Familial hypercholesterolaemia

Part 1: An unmet need in the management of a lipid disorder

Of the estimated 40,000 cases of familial hypercholesterolaemia in Australia, roughly 80% remain undetected. The underdiagnosis of this condition is a universal problem.

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Familial hypercholesterolaemia (FH) was the first genetic disease of lipid metabolism to be characterised clinically and molecularly. The marked hypercholesterolaemia leads to premature coronary heart disease (CHD). The mean age of CHD is between 40 and 45 years in men with FH and a decade later in women with FH. Most people with FH are undiagnosed or diagnosed only after their first coronary event.

The first part of this two-part article discusses the metabolic basis of FH and current methods used to diagnose the condition. Part 2, published next month, reviews treatment options and discusses potential screening approaches.

Variations in LDL-cholesterol levels

Cholesterol is a simple lipid that constitutes a structural component of cell membranes and is the precursor of steroid hormones, vitamin D, and bile acids. As shown in the box on page 41, within the liver and intestine, excess cholesterol is esterified with fatty acids to form cholesteryl esters. These are either stored as lipid droplets or assembled and secreted with other lipids and apolipoproteins to produce very low density lipoprotein (VLDL) and chylomicrons (CM). Lipids are transported through the circulation in the form of lipoproteins from their sites of absorption or synthesis to the peripheral tissues.

In the circulation, VLDL is converted to low-density lipoprotein (LDL), the main carrier of cholesterol in the blood. About 70% of LDL is removed from the blood by LDL-receptor-mediated uptake in the liver.

CHD risk is directly related to plasma total cholesterol and LDL-cholesterol concentrations

IN SUMMARY

- **Familial hypercholesterolaemia (FH) is an autosomal co-dominant disorder of lipoprotein metabolism caused by mutations in the low density lipoprotein receptor gene. It leads to premature coronary heart disease (CHD).**
- **Most people with FH are undiagnosed or diagnosed only after their first coronary event.**
- **Primary clinical diagnostic criteria for FH are hypercholesterolaemia, presence of tendon xanthomas in the patient or first degree relative, and dominant pattern of inheritance of premature CHD or hypercholesterolaemia.**
- **Patients with FH should be reviewed six monthly, and the physician should search actively for symptoms of cardiovascular disease.**
- **In patients with FH, additional atherogenic risk factors of environmental, metabolic and genetic origin can modulate the clinical severity of the condition.**

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Overview of LDL metabolism

Dietary lipids are packaged with apolipoproteins in the enterocytes of the small intestine and secreted into the lymphatic system as chylomicrons (CM). In the circulation, the core triglyceride from CM particles are hydrolysed by lipoprotein lipase (LPL), forming CM-remnants (CM-R) that are cleared by the liver.

In the liver, dietary-derived cholesterol has several fates. It can be:

- stored as cholesteryl esters
- assembled into very-low density lipoprotein (VLDL) particles and secreted into the circulation
- secreted into the bile, either directly or after conversion into bile acids.

VLDL particles secreted into plasma are hydrolysed by LPL to form intermediate density lipoprotein (IDL). The liver removes about 50% of IDL by the low density lipoprotein (LDL)-receptor, whereas the balance is converted into LDL. About 70% of circulating LDL particles are also cleared by hepatic LDL-receptors.

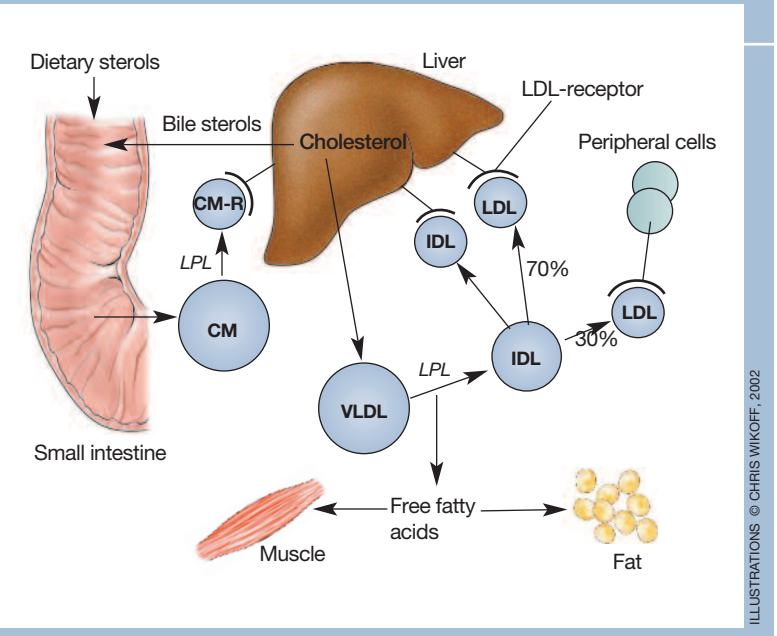

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Figure 1. LDL metabolism. (For simplicity, several enzymes, proteins and receptors have been omitted from this illustration.)

