuals with “definite” HeFH.¹⁹ The SBR guidelines required documentation of tendon xanthomas, which are very specific for HeFH but relatively insensitive, since they are not clinically apparent in about 30% of people with HeFH and often not until the fourth decade of life.^{17,21}

Efficacy of the DLN and SBR criteria was evaluated recently in a study involving 408 Danes with HeFH.²¹ Molecular diagnosis revealed little difference in sensitivity and specificity between the DLN and SBR criteria (Table 2), which suggests that either approach would be helpful in clinical diagnosis (although each left much to be desired).

Routine molecular genetic testing to diagnose HeFH is unclear at this time. Civeira and associates²² recommended limiting genetic analysis to populations in which only a few *LDLR* mutations account for most HeFH cases; populations in which most causative mutations are known and rapid inexpensive genetic tools have been developed; and subjects with an uncertain clinical diagnosis who are members of HeFH-affected families in which the mutation is already known. Leren and colleagues²³ further suggested that with cascade testing a clinical and biochemical diagnosis might be insuffi-

cient, and that DNA testing would increase diagnostic certainty. However, this position remains controversial for many care providers, including ourselves. The potential value of genetic diagnosis of HeFH in Canada is context-dependent.

In Quebec, about 90% of patients with HeFH will have 1 of about 11 mutations (Appendix 1, www.cmaj.ca/cgi/content/full/174/8/1124/DC1), and in some areas over 80% of patients will have 1 of 5 or fewer possible mutations.^{6,24-30} Furthermore, the incidence of HeFH in Quebec is about 2.5-fold higher than in the rest of Canada because of founder effects.^{6,27} Quebec's high incidence and prevalence of HeFH and high rate of recurrence of mutation in affected people make diagnostic DNA testing a reasonable consideration. In contrast, there are very few recurrent HeFH mutations among Ontario patients (Appendix 1, www.cmaj.ca/cgi/content/full/174/8/1124/DC1). Screening of a person's entire *LDLR* gene to detect one of many possible known or unknown mutations is more costly than a dedicated screening method designed to provide a simple positive-or-negative result for a few well-characterized *LDLR* mutations. Population-based genetic findings indicate that, with current technologies, DNA-based diagnosis of HeFH cannot yet be routinely considered in Ontario patients.

Thus, in nonfounder populations, there appear to be general obstacles to the imminent use of routine diagnostic genetic testing. Perhaps fortuitously, these impediments permit us to defer the potential psychological and ethical issues that might arise from DNA analysis. Pilot studies seem to indicate that the attitudes of members of HeFH families toward genetic methods of diagnosis are generally favourable.³¹ However, even without DNA testing, potential issues arise from approaching relatives to detect HeFH by screening plasma LDL-C. For instance, clinical geneticists in Canada have traditionally relied on probands to contact at-risk relatives (i.e., family contact) and advise them of the need for screening. But since HeFH is potentially fatal and easily treatable, some European investigators have argued that it is acceptable, and

Table 2: Performance of various diagnostic criteria in the prediction of HeFH-related DNA mutations in patients

Test	Sensitivity, %	Specificity, %
Biochemical only		
Utah MEDPED (families)		
Total cholesterol	63.4	73.4
LDL cholesterol	70.3	69.8
Clinical		
Dutch Lipid Network		
Definite	41.5	87.9
Probable	66.7	64.5
Possible	99.3	5.9
Simon Broome Register		
Definite	34.1	89.4
Possible	90.4	28.6

Note: HeFH = heterozygous familial hypercholesterolemia, MEDPED = Make Early Diagnosis to Prevent Early Deaths (Medical Pedigree project), LDL = low-density lipoprotein.

more efficient, for a health care worker to contact relatives on behalf of the consenting proband (direct contact). HeFH family-contact programs in Norway³¹ and direct-contact programs in Holland³² show no apparent differences in the reactions of contacted relatives. In general, relatives believed strongly that the contact had been beneficial.

Treatment

Once a diagnosis of HeFH has been made, treatment is relatively straightforward. Experience has shown that even when very elevated plasma TC concentrations are detected in a young adult (as in this report's proband), specific treatments or follow-up are not always advised. However, current treatment guidelines such as those from the Canadian Hypercholesterolemia Working Group³³ recommend target LDL-C levels under 2.5 mmol/L for primary CAD prevention in patients at high risk, such as those with HeFH.

CAD prevention in HeFH requires a global risk-reduction program that focuses on modifiable risk factors, including weight control, prudent diet, moderate exercise, smoking cessation and appropriate control of diabetes and hypertension.³³ The dietary protocol in HeFH minimizes cholesterol intake and replaces saturated fats with unsaturated fats.³⁴ Consumption of plant sterols and stanols can also reduce plasma LDL-C levels by about 10%.^{35,36}

Pharmacotherapy is frequently required in HeFH patients because the plasma LDL-C targets usually cannot be reached with diet and lifestyle changes alone.³⁷ Statins — also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors — have become the agents of first choice. They block the rate-limiting step of cholesterol synthesis in the liver, depleting liver cholesterol content and upregulating the expression of cell-surface LDL receptor, which results in increased removal of LDL from plasma.¹ Subjects with HeFH have 1 normal *LDLR* allele to upregulate. Plasma LDL-C reductions of up to 50% can be achieved with higher-dose statin monotherapy,^{38–44} although higher doses may be associated with an increased risk of adverse events.

