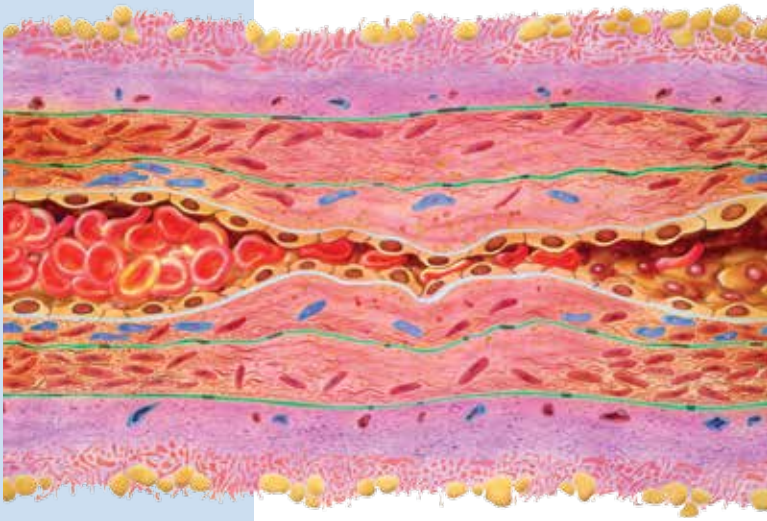
Familial hypercholesterolaemia

Detect in an individual, treat the extended family



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Testing the family members of individuals who have been diagnosed with familial hypercholesterolaemia is a fundamental aspect of care of a person with this condition, and provides an opportunity for primary prevention.

Case 1: The index case, Mr DK

Mr DK, a 34-year-old mine worker, presented to his GP for a routine medical check up. He was a smoker and weighed 116 kg (BMI 35.8 kg/m²), and his blood pressure was 138/88 mmHg. He underwent fasting blood tests, including a lipid profile. The results were as follows:

- *total cholesterol 7.8 mmol/L (laboratory reference range <5.5 mmol/L)*
- *triglycerides 2.6 mmol/L (laboratory reference range <1.7 mmol/L)*
- *HDL-cholesterol 0.8 mmol/L (laboratory reference range >1.0 mmol/L)*
- *LDL-cholesterol 5.8 mmol/L (laboratory reference range <3.5 mmol/L).*

The laboratory results were accompanied by the following interpretative comment: 'Familial hypercholesterolaemia (FH), an inherited condition associated with elevated LDL-cholesterol and premature heart disease, is possible. Recommend review family history, repeat LDL-cholesterol, exclude secondary causes and calculate the likelihood of FH (www.athero.org.au/calculator)'.

The GP phoned Mr DK and asked him back for review. On questioning of his family history, Mr DK's father had died of a heart attack aged 41 years and his paternal grandmother had had a heart attack at age 57 years and died of vascular disease aged 64 years. Mr DK was unsure if his father had elevated cholesterol levels, but knew he was a smoker and was overweight.

Secondary causes of elevated LDL-cholesterol levels, including hypothyroidism, cholestasis, nephrotic syndrome and steroid use, were excluded. The GP repeated and confirmed the lipid profile, then calculated Mr DK's likelihood of having FH using the Dutch Lipid Clinic Network criteria (DLCNC, see Table). Mr DK's DLCNC score was 4, equating to possible FH. He was subsequently advised to stop smoking, lose weight and eat a Mediterranean diet. He was referred to the local lipid disorders clinic for assessment and management advice.

Scientific background

FH is the most common autosomal dominant cause of premature atherosclerotic heart disease, and has been previously discussed in the case study section in *Cardiology Today* in November 2012 and June 2013.[1,2] Most individuals with FH remain undiagnosed, with fewer than 5% of people in Australia with FH currently diagnosed with this condition. FH was previously believed to have a prevalence of one in 500 people in the general population, with a higher prevalence in certain ethnic groups (Africans, Christian Lebanese and Québécois). However, recent evidence suggests the prevalence is approximately one in 250 people in the general population. Treatment with cholesterol-lowering therapy, predominantly statins, has led to a significant reduction in mortality and

Key points

- **Familial hypercholesterolaemia (FH) is the most common monogenic condition associated with elevated LDL-cholesterol levels and premature coronary disease.**
- **Half of the first-degree relatives of individuals with FH are also expected to have inherited this condition due to its autosomal dominant inheritance.**
- **Most individuals with FH remain undiagnosed.**
- **Cascade testing the family members of individuals with genetically confirmed FH is cost effective and detects an average of two additional patients per index case.**

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morbidity in individuals with FH. Despite this knowledge, most individuals with FH are undiagnosed and untreated, highlighting the need for increased awareness and detection of this condition.

