

## 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  $\geq$  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 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 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. Familial hypercholesterolemia is the most common genetic disorder causing premature cardiovascular disease (CVD) and death in both men and women. Familial hypercholesterolemia is both underdiagnosed and undertreated worldwide despite the knowledge that early diagnosis and treatment can normalize life expectancy.<sup>1-3</sup> It is estimated that roughly 1 in 250 Canadians has familial hypercholesterolemia, most of whom are undiagnosed.<sup>1,4</sup>

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

Most cases (80-90%) of familial hypercholesterolemia are caused by mutations in the LDL receptor gene *LDLR*, in which over 1700 different mutations have been identified.<sup>2,5,6</sup> The LDLR protein binds LDL, which is the major cholesterol-carrying lipoprotein of plasma, and transports LDL into cells by endocytosis. Mutations 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.<sup>2</sup> Mutations in *APOB* disrupt binding of LDL particles to the receptor, while mutations in *PCSK9* cause increased degradation of the receptor. These mechanisms lead to elevated LDL levels and premature development of atherosclerotic plaque.

### PATTERN OF INHERITANCE

Familial hypercholesterolemia is typically inherited in an autosomal dominant manner, and can be present in a heterozygous form (HeFH), where only one copy of a familial hypercholesterolemia-causing gene is mutated. Familial hypercholesterolemia can also be present in a homozygous form (HoFH) where an individual has a mutation in both copies of one familial hypercholesterolemia-causing gene. The two mutations can be identical or different. Rarely there is a mutation in one copy of two different familial hypercholesterolemia genes. All individuals with HoFH have an extremely high risk of early onset cardiovascular disease.<sup>1,3</sup> 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 <sup>3</sup>	Mutation in one copy of one familial hypercholesterolemia gene: <ul style="list-style-type: none"> <li>— Genes known to be associated with HeFH: <i>LDLR</i>, <i>APOB</i>, <i>PCSK9</i></li> </ul>	Mutation in both copies of one familial hypercholesterolemia gene: <ul style="list-style-type: none"> <li>— Genes known to be associated with HoFH: <i>LDLR</i>, <i>APOB</i>, <i>PCSK9</i></li> </ul>
LDL-C levels	≥ 5 mmol/L with the additional features shown in following boxes <sup>1,9</sup>	>13 mmol/L <i>lower LDL-C levels, especially in children or in treated patients, do not exclude HoFH<sup>7,8</sup></i>
Cardiovascular disease <sup>3</sup>	<55 years in men <65 years in women <sup>5</sup>	<20 years (can be as early as the first year of life)
Other atherosclerotic disease risks <sup>10</sup>	<ul style="list-style-type: none"> <li>— Stroke or transient ischaemic attack (TIA)</li> <li>— Peripheral vascular disease (PVD)</li> </ul>	
Physical findings <sup>1</sup>	<ul style="list-style-type: none"> <li>— Cholesterol deposits in the tendons (xanthomata) and/or around the eyes (xanthelasma)</li> <li>— Arcus cornealis (white, grey, or blue opaque ring in the corneal margin) with onset &lt;45years</li> </ul>	
Family history <sup>1</sup>	<ul style="list-style-type: none"> <li>— Early onset CVD</li> <li>— Hyperlipidemia, often requiring treatment</li> </ul>	

