

Bottom line: Familial hypercholesterolemia (FH) is a common (>1/500) autosomal dominant disorder that results in a 20-fold increase in premature cardiovascular disease (CVD) and death. Early diagnosis and treatment can normalize life expectancy. Key features of FH are elevated LDL-C \geq 5mmol/L with additional features such as early onset CVD (<55 years in men, <65 years in women), cholesterol deposition in the tendons (xanthomata) and/or around the eyes (xanthelasma), arcus cornealis onset <45years, and family history of early onset CVD or hyperlipidemia requiring treatment. Cascade screening of family members with LDL-C levels or genetic testing for the familial gene mutation when possible, allows for early identification and treatment of at-risk individuals, with statins as first-line treatment.

WHAT IS FAMILIAL HYPERCHOLESTEROLEMIA?

Familial hypercholesterolemia (FH) is a common autosomal dominant genetic condition where the uptake of low-density lipoprotein cholesterol (LDL-C) into cells is either decreased or inhibited. Most cases (80-90%) of FH are caused by mutations in the LDL receptor gene *LDLR*. This results in lifetime exposure to very high levels of LDL-C. FH results in a 20-fold increase in premature cardiovascular disease (CVD) and death in both men and women.

At least 1 in 500 Canadians is thought to have the heterozygous form of familial hypercholesterolemia (HeFH). FH is more common in certain populations (e.g. 1/270 in French Canadians, 1/100 in Lebanese and Afrikaners, and 1/67 in Ashkenazi Jews in South Africa) due to founder effects.

Table 1. Clinical features of familial hypercholesterolemia in heterozygotes (HeFH) and homozygotes (HoFH).

Clinical features	HeFH	HoFH
Genetics	Mutation in one copy of one FH gene	Mutation in both copies of an FH gene
LDL-C levels	\geq 5mmol/L with additional features shown in following boxes	>12 mmol/L <i>lower LDL-C levels, especially in children or in treated patients, do not exclude HoFH</i>
Cardiovascular disease onset	<55 years of age in men <65 years of age in women	<20 years of age (can be as early as the first year of life)
Physical findings	<ul style="list-style-type: none"> — Cholesterol deposits in the tendons (xanthomata) and/or around the eyes (xanthelasma) — Arcus cornealis (white, grey, or blue opaque ring in the corneal margin) onset <45years 	
Family history	<ul style="list-style-type: none"> — Early onset CVD — Hyperlipidemia, often requiring treatment 	

HOW IS FAMILIAL HYPERCHOLESTEROLEMIA DIAGNOSED?

While there are no Canadian-specific FH diagnostic criteria, the Canadian Cardiovascular Society (CCS) recommends using those published by the Dutch Lipid Clinic Network (see the [FH Point of Care Tool](#)). Alternatively, criteria from the Simon Broome Registry can be used, and include lower thresholds for children with suspected FH (Table 3). Both sets of diagnostic criteria are internationally accepted and used for diagnosis of FH, although neither is designed to diagnose HoFH; in this case, other criteria have been suggested. See the [FH Point of Care Tool](#) for more on diagnostic criteria.

HOW TO RECOGNIZE INDIVIDUALS WITH FH:

- ▶ An individual (>30years) with hypercholesterolemia (LDL-C \geq 5mmol/L)
 - * Exclusion of secondary causes of elevated LDL-C, e.g. obstructive liver disease, hypothyroidism, nephrotic syndrome, anorexia nervosa

AND

- ▶ Personal or family history of clinical stigmata of FH

OR

- ▶ Personal or family history of premature CVD

OR

- ▶ Family history of significant hypercholesterolemia, often requiring treatment

Individuals with LDL-C \geq 5mmol/L and at least one of the features above are considered to have a *possible* FH diagnosis. Those with LDL-C \geq 5mmol/L and 2 additional features are considered to have a *probable* FH diagnosis. Individuals with possible or probable diagnosis should be referred to a lipid specialist for diagnosis and management.

CASCADE SCREENING

The most cost-effective approach for identification of new FH cases is cascade screening of family members of a known index case (the first individual with a confirmed diagnosis). Screening can be by LDL-C measurements, genetic testing for a known familial gene mutation when possible or use of diagnostic criteria (See the [FH Point of Care Tool](#)). Some experts recommend referral for specialist consultation beginning at age 2 years for those at high risk for HoFH (individuals where both parents have HeFH).

WHERE DO I REFER MY PATIENT?

[Find a Canadian FH specialist here.](#)

You should refer your patient [to your local genetics centre](#) if s/he has had a positive genetic test result and would like genetic counselling to discuss the implications for self and family. Include all relevant information on your referral (e.g. family history, genetic test results, and investigations like LDL-C) to prevent unnecessary delays due to further clarification needed before an appointment can be booked.

Note that genetics clinics vary with regard to the referrals they choose to accept. You may want to contact [your local centre](#) for more information.

SURVEILLANCE AND MANAGEMENT

Statins are the drug class of choice for individuals with HeFH. LDL-C should be lowered as fast and as far as possible. **The CCS recommends a >50% reduction of LDL-C from baseline beginning at age 18 as primary prevention with a goal of LDL-C <2.0mmol/L for secondary prevention.** Some individuals with FH will require combination and/or emerging therapy to obtain optimal LDL-C. Families with FH should be counselled about the importance of lifestyle modification such as: smoking cessation and avoidance of passive smoking; diet; exercise; daily activity beginning early in life; maintenance of ideal body weight; and stress reduction.

CHILDREN: Lifestyle modifications discussed above remain the cornerstone of CVD prevention in both children and teens with FH and referral to a specialist for treatment decisions is recommended.

See www.geneticseducation.ca for the comprehensive [GEC-KO Messenger](#) with complete reference list and more on HoFH, risks, benefits and limitations of genetic testing for FH. For Canadian screening, diagnosis and management guidelines see Genest J, Hegele RA, Bergeron J, et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. Can J Cardiol 2014; 30(12): 1471-81.

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