and inversely related to high density lipoprotein (HDL)-cholesterol levels. About a half of the inter-individual variation in plasma LDL-cholesterol concentrations is due to genetic variation, the major portion being polygenic in nature. However, some subjects with very high plasma LDL-cholesterol levels have monogenic forms of hypercholesterolaemia, associated with increased risk of CHD. FH is the most common and severe form of monogenic hypercholesterolaemia.

Metabolic basis of FH

FH is an autosomal co-dominant inherited disorder of lipoprotein metabolism caused by mutations in the LDL-receptor (*LDLR*) gene. The typical inheritance observed in heterozygous FH is shown in Figure 2.

Mutations in the *LDLR* locus number in excess of 800 and result in reduced plasma LDL-cholesterol clearance. In heterozygous FH, only 50% of the LDL-receptors are functional, which increases plasma total cholesterol to between 7.5 and 16 mmol/L. In homozygous FH, which is extremely rare, none of the LDL-receptors are functional.

Recently, gene loci have been identified as being responsible for other monogenic disorders of hypercholesterolaemia with phenotypes similar to FH, such as:

- familial ligand-defective apoB-100
- familial hypercholesterolaemia 3 (FH3)

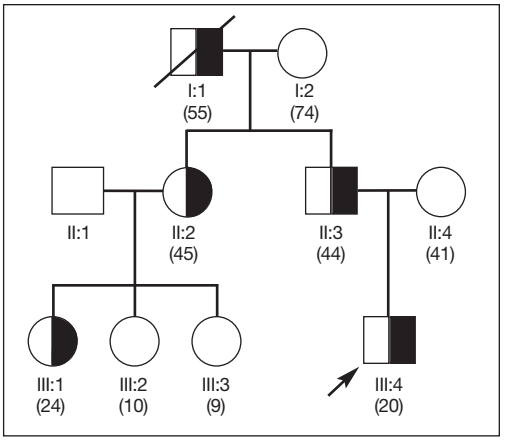

Figure 2. Pedigree of a family showing the typical inheritance observed in heterozygous FH. The arrow indicates the proband; shaded symbols are subjects with heterozygous FH; ages in years are given in brackets.

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- autosomal recessive hypercholesterolaemia
- β-sitosterolaemia.

Familial ligand-defective apoB-100 is caused by several mutations in the apolipoprotein B (*APOB*) gene, and, like FH, leads to an accumulation of LDL particles in the circulation. The most common mutation affects about one in 500 to 1000 people of European descent, but it is less common in other populations. Compared with heterozygous FH, the hypercholesterolaemia in familial ligand-defective apoB-100 is milder, the presence of tendon xanthomas less common and there is a lower incidence of CHD.

Table 1. FH diagnosis: USA MEDPED criteria*

Age (years)	Total cholesterol (LDL-cholesterol) mmol/L		
	First-degree relative	Second-degree relative	General population
<20	5.7 (4.0)	5.9 (4.2)	7.0 5.2)
20-29	6.2 (4.4)	6.5 (4.7)	7.5 (5.7)
30-39	7.0 (4.9)	7.2 (5.2)	8.8 (6.2)
≥40	7.5 (5.3)	7.8 (5.5)	9.3 (6.7)

*Cut points (in mmol/L) are expected to diagnose FH with 98% specificity. MEDPED = Make Early Diagnosis, Prevent Early Deaths program.

Table 2. FH diagnosis: Dutch Lipid Clinic Network criteria

	Score
Family history	
• First-degree relative with premature (men <55 years; women <60 years) coronary or vascular disease	1
• First-degree relative with LDL-cholesterol >95th percentile, and/or	1
– First-degree relative with tendon xanthomas and/or corneal arcus	2
– Children <18 years with LDL-cholesterol >95th percentile	2
Clinical history	
• Coronary heart disease	2
• Premature peripheral or cerebrovascular disease	1
Physical examination	
• Tendon xanthomas	6
• Corneal arcus <45 years of age	4
Blood analysis (normal HDL-cholesterol and triglyceride levels)	
• LDL-cholesterol ≥8.5 mmol/L	8
• LDL-cholesterol 6.5-8.4 mmol/L	5
• LDL-cholesterol 5.0-6.4 mmol/L	3
• LDL-cholesterol 4.0-4.9 mmol/L	1
DNA analysis	
• Functional mutation in LDL-receptor present (or familial ligand-defective apoB-100)	8

Diagnostic total score: certain >8; probable 6 to 8; and possible 3 to 5.