#### HOW COMMON IS FAMILIAL HYPERCHOLESTEROLEMIA?

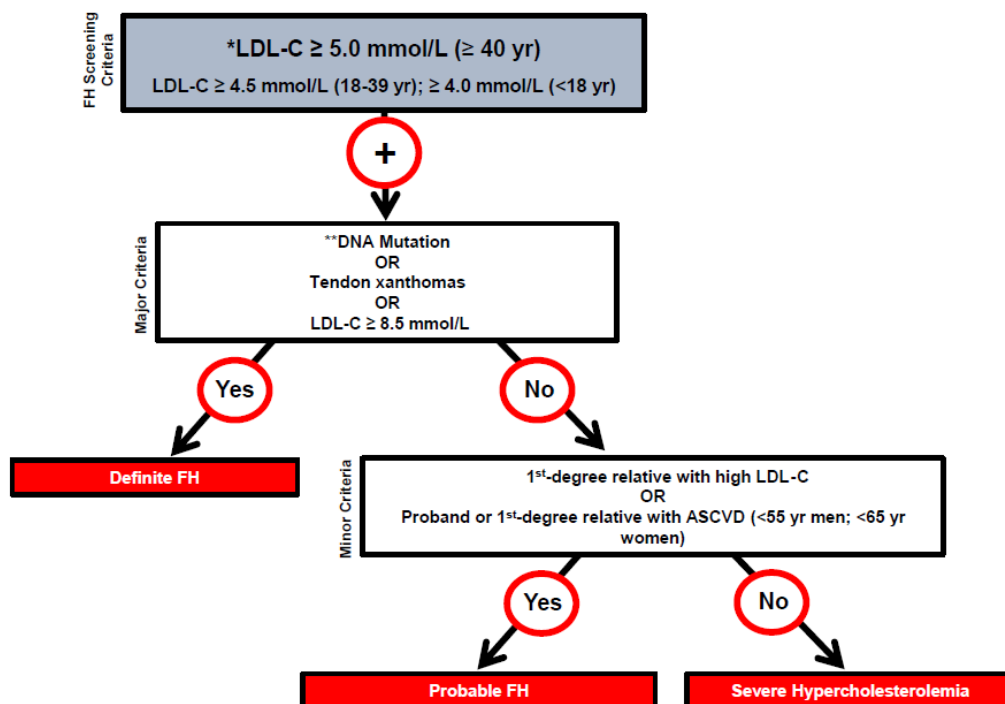
About 1 in 250 Canadians is thought to have HeFH, however familial hypercholesterolemia is significantly under-recognized in Canada.<sup>1</sup> HoFH is much rarer and expected to affect between 1 in 250,000 and 1 in 1,000,000 Canadians.<sup>8</sup> Familial hypercholesterolemia is more common in certain 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.<sup>2,8,11,12</sup>

## HOW IS FAMILIAL HYPERCHOLESTEROLEMIA DIAGNOSED?

The Canadian Cardiovascular Society (CCS) recommends the use of the Canadian diagnostic criteria for familial hypercholesterolemia proposed by the Familial Hypercholesterolemia Canada (FHCanada) network (Figure 1).<sup>13</sup> 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.<sup>8,13</sup> The Simon Broome Registry criteria include lower thresholds for children with suspected familial hypercholesterolemia.<sup>9</sup> Neither the DLCNC nor Simon Broome Registry is designed to diagnose HoFH, for which other criteria have been suggested.<sup>7</sup> 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 ([Requisition here](#)) focused on the most common gene mutations found in French Canadians with familial hypercholesterolemia. This test is of limited utility in other ethnic groups as it does not rule out the hundreds of gene mutations seen in other ethnicities residing in Canada.<sup>1</sup> If available, genetic testing should be offered to individuals with either a probable or definite diagnosis of familial hypercholesterolemia.<sup>1</sup> The CCS does not recommend the use of conventional cardiovascular risk calculators, e.g. Framingham Risk Score, in individuals with familial hypercholesterolemia as these greatly underestimate lifetime CVD risk.<sup>1,2</sup>

Figure 1: Canadian criteria for the clinical diagnosis of familial hypercholesterolemia (FH). From Ruel I et al, 2018<sup>13</sup>. Reprinted with permission under the CC BY-NC-ND license

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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) \*\* Causal DNA mutation refers to the presence of a known FH-causing variant in the *LDLR*, *APOB*, or *PCSK9* gene in the individual or a first-degree relative. FH diagnosis in a patient with a DNA mutation 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.<sup>3,8</sup>

