FAMILIAL HYPERCHOLESTEROLEMIA

Bottom line: Familial hypercholesterolemia is a common (~1/250) autosomal dominant disorder that results in a 6 to 22-fold increase in premature cardiovascular disease (CVD) and death. Early diagnosis and treatment can normalize life expectancy. Key features of familial hypercholesterolemia are elevated LDL-C ≥ 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 with onset <45years, and family history of early onset CVD or hyperlipidemia requiring treatment. In Canada, a diagnosis of familial hypercholesterolemia is typically based on an individual's clinical presentation correlating with one of three familial hypercholesterolemia definitions. Genetic testing is not generally available, and a clinical diagnosis guides treatment and screening of family members. Once a person is diagnosed with familial hypercholesterolemia, cascade screening of family members using measurement of LDL-C levels is recommended. This enables early identification and treatment of at-risk individuals, with statins as first-line treatment.

WHAT IS FAMILIAL HYPERCHOLESTEROLEMIA?

Familial hypercholesterolemia (FH) is an autosomal dominant genetic condition where the uptake of low-density lipoprotein cholesterol (LDL-C) into cells is either decreased or inhibited. This results in lifetime exposure to very high levels of LDL-C. FH is the most common genetic disorder causing premature cardiovascular disease (CVD) and death in both men and women.

About 1 in 250 Canadians is thought to have the heterozygous (HeFH) form of FH. FH is more common in certain populations due to founder effects: in certain areas of Quebec, the prevalence is as high as 1 in 80; it affects approximately ~1/100 Lebanese and Afrikaners, and 1/67 South African Ashkenazi Jews. FH is under diagnosed and under treated both in Canada and worldwide, despite the knowledge that early diagnosis and treatment can normalize life expectancy.

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

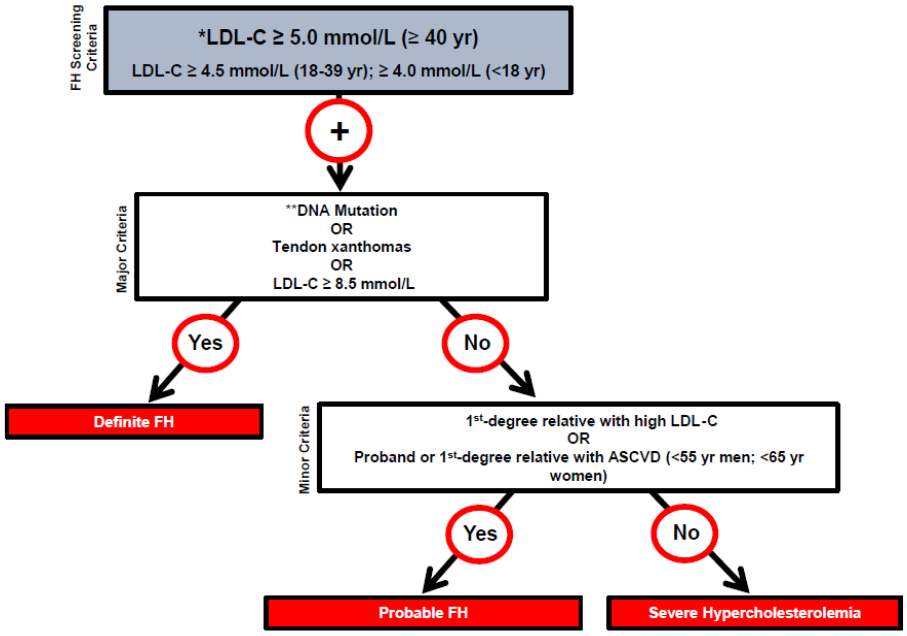
Clinical features	HeFH	HoFH
Genetics	Mutation in one copy of one FH gene	Mutations in two FH genes, one inherited from each parent
LDL-C levels	≥ 5mmol/L with additional features shown in following boxes	>12 mmol/L *lower LDL-C levels, especially in children or in treated patients, do not exclude HoFH*
Cardiovascular disease (CVD) 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)
Other atherosclerotic disease risks	— Stroke or transient ischaemic attack — Peripheral vascular disease	
Physical findings	— 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	— Early onset CVD — Hyperlipidemia, often requiring treatment	

How is familial hypercholesterolemia diagnosed?

The Canadian Cardiovascular Society (CCS) recommends the use of the Canadian diagnostic criteria for FH proposed by the Familial Hypercholesterolemia Canada (FHCanada) network (Figure 1). While these criteria are relatively new, they are less complicated than those published by the Dutch Lipid Clinic Network (DLCNC) or the Simon Broome Registry (see the GEC-KO Messenger for more on these criteria) and have been validated against each of these criteria, which are internationally accepted for the diagnosis of HeFH.

Genetic testing is not necessary for diagnosis, and is not routinely available in most of Canada. In Quebec, health care providers can order testing from CHU Sainte Justine Molecular Laboratory focused on the most common gene mutations found in French Canadians with familial hypercholesterolemia

Figure 1: Canadian criteria for the clinical diagnosis of familial hypercholesterolemia (FH). From Ruel I *et al.*, 2018 Can J Cardiol. Reprinted with permission under the CC BY-NC-ND license



ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol. * Secondary causes of high LDL-C should be ruled out (severe or untreated hypothyroidism, nephrotic syndrome, hepatic disease [biliary cirrhosis], medication, especially antiretroviral agents).

Cascade Screening

The most cost-effective approach for identification of new familial hypercholesterolemia cases is cascade screening of family members of the first individual with a confirmed diagnosis, known as the index case. **This approach is recommended by the Canadian Cardiovascular Society (CCS).** Screening can include lipid profiles of relatives and/or genetic testing for a known familial mutation when available. Each newly diagnosed individual becomes a new index case and cascade screening of relatives continues.

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. For the updated Canadian definition of FH visit www.FHCanada.net to find Ruel et al., Simplified Canadian definition for familial hypercholesterolemia. Can J Cardiol 2018 34: 1210-1214.

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