Prevalence and shortfall in diagnosis

FH affects roughly one in 500 people in most populations. There are estimated to be 10 million subjects with FH worldwide, and about 40,000 in Australia. The prevalence is higher in founder populations such as the Afrikaners (prevalence of 1:70), Christian Lebanese (1:170) and Québécois (1:200). To draw an important parallel, patients with heterozygous FH occur almost as commonly in our community as do those with type 1 diabetes mellitus or HIV infection.

The underdiagnosis of FH is a universal problem. Conservatively, we estimate that in Australia at least 80% of cases of FH remain undetected, representing a major unmet need of our health care system.

Diagnosis

The diagnosis of FH is currently based on clinical, biochemical and genetic criteria rather than on the identification of disease-causing mutations. Several groups have developed criteria for the diagnosis of FH, as shown in Tables 1, 2 and 3.

Clinical diagnosis

The primary clinical diagnostic criteria for FH are:

- hypercholesterolaemia
- tendon xanthomas in the patient or a first-degree relative
- dominant pattern of inheritance of premature CHD or hypercholesterolaemia (because of the known later expression of CHD in women with FH compared with men, a family history of premature CHD may not be demonstrable when a patient's mother is affected).

The hallmark physical finding in adult patients is the presence of tendon xanthomas, characteristically seen in the extensor tendons of the hands and the Achilles tendons (Figures 3a and b). Less common are xanthomas in the olecranon

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process and the tibial tuberosity. Corneal arcus and palpebral xanthomas may also be seen, but are less specific features of FH (Figures 3c and d).

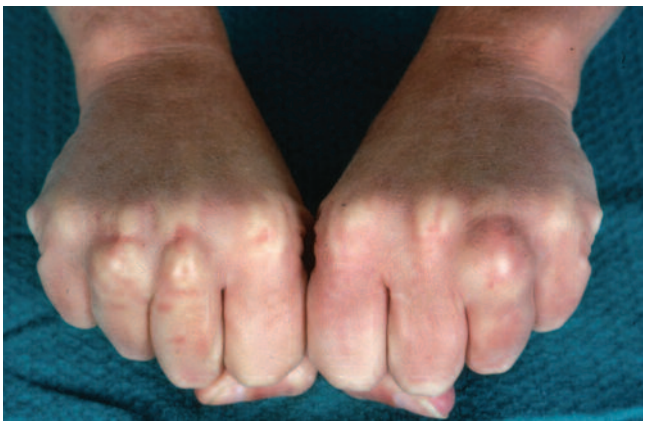
Patients with persistent and severe hypercholesterolaemia may also exhibit carotid and aortic bruits consistent with extracardiac atherosclerosis, as well as a midsystolic murmur consistent with aortic sclerosis.

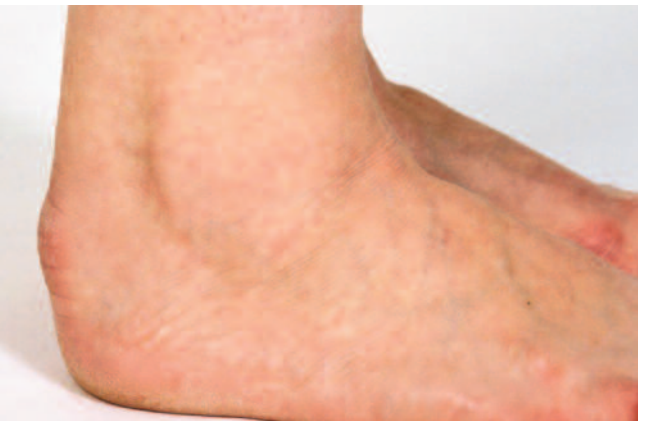
Biochemical diagnosis

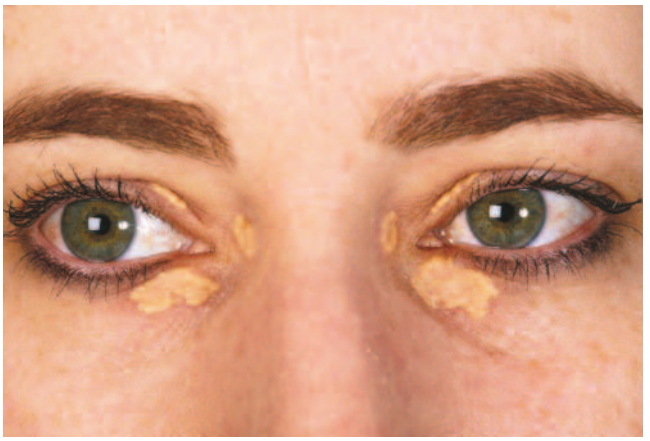
In routine practice an accredited laboratory should measure LDL-cholesterol as part of a fasting lipoprotein profile. LDL-cholesterol is calculated using the Friedewald equation (LDL-cholesterol = total cholesterol – HDL-cholesterol – [triglyceride/2.2]) unless the triglyceride