Recent literature has confirmed that the community laboratory can play an important role in the detection of FH.[3] Community laboratories perform a large number of lipid profiles, with most requested by GPs.[3] GPs prefer interpretative comments appended to the lipid results to alert them when a patient is at risk of FH.[4] These interpretative comments have been shown to be associated with additional LDL-cholesterol reductions. A phone call between the chemical pathologist and the GP of individuals at very high risk of FH (those with an LDL-cholesterol level ≥6.5 mmol/L) led to a significant increase in referrals for specialist review. Over 70% of these people were subsequently diagnosed with FH, and 30% had an identifiable genetic mutation causative of FH.[3]

The prevalence of FH of one in 250 people in the general population also reinforces that GPs are central to the detection and management of FH, with specialist centres required to confirm the diagnosis in ambiguous cases and manage individuals with complicated FH. These centres may also perform genetic testing to confirm the diagnosis and aid family cascade screening. The autosomal dominant inheritance of FH suggests half of the first-degree family members of an individual with FH will also have inherited FH.

Table. Dutch Lipid Clinic Network Criteria for making a diagnosis of familial hypercholesterolaemia in adults

Feature	Score
Family history	
First-degree relative with known premature coronary and/or vascular disease (men aged <55 years, women aged <60 years) OR First-degree relative with known LDL-cholesterol above the 95th percentile for age and sex	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-cholesterol above the 95th percentile for age and sex	2
Clinical history	
Patient with premature coronary artery disease (men aged <55 years, women aged <60 years)	2
Patient with premature cerebral or peripheral vascular disease (ages same as above)	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
LDL-cholesterol levels (mmol/L)	
≥8.5	8
6.5–8.4	5
5.0–6.4	3
4.0–4.9	1
DNA analysis	
DNA analysis: functional mutation in the *LDLR*, *APOB* or *PCSK9* gene	8
Stratification	**Total score**
Definite FH	≥8
Probable FH	6–7
Possible FH	3–5
Unlikely FH	<3

Abbreviations: FH = familial hypercholesterolaemia; LDL = low-density lipoprotein.

Specialist review

The specialist reviewed the index case, after discussion with the GP, because Mr DK's lipid profile suggested a high risk for FH in the context of a strong family history of premature ischaemic heart disease with evidence of vertical transmission (father and paternal grandmother). Mr DK was still smoking 30 cigarettes per day and already had a 30-pack year smoking history. He was informed of the severe increase in risk of coronary artery disease associated with FH (about 50% by the age of 50 years for a man), which is further increased by smoking. His apolipoprotein B level was elevated at 1.85 g/L, but he had a normal lipoprotein (a) level (<0.3 g/L).

Using a penlight the specialist was able to detect subtle corneal arcus in Mr DK, raising the likelihood of FH to probable (his DLCNC score increased from 4 to 8). Mr DK was also very likely to have overlying hypertriglyceridaemia and a low HDL-cholesterol, which, because of his body habitus, are probably related to insulin resistance, adding to the elevation of LDL-cholesterol levels seen with classic FH. This makes differentiating FH from familial combined hyperlipidaemia more difficult. However, Mr DK's premature corneal arcus

and LDL-cholesterol level of 5.8 mmol/L and his father having had premature cardiovascular disease equates to a high likelihood of FH, although familial combined hyperlipidaemia could also be possible.