Because of their high baseline levels of plasma LDL-C, patients with HeFH generally require more than 1 medication to reach targets. Ezetimibe, a cholesterol absorption inhibitor that appears well tolerated, is now increasingly used in combination with statins in people who require large absolute and relative reductions in plasma LDL-C levels, such as those with HeFH. When used in combination with a statin, a further decrease in plasma LDL-C concentration of up to 25% has been seen with ezetimibe.⁴⁵ Other agents such as bile-acid sequestrants and niacin preparations have also been used as part of combination therapy regimens to reduce plasma LDL-C in patients with HeFH.^{46,47}

A common clinical concern is the approach to primary CAD prevention when HeFH has been diagnosed in children or adolescents. Dietary and lifestyle advice form the therapeutic foundation. Drug treatment of pediatric HeFH is an evolving field. Bile-acid sequestrants have the advantage of not being systemically absorbed, but they are poorly tolerated. Tolerability is also an issue with short-acting niacin preparations. Ezetimibe has

theoretical advantages, but at present is not indicated for use in children or adolescents. Statin trials involving children and adolescents so far have been short-term: 6 months for atorvastatin,⁴¹ 1 year for lovastatin³⁸ and simvastatin,³⁹ respectively, and 2 years for pravastatin.⁴² Over relatively short periods, no difference in clinically significant adverse events was apparent between the placebo and statin-treated groups. Mean decreases in LDL-C ranged from about 25% to 45%.^{38–40,42} The 2-year pravastatin study showed significant regression of intima-media thickening in the carotid arteries.⁴² In 2005, Health Canada approved atorvastatin for treatment of HeFH in boys and postmenarche girls aged 10–17 years if their LDL-C levels were 4.9 mmol/L or greater; their levels were at least 4.1 mmol/L with a family history for premature CAD; or they had 2 or more risk factors for CAD. However, the exact time to initiate treatment and the applicability of adult targets in children are uncertain. Referral for a specialist's opinion remains a very appropriate alternative for children with HeFH.

Drug treatment of HeFH is very cost-effective. For example, in primary CAD prevention, treatment with lovastatin for 10 years was shown to save both lives and money (i.e., negative cost per life-year saved) among men aged 35–44 years with HeFH but no other risk factors, and among women aged 35–44 with HeFH and at least 1 additional risk factor.⁴³ In the Netherlands, cascade testing to detect new HeFH patients who then received statin treatment prevented 26 MIs for every 100 people aged 20–60 treated for 10 years, gaining a mean of 3.3 years of life for each patient so found and treated.⁴⁴ The total lifetime cost for screening and testing, lifetime drug treatment and treatment of CAD events was about Can\$9000 per new case detected, and the cost per life-year gained was about \$11 000.⁴⁴ In England, the cost per death avoided over 10 years of use of cascade testing to detect HeFH and treat such patients with statins was around \$7000.⁴⁸

Conclusion

Had the proband we have described received a clinical diagnosis of HeFH before his MI, initiation of treatment to lower his elevated plasma LDL-C levels would likely have delayed the onset of vascular symptoms. Diagnosis of HeFH is based on clinical and biochemical criteria, with no single set of criteria clearly superior to the others. Nevertheless, the proband reported herein would have met clinical criteria for definite HeFH by either DLN¹⁹ or SBR criteria,¹⁷ even without DNA testing. Cascade testing of relatives of people known to have HeFH appears to be an effective strategy to detect new cases (the proband patient's relatives are in the process of being clinically screened). The population genetics of HeFH precludes advice favouring the routine use of DNA testing to diagnose HeFH at this time. Cost-benefit analyses have suggested that family-based ascertainment and drug treatment of HeFH represents good value for money. Most patients who are affected require combination drug treatment to lower their plasma LDL-C concentrations. Finally, although our experience with pharmacotherapy in children and adolescents with HeFH has been increasing, the risks and benefits of their use must be carefully evaluated for individual patients.

This article has been peer reviewed.

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Competing interests: None declared for George Yuan and Jian Wang. Robert Hegele has received speaker's fees from, and is an ongoing paid consultant of, AstraZeneca, Fournier, Merck Frosst, Merck Shering, Pfizer and Oryx.

Contributors: All authors contributed substantially to the case description, the acquisition and interpretation of the information reviewed, and the iterative rewriting process. All approved the final version of the manuscript.

Acknowledgements: We greatly appreciate the expert technical assistance of Ms. Brooke Miskie, Ms. Stefanie Bombardier and Mr. Matthew Ban.

This research was supported by the Jacob J. Wolfe Chair in Functional Genomics, the Edith Schulich Vinet Canada Research Chair (Tier I) in Human Genetics, a Career Investigator award from the Heart and Stroke Foundation of Ontario and operating grants from the Canadian Institutes for Health Research, the Heart and Stroke Foundation of Ontario, the Ontario Research and Development Challenge Fund (99-0507) and Genome Canada. George Yuan was supported by the University of Western Ontario Summer Research Training Program and by the Heart and Stroke Foundation of Ontario Irwin Bernick Scholarship.

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