FAMILIAL HYPERCHOLESTEROLEMIA

Bottom line: Familial hypercholesterolemia (FH) is a common (~1/250) autosomal dominant condition 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 FH 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 FH is typically based on an individual's clinical presentation and history as outlined in the Canadian Cardiovascular Society algorithm. Genetic testing is not widely clinically available in Canada with some exceptions. A clinical diagnosis guides treatment and screening of family members. Once a person is diagnosed with FH, cascade screening of family members using measurement of LDL-C levels and/or genetic testing 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. FH is both underdiagnosed and undertreated worldwide despite the knowledge that early diagnosis and treatment can normalize life expectancy.[1-3] It is estimated that roughly 1 in 250 Canadians has FH, and that only about 10% have been identified.[1,4]

WHAT DO I NEED TO KNOW ABOUT THE GENETICS OF FAMILIAL HYPERCHOLESTEROLEMIA?

Most cases (up to 80%) of familial hypercholesterolemia (FH) are caused by pathogenic/likely pathogenic (P/LP) variants (*what used to be called mutations*) in the LDL receptor gene *LDLR,* in which over 1700 different P/LP variants have been identified.[2,5,6] The LDLR protein binds LDL, which is the major cholesterol-carrying lipoprotein of plasma, and transports LDL into cells by endocytosis. P/LP variants in the *LDLR* gene can reduce the number of LDL receptors produced within cells or disrupt the ability of the receptor to bind LDL-C.[2] P/LP variants in *APOB* disrupt binding of LDL particles to the receptor, while P/LP variants in *PCSK9* cause increased degradation of the receptor. These mechanisms lead to elevated LDL levels and premature development of atherosclerotic plaque.

Additional genes (e.g. *ABCG5, ABCG8, APOE, LDLRAP1, LIPA*) are known to be associated with FH, although rare. With advances in genetic testing technology additional rare genes can be added to gene panels with little extra cost. Genetic testing for FH may involve a gene panel with comprehensive analysis of three or more genes or may be targeted ancestry-based testing looking for the presence or absence of specific P/LP variants.[7]

PATTERN OF INHERITANCE

Familial hypercholesterolemia (FH) is typically inherited in an autosomal dominant manner. FH can be present in a heterozygous form (HeFH), where only one copy of a FH-causing gene contains a P/LP variant. FH can also be present in a homozygous form (HoFH) where an individual has a P/LP variant in both copies of a FH-causing gene. The two P/LP variants can be identical or different. Rarely there is a P/LP variant in one copy of two different FH genes. All individuals with HoFH have an extremely high risk of early onset cardiovascular disease.[1,3] If both parents have HeFH, their child has a 25% chance to have HoFH, which is associated with an extremely high CVD risk.

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

Clinical features	HeFH	HoFH
Genetics pathogenic/likely pathogenic (P/LP) variants (*what used to be called mutations*)	P/LP variant in one copy of one FH gene	P/LP variant in two FH genes, one inherited from each parent
Untreated* LDL-C levels	≥ 5mmol/L at age 40 years or older ≥4.5mmol/L at age 18-39 years ≥4mmol/L at age younger than 18 years 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	

*The CardioRisk app has a validated algorithm to impute a baseline value from LDL-C levels while on lipid lowering medications, additionally it can be used for the clinical diagnosis of FH, assessing the degree of severity of FH for new patients and helps facilitate FH diagnosis.

How common is Familial Hypercholesterolemia?

About 1 in 250 Canadians is thought to have heterozygous familial hypercholesterolemia (HeFH), however FH is significantly under-recognized in Canada.[1] Homozygous-FH (HoFH) is much rarer and expected to affect between 1 in 250,000 and 1 in 1,000,000 Canadians.[9] Familial hypercholesterolemia 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.[2,9,12,13]

How is familial hypercholesterolemia diagnosed?

The Canadian Cardiovascular Society (CCS) recommends the use of the Canadian diagnostic criteria for familial hypercholesterolemia (FH) proposed by the Familial Hypercholesterolemia Canada (FHCanada) network (Figure 1).[14] While these criteria are relatively new, they are less complicated than those published by the Dutch Lipid Clinic Network (DLCNC) (Table 2) or the Simon Broome Registry (Table 3) and have been validated against each of these criteria, which are internationally accepted for the diagnosis of HeFH.[9,14] The Simon Broome Registry criteria include lower thresholds for children with suspected FH.[10] Neither the DLCNC nor Simon Broome Registry is designed to diagnose HoFH, for which other criteria have been suggested.[8] Genetic testing is not necessary for diagnosis, and is not yet routinely clinically available in most of Canada.