Case 1 continued

Mr DK was started on rosuvastatin, which was titrated to 40 mg per day with no muscle side effects. This led to an improvement in his lipid profile, but his LDL-cholesterol levels still remained high at 3.6 mmol/L. Ezetimibe was therefore added and his LDL-cholesterol level reduced to 2.8 mmol/L. Mr DK underwent an exercise stress test, with a negative result. He consented to genetic testing, which revealed a large deletion in the LDL receptor (LDLR) *gene. Mr DK was offered family cascade screening, during which time he mentioned that his brother Mr JK and first cousin Mr AM were also interested in being tested. Mr DK did not have any children at this stage.*

Case 2: The index case's brother, Mr JK

Mr JK, the index case's brother, was a 38-year-old plumber who had never smoked, did not exercise outside of work and consumed six to eight units of alcohol daily. He weighed 108 kg (BMI 31.8 kg/m^2) and his blood pressure reading was 128/82 mmHg. He consented to lipid and genetic testing, which demonstrated he had not inherited the deletion in the LDLR *gene. His fasting lipid profile was as follows:*

- *total cholesterol 5.6 mmol/L (<5.5 mmol/L)*
- *triglyceride 2.6 mmol/L (<1.7 mmol/L)*
- *HDL-cholesterol 0.8 mmol/L (>1.0 mmol/L)*
- *LDL-cholesterol 3.6 mmol/L (<3.5 mmol/L).*

He was advised to lose weight by improving his lifestyle and reducing his alcohol intake, and he was discharged back to his GP. Mr JK could have had his lipid profile tested before genetic testing was performed, as in this case genetic testing may not have been required. However, testing for a known family mutation is relatively inexpensive and conclusively establishes inheritance.

Case 3: The index case's cousin, Mr AM

Mr AM, the index case's cousin, was a 32-year-old miner. He attended the cascade screening clinic and was noted to be a nonsmoker, had a BMI of 21.8 kg/m^2 and had a blood pressure reading of 120/72 mmHg. He was currently training for an iron man competition and exercised for two to three hours six days per week. Genetic testing was performed, which demonstrated that he had the same large deletion in the LDLR *gene as the index case. Testing of his lipid profile revealed an elevated fasting LDL-cholesterol level, with no secondary cause. The results of his fasting lipid profile were:*

- *total cholesterol 7.6 mmol/L (<5.5 mmol/L)*
- *triglyceride 0.6 mmol/L (<1.7 mmol/L)*
- *HDL-cholesterol 1.3 mmol/L (>1.0 mmol/L)*
- *LDL-cholesterol 6.0 mmol/L (<3.5 mmol/L).*

Mr AM was offered lipid therapy, which was titrated up to 20 mg rosuvastatin and 10 mg ezetimibe. This led to a reduction in his LDL-cholesterol level to 2.8 mmol/L. He consented to cascade screening and his mother Mrs SM (the index case's aunt) also attended.

Case 4: The index case's aunt, Mrs SM

Mrs SM was a 58-year-old housewife who had a BMI of 22.5 kg/m^2 and a blood pressure reading of 126/72 mmHg. She was a nonsmoker and consumed two units of alcohol three to four nights per week. She had noted some shortness of breath walking her dog around the block (about 800 m) but had put this down to lack of fitness. Genetic testing confirmed her to carry the LDLR mutation and she had an elevated LDL-cholesterol level of 5.8 mmol/L.

She underwent a CT coronary angiogram and calcium scoring. This showed a calcium score on the 98th percentile for her age and widespread moderate-to-severe atherosclerotic calcific and noncalcific plaques, including an approximately 70% lesion in the ostium of the left anterior descending artery. A stress echocardiogram confirmed significant inducible ischaemia, and very significant atherosclerosis was confirmed on formal angiography. She underwent a 4x coronary artery bypass operation. This was successful and her breathlessness resolved.

Mrs SM later commented to her GP that she had avoided an early heart attack or worse thanks to her nephew being detected with FH – and how great it was that other family members could avoid this also.

Concluding comment

Formally testing the family members of individuals with FH is a fundamental aspect of the care of individuals with FH. Cascade testing, referring to the testing of family members of an individual with FH, has been demonstrated to be the most cost-effective way of detecting FH. Cascade testing can detect an average of two additional people with FH per index case, providing an opportunity for primary prevention in these people.[5] Cascade testing can occur using genotype, if the family mutation is known, or using measurement of LDL-cholesterol levels and clinical features (phenotype) if it is unknown. Cascade screening may be best co-ordinated by the regional lipid clinic in conjunction with the national FH registry, although in future this should be integrated into primary care. **CT**

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