Criteria	Points
<b>Family History</b>	
First-degree relative with: <ul style="list-style-type: none"> <li>○ premature cardiovascular disease (&lt;55 years in men, &lt;60 years in women)</li> </ul> <b>OR</b> <ul style="list-style-type: none"> <li>○ LDL-C &gt;95<sup>th</sup> percentile for age and sex</li> </ul>	1
First-degree relative: <ul style="list-style-type: none"> <li>○ With tendinous xanthomata and/or arcus cornealis</li> </ul> <b>OR</b> <ul style="list-style-type: none"> <li>○ Child (&lt;18 years) with LDL-C &gt;95<sup>th</sup> percentile for age and sex</li> </ul>	2
<b>Clinical History</b>	
Personal history of: <ul style="list-style-type: none"> <li>○ Premature peripheral or cerebrovascular disease</li> <li>○ Coronary artery disease</li> </ul>	1 2
<b>Physical examination</b>	
Tendinous xanthomata	6
Arcus cornealis <45 years of age	4
<b>LDL-C</b>	
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
<b>Genetics</b>	
Pathogenic mutation in the <i>LDLR</i> gene or other gene known to cause familial hypercholesterolemia e.g. <i>APOB</i> , <i>PCSK9</i>	8
<b>Scoring</b>	
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<sup>9,14</sup>

Definite familial hypercholesterolemia diagnosis
<p>High cholesterol:</p> <p>Children (&lt;16 years)</p> <ul style="list-style-type: none"> <li>○ Total cholesterol &gt;6.7mmol/L OR LDL-C &gt;4.0mmol/L</li> </ul> <p>Adults (&gt;16 years)</p> <ul style="list-style-type: none"> <li>○ Total cholesterol &gt;7.5mmol/L OR LDL-C &gt;4.9mmol/L</li> </ul> <p><b>AND</b></p> <p>Tendon xanthomata in the individual or a first- or second-degree relative</p> <p><b>OR</b></p> <p>Pathogenic mutation in the <i>LDLR</i> gene or other gene known to cause FH e.g. <i>APOB</i>, <i>PCSK9</i></p>
Possible familial hypercholesterolemia diagnosis
<p>High cholesterol:</p> <p>Children (&lt;16 years)</p> <ul style="list-style-type: none"> <li>○ Total cholesterol &gt;6.7mmol/L OR LDL-C &gt;4.0mmol/L</li> </ul> <p>Adults (&gt;16 years)</p> <ul style="list-style-type: none"> <li>○ Total cholesterol &gt;7.5mmol/L OR LDL-C &gt;4.9mmol/L</li> </ul> <p><b>AND one of the following</b></p> <p>Family history of premature myocardial infarction</p> <ul style="list-style-type: none"> <li>&lt;60 years in a first-degree relative OR</li> <li>&lt;50 years in a second-degree relative</li> </ul> <p><b>OR</b></p> <p>Family history of raised cholesterol</p> <ul style="list-style-type: none"> <li>Child (&lt;16 years), first-degree relative: Total cholesterol &gt;6.7mmol/L OR LDL-C &gt;4.0mmol/L OR</li> <li>Adult (&gt;16 years) first- or second-degree relative: Total cholesterol &gt;7.5mmol/L OR LDL-C &gt;4.9mmol/L</li> </ul>

### CASCADE SCREENING FOR FAMILY MEMBERS

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.<sup>4,9,15</sup> 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 subsequently lowered lipid levels.<sup>16</sup>

The Canadian Cardiovascular Society (CCS) recommends screening of first-degree relatives of the index case.<sup>1</sup> 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

### ADULTS

#### 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.<sup>1</sup> LDL-C should be lowered as fast and as far as possible.<sup>3</sup> **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.**<sup>17</sup> The use of high-dose statins alone is usually sufficient to achieve LDL-C reduction; however, some individuals with familial hypercholesterolemia will require combination and/or emerging therapy to obtain optimal LDL-C. Specialist referral is recommended.<sup>1-3,18</sup> Statins should not be used during pregnancy.<sup>1</sup> For the most recent recommendations on management and treatment of individuals with HoFH please see Cuchel et al. 2014.<sup>7</sup>

#### LIFESTYLE

Families with familial hypercholesterolemia should be counselled about the importance of lifestyle modification such as<sup>1-3,18</sup>:

- ✓ 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](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.<sup>1</sup> 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.

**RESOURCES FOR HEALTH PROFESSIONALS**

[Familial Hypercholesterolemia \(FH\) Canada](#)

**RESOURCES FOR THE PUBLIC**

[Familial Hypercholesterolemia \(FH\) Canada](#) - [Patient brochure](#) and resource information

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