In Quebec, clinicians can order genetic testing of the three major FH genes through The Core Molecular Diagnostic Laboratory at the McGill University Health Centre when clinical criteria are met. CHU Sainte Justine Molecular Laboratory offers targeted genetic testing for only the most common P/LP variants in those French-

Canadian (FC) ancestry. As a targeted test this has limited/no value in those not of FC ancestry. A negative result would not rule out an FH diagnosis

In Ontario, any physician can order genetic testing for FH through London Health Sciences Centre and Trillium Health Partners. An 8-gene panel is available for those that meet criteria.

Other provinces are looking at how to implement genetic testing and screening.

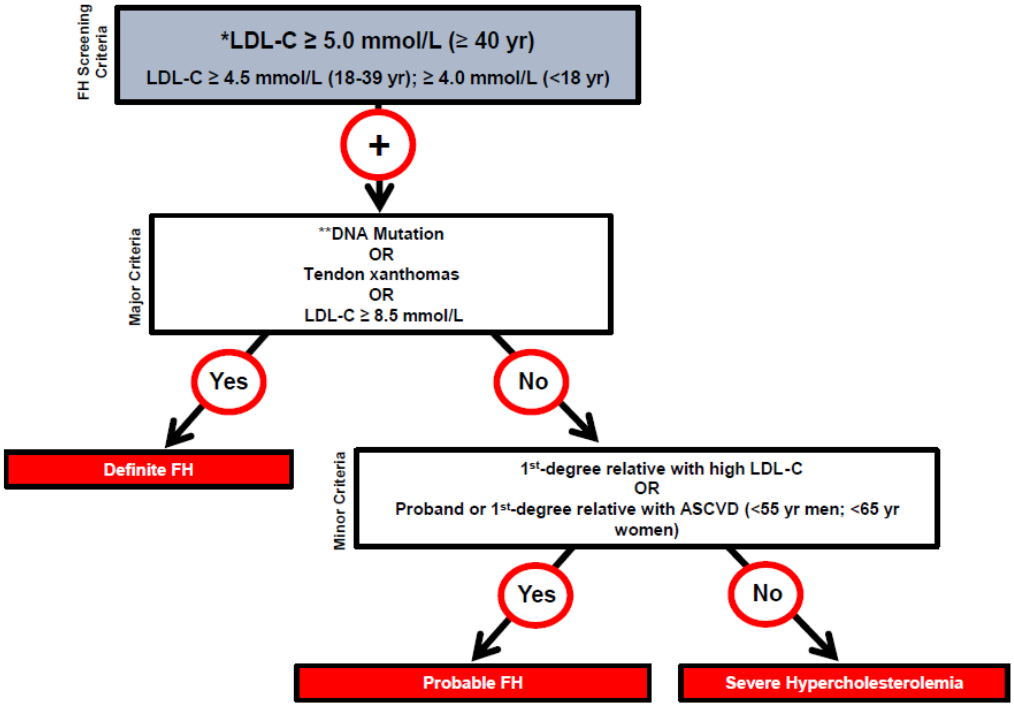

Figure 1. Canadian criteria for the clinical diagnosis of familial hypercholesterolemia (FH). From Ruel I *et al*, 2018[14]. Reprinted with permission under the CC BY-NC-ND license https://creativecommons.org/licenses/by-nc-nd/4.0/. DOI: 10.1016/j.cjca.2018.05.015

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) ** DNA mutation refers to the presence of a known FH-causing variant in a FH gene in the individual or a first-degree relative. FH diagnosis in a patient with a P/LP variant but normal LDL-C levels is unclear. Yearly follow-up of the individual is suggested and cascade screening of family members should be initiated.

Table 2. Dutch Lipid Clinic Network.[3,9]

Criteria	Points
Family History	
First-degree relative with: ○ premature cardiovascular disease (<55 years in men, <60 years in women) **OR** ○ LDL-C >95th percentile for age and sex	1
First-degree relative: ○ With tendinous xanthomata and/or arcus cornealis **OR** ○ Child (<18 years) with LDL-C >95th percentile for age and sex	2
Clinical History	
Personal history of: ○ Premature peripheral or cerebrovascular disease ○ Coronary artery disease	1 2
Physical examination	
Tendinous xanthomata	6
Arcus cornealis <45 years of age	4
LDL-C	
Between 4.01 and 4.89mmol/L (155-189mg/dL)	1
Between 4.91 and 6.44mmol/L (190-249mg/dL)	3
Between 6.46 and 8.51mmol/L (250-329mg/dL)	5
Greater than 8.53mmol/L (>330mg/dL)	8
Genetics	
Pathogenic or likely pathogenetic variant in the *LDLR* gene or other gene known to cause familial hypercholesterolemia e.g. *APOB, PCSK9*	8
Scoring	
Unlikely familial hypercholesterolemia diagnosis	<3
Possible familial hypercholesterolemia diagnosis	3 to 5
Probable familial hypercholesterolemia diagnosis	6 to 7
Definite familial hypercholesterolemia diagnosis	8 or more