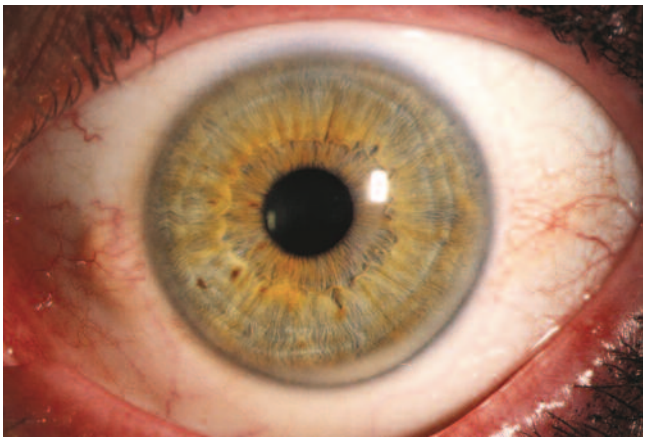
Table 3. FH diagnosis: Simon Broome Register Group definition

Definite FH	Possible FH
One of the following: • Total cholesterol >7.5 mmol/L in adults or >6.7 mmol/L in children <16 years of age. • LDL-cholesterol >4.9 mmol/L in adults (4.0 mmol/L in children) either pretreatment or highest on treatment. Plus: • Tendon xanthomas in patient or relative (parent, sibling, grandparent, aunt or uncle).	One of the following: • Total cholesterol >7.5 mmol/L in adults or >6.7 mmol/L in children <16 years of age. • LDL-cholesterol >4.9 mmol/L in adults (4.0 mmol/L in children) either pretreatment or highest on treatment. Plus one of the following: • Family history of myocardial infarction at age <50 years of age in a relative. • Family history of hypercholesterolaemia in a parent, sibling or child, or >7.5 mmol/L in a grandparent, aunt or uncle.









Figures 3a to d. Manifestations of FH. a (top left). Extensor tendon xanthomas. b (top right). Achilles tendon xanthomas. c (above left). Palpebral xanthomas. d (above right). Corneal arcus.

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Table 4. Factors associated with raised CVD risk in FH patients

Lipid related	Lifestyle related
Tendon xanthomas	Unhealthy diet
Increased total and LDL-cholesterol	Cigarette smoking
Increased apoB-100	Hypertension
Decreased HDL-cholesterol	Central obesity
Increased triglycerides	Hyperinsulinaemia
Increased VLDL-cholesterol	Diabetes mellitus/glucose intolerance
Increased lipoprotein (a)	Increased homocysteine
Increased cholesterol-years score	

Consultant's comment

Familial hypercholesterolaemia affects one in 500 Australians and most GPs would have several affected individuals in their practice. Untreated, the condition has severe consequences, and unfortunately most cases are not diagnosed until vascular disease has become manifest. This excellent two-part article gives a comprehensive guide to the diagnosis and treatment of this important condition, and I strongly recommend it to all readers.

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concentration exceeds 4.5 mmol/L or familial dysbetalipoproteinaemia (type III hyperlipidaemia) is present. In these settings, LDL-cholesterol can be measured directly using new generation homogeneous assays.

Measurement of glucose and creatinine levels and test of liver and thyroid functions will exclude secondary causes of hypercholesterolaemia and aid in global risk assessment.

ApoB measurement by immunochemical technique reflects the number of atherogenic lipoprotein particles and, in our opinion, offers benefit over and above LDL-cholesterol or non-HDL-cholesterol measurements in determining CHD risk.

Consideration should be given to the measurement of lipoprotein (a), homocysteine and highly sensitive C-reactive protein. However, further studies are required before these analytes become an integral part of routine clinical practice.

Molecular diagnosis

The molecular diagnosis of FH is labour-intensive, time-consuming and expensive because of the size of the *LDLR* gene and the presence of many different mutations in this gene in the Australian population.