Table 3. Simon Broome Registry [10,15]

Definite familial hypercholesterolemia diagnosis
High cholesterol: Children (<16 years) ○ Total cholesterol >6.7mmol/L OR LDL-C >4.0mmol/L Adults (>16 years) ○ Total cholesterol >7.5mmol/L OR LDL-C >4.9mmol/L **AND** Tendon xanthomata in the individual or a first- or second-degree relative **OR** Pathogenic/likely pathogenic variant in the *LDLR* gene or other gene known to cause FH e.g. *APOB, PCSK9*
Possible familial hypercholesterolemia diagnosis
High cholesterol: Children (<16 years) ○ Total cholesterol >6.7mmol/L OR LDL-C >4.0mmol/L Adults (>16 years) ○ Total cholesterol >7.5mmol/L OR LDL-C >4.9mmol/L **AND one of the following** Family history of premature myocardial infarction <60 years in a first-degree relative OR <50 years in a second-degree relative **OR** Family history of raised cholesterol Child (<16 years), first-degree relative: Total cholesterol >6.7mmol/L OR LDL-C >4.0mmol/L OR Adult (>16 years) first- or second-degree relative: Total cholesterol >7.5mmol/L OR LDL-C >4.9mmol/L

Cascade Screening For Family Members

The most cost-effective approach for identification of new familial hypercholesterolemia (FH) cases is cascade screening of family members of the first individual with a confirmed diagnosis, known as the index case.[4,10,16] Data from the UK have shown that cascade screening reduces the average age at which an individual is diagnosed and results in an increased number of individuals who are treated with statins and have subsequent lowered lipid levels.[17]

The Canadian Cardiovascular Society (CCS) recommends screening of first-degree relatives of the index case.[1] Screening can include lipid profiles of relatives and/or genetic testing for a known familial P/LP variant, when available. Each newly diagnosed individual becomes a new index case and cascade screening of relatives continues.

When ordering genetic testing for relatives it is important to include documentation of the familial genetic variant either with a molecular report or a family letter. This ensures accurate interpretation of testing.

Surveillance and Management

Adults

The Canadian Cardiovascular Society (CCS) does not recommend the use of conventional cardiovascular risk calculators, e.g. Framingham Risk Score, in individuals with familial hypercholesterolemia (FH) as these greatly underestimate lifetime CVD risk.[1,2]

FH diagnosis in a patient with a P/LP variant but normal LDL-C levels is unclear. Yearly follow-up of the individual is suggested and cascade screening of family members should be initiated.[1]

Pharmaceuticals

Statins are the drug class of choice for individuals with HeFH. Observational studies have shown a dramatic decrease in cardiac events in statin-treated individuals with familial hypercholesterolemia.[1] LDL-C should be lowered as fast and as far as possible.[3] **The CCS recommends a >50% reduction of LDL-C from baseline beginning at age 18 as primary prevention and that an ideal goal of LDL-C <2.0mmol/L is recommended for secondary prevention.**[18] The use of high-dose statins alone is usually sufficient to achieve LDL-C reduction; however, some individuals with FH will require combination and/or emerging therapy to obtain optimal LDL-C. Specialist referral is recommended.[1-3,19] Statins should not be used during pregnancy.[1] For the most recent recommendations on management and treatment of individuals with HoFH please see Cuchel et al. 2014.[8]

Lifestyle

Families with FH should be counselled about the importance of lifestyle modification such as[1-3,19]:

- ✓ Smoking cessation and avoidance of passive smoking
- ✓ Diet
  - High in fibre (soluble), plant sterols/stanols and unsaturated fatty acids
  - Low in trans and saturated fatty acids, refined sugars
  - Moderate alcohol use only
- ✓ Exercise
  - Daily activity beginning early in life
- ✓ Maintenance of ideal body weight
- ✓ Stress reduction

For general population guidelines on management of dyslipidemia in adults please see Anderson *et al.,* 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult http://www.onlinecjc.ca/article/S0828-282X(16)30732-2/pdf.

Children

Lifestyle modifications discussed above remain the cornerstone of CVD prevention in both children and adolescents with familial hypercholesterolemia and referral to a specialist for treatment decisions is recommended.[1] **The CCS recommends that children with HoFH are referred to a lipid specialist centre**

for cholesterol-lowering therapies when >15kg in weight. Some experts recommend referral for specialist consultation beginning at age 2 years.

Additional guidance on management of dyslipidemia in children and adolescence by the CCS can be found here.

RESOURCES

- FH Canada for physicians
- FH Canada for the public

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