A mutation is detected in only half of 'clinically' identified cases. This, in part, reflects the lack of sensitivity of some screening methods, along with misdiagnosis on clinical and biochemical criteria. Furthermore, most mutations are unique. Consequently, very few clinical laboratories offer molecular testing for FH, and those that do limit the analysis to a subset of mutations that are prevalent in certain ethnic groups. However, advances in gene microchip technology will eventually allow rapid molecular diagnosis of FH at a reasonable cost.

Assessing subclinical atherosclerosis

Once patients have been diagnosed with FH, they should be assessed for subclinical atherosclerosis. Noninvasive measures used to assess subclinical atherosclerosis in FH patients include:

- stress tests, looking for myocardial ischaemia
- computerised tomography, to detect coronary atherosclerotic plaques
- ultrasonography, to assess carotid intima-medial thickening and the presence of aortic aneurysm
- ankle-brachial blood pressure index.

Although flow-mediated dilatation of the brachial artery and carotid intima-medial thickness are measured noninvasively with ultrasonography, they remain mainly research techniques. However, impaired brachial artery flow-mediated dilatation and increased carotid intima-medial thickness have both been shown to be predictive of cardiovascular events in non-FH populations.

Post-ischaemic flow-mediated dilatation of the brachial artery is an estimate of endothelial dysfunction, as demonstrated in children with FH. The extent of impairment of flow-mediated dilatation is directly correlated with the degree of elevation of plasma LDL-cholesterol and can be reversed with HMG-CoA reductase inhibitor ('statin') therapy.

Carotid intima-medial thickness is significantly increased in FH patients compared with controls and is also an important tool for assessing risk and response to cholesterol lowering treatment. A recent trial showed that aggressive lowering of LDL-cholesterol with high doses of a statin compared with a weaker statin regimen resulted in relative regression of carotid atherosclerosis in heterozygous FH.

It has been recommended that FH patients should be reviewed six monthly

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and that the physician actively searches for symptoms of cardiovascular disease (CVD). It is also recommended that the following FH patients undergo a test for myocardial ischaemia every three to five years:

- high risk patients aged over 20 years
- all patients with noncoronary atherosclerotic disease
- all men aged over 30 years and women aged over 45 years.

Variation in clinical expression

Although FH is monogenic, there is substantial variation in the onset and severity of symptomatic atherosclerotic disease. Additional atherogenic risk factors of environmental, metabolic and genetic origin can modulate the clinical severity of FH. Examples of some of these factors are listed in Table 4. Given the high prevalence of atherosclerotic disease in FH, subclinical CHD should be actively sought.

Environmental factors

An unhealthy diet, smoking, lack of physical exercise and obesity compound the risk of CVD in subjects with FH. The increasing trend in obesity in developed and developing populations is evidently critical. Patients with FH who develop central obesity are more likely to have hypertriglyceridaemia, low HDL-cholesterol concentrations, insulin resistance and hypertension, as well as increased predisposition to type 2 diabetes.

Metabolic factors

The potential metabolic factors that can influence the clinical severity of FH include plasma triglyceride, HDL-cholesterol, C-reactive protein and lipoprotein (a) levels. Among these, there are data suggesting that low HDL-cholesterol and elevated lipoprotein (a) are independent risk factors for CVD in patients with FH.

Genetic factors

Genetic factors that could also account for variation in CVD among FH patients include mutations in the LDL-receptor, apoE, paraoxonase, cholesteryl ester transfer protein and angiotensin-II type 1-receptor genes.

Patients with 'null' LDL-receptor mutations, and hence no residual LDL-receptor function, have higher plasma LDL-cholesterol concentrations and a greater risk of CVD than do patients with other mutations that result in some residual LDL-receptor function.

A polymorphism in the cholesteryl ester transfer protein (the CETP *Taq*1B2 polymorphism) has been reported to be associated with a more favourable lipid profile, with lower LDL-cholesterol and higher HDL-cholesterol among patients with heterozygous FH.

The enzyme paraoxonase, carried on HDL particles, protects LDL from oxidation. A recent study showed that a common polymorphism in the paraoxonase gene was associated with variation in carotid intima-medial thickness and, by implication, risk of CVD.

Conclusion

FH is the most common and severe form of monogenic hypercholesterolaemia. The marked hypercholesterolaemia leads to a commensurate increased risk of CHD. Most people with FH are undiagnosed or diagnosed only after their first coronary event.

Diagnosis is currently based on biochemical, clinical and genetic criteria rather than on the identification of disease-causing mutations. Using these criteria, index cases can be easily and accurately identified and effective treatments administered. The treatment of FH is described in the second part of this article, which also summarises potential approaches to screening for this condition. MT

Further reading

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DECLARATION OF INTEREST: None.

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