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FAMILIAL HYPERCHOLESTEROLEMIA

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 ≥ 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 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 only about 15% of Canadians who have heterozygous FH (HeFH, *where an individual has a mutation in one copy of an FH-causing gene*) have been diagnosed[4].

WHAT DO I NEED TO KNOW ABOUT THE GENETICS OF FH?

Most cases (80-90%) of FH are caused by mutations in the LDL receptor gene *LDLR,* in which more than over 1200 different mutations have been identified[2,5]. 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 the cells or disrupt the ability of the receptor to bind LDL-C[2]. Mutations in *APOB* disrupt the binding of LDL particles to the receptor, while mutations in *PCSK9* cause increased degradation of the receptor. All these mechanisms lead to elevated LDL levels and consequent premature development of atherosclerotic plaque.

PATTERN OF INHERITANCE

FH is inherited in an autosomal dominant manner and can be present in a heterozygous form (HeFH) and in a homozygous form (HoFH, *where an individual has a mutation in both copies of one FH-causing gene*). The two mutations can be identical or different. Rarely there is a mutation in one copy of two different FH genes. All individuals with HoFH have an extremely high risk of early onset cardiovascular disease.[1,3]

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

Clinical features	HeFH	HoFH
Genetics[3]	Mutation in one copy of one FH gene — Genes known to be associated with HeFH *LDLR, APOB, PCSK9*	Mutation in both copies of one FH gene — Genes known to be associated with HoFH *LDLR, APOB, PCSK9, LDLRAP1*
LDL-C levels	≥ 5 mmol/L with additional features shown in following boxes[1,9]	>12 mmol/L *lower LDL-C levels, especially in children or in treated patients, do not exclude HoFH*[1,6]
Cardiovascular disease[3]	<55 years in men <65 years in women[5]	<20 years (can be as early as the first year of life)
Physical findings[1]	— 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[1]	— Early onset CVD — Hyperlipidemia, often requiring treatment	

HOW COMMON IS *FH*?

At least 1 in 500 Canadians is thought to have HeFH, however FH is significantly under-recognized in Canada. HoFH is much rarer and expected to affect between 1 in 250,000 and 1 in 1,000,000 Canadians[1]. FH is more common in certain populations (e.g. 1/270 in French Canadians[1], ~1/100 in Lebanese and Afrikaners[5], and 1/67 in Ashkenazi Jews in South Africa[8]) due to founder effects[1-3].

WHO SHOULD BE SCREENED FOR FH?

Early screening and identification of index cases is the basis of CVD prevention. [1,4,9]

HOW TO RECOGNIZE INDIVIDUALS WITH FH: [1,4,9]

- An individual (>30years) with hypercholesterolemia (LDL-C ≥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 ≥5mmol/L and at least one of the features above are considered to have a *possible* FH diagnosis. Those with LDL-C ≥ 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 the first individual with a confirmed diagnosis, known as the index case[5,9]. 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[11].

- Screen first-, second- and third-degree relatives of the index case
  - Each newly diagnosed individual becomes a new index case and cascade screening of relatives continues
  - Screening can be by LDL-C measurements, genetic testing for a known familial gene mutation when possible, or use of published diagnostic criteria (see Tables 2 and 3)

CHILDREN

The Canadian Cardiovascular Society (CCS)[1] recognizes that while universal screening potentially allows for more complete case ascertainment there are too many uncertainties in modelling its cost-effectiveness, and instead recommends targeted screening of children and adolescents with cardiovascular risk factors, such as:

- Family history of FH
- Family history of premature CVD
- Obesity
- Smoking
- Hypertension
- Type 2 diabetes

If both parents have HeFH, their child has a 25% chance to have HoFH. This is associated with an extremely high CVD risk. The CCS recommends that individuals with HoFH should be referred to a lipid specialist centre for cholesterol-lowering therapies when >7 years of age and >15kg in weight. Some experts recommend referral for specialist consultation beginning at age 2 years.

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 (Table 2)[1]. Alternatively, criteria from the Simon Broome Registry, which include lower thresholds for children with suspected FH, can be used (Table 3). Both sets of diagnostic criteria are internationally accepted and used for diagnosis of FH, although neither is designed to diagnose HoFH, for which other criteria have been suggested[6].They have comparable utility for diagnosing HeFH in adults[1].

Table 2. Dutch Lipid Clinic Network.[1,3]

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 mutation in the *LDLR* gene or other gene known to cause FH e.g. *APOB, PCSK9*	8
Scoring	
Unlikely FH diagnosis	<3
Possible FH diagnosis	3 to 5
Probable FH diagnosis	6 to 7
Definite FH diagnosis	8 or more

Table 3. Simon Broome Registry [1, 10]

Definite FH 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 mutation in the *LDLR* gene or other gene known to cause FH e.g. *APOB, PCSK9*
Possible FH 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

Individuals with possible or probable diagnosis should be referred to a lipid specialist for diagnosis and management.

WHO SHOULD BE OFFERED GENETIC TESTING?

Genetic testing should be considered for:

Heterozygous FH (HeFH)[1]

- Individuals meeting FH **definite** or **probable** or **possible** diagnostic criteria (Tables 2 and 3) First-, second- and third-degree family members of an individual with a known mutation in an FH gene (*LDLR, APOB, PCSK9)*

Homozygous FH (HoFH)[1,6]

- Individuals where both parents have known mutations in FH causing genes (*LDLR, APOB, PCSK9, LDLRAP1).* These individuals have a 25% risk for HoFH.

OR

- An untreated LDL-C >12mmol/L or treated LDL-C ≥8mmol/L*

  **lower LDL-C levels do not exclude HoFH, especially in children or in individuals who are treated for hyperlipidemia*

WITH either

- Cutaneous or tendon xanthomata before age 10 years

OR

- Both parents have elevated LDL-C levels consistent with HeFH

WHAT DOES THE GENETIC TEST RESULT MEAN?

A **positive genetic test** confers a definite FH diagnosis and offers the opportunity for cascade screening of family members. Compared to controls, individuals with HeFH have a 20-fold higher risk of premature CVD[12]. Untreated, a fatal or non-fatal coronary event will occur in about 50% of males by age 50 and about 30% of females by age 60[12].

Conventional cardiovascular risk calculators, e.g. Framingham Risk Score, cannot be used in individuals with FH as these greatly underestimate CVD risk[1, 2]. **The CCS recommends that all adults with mutations in FH-causing genes be classified as 'high risk' for CVD[1]**. Close to 100% of individuals with a positive genetic test result will develop hypercholesterolemia[13].

A **negative genetic test** in an individual who meets definite, probable or possible FH criteria does not rule out an FH diagnosis. When an individual is classified on the basis of the Simon Broome Registry about 60% with a definite FH diagnosis and about 30% with a possible FH diagnosis have identifiable mutations in an FH-causing gene[13]. When an individual is classified on the basis of the Dutch Lipid Clinic Network Criteria about 70% with a definite FH diagnosis, about 29% with a probable FH diagnosis, and about 11% with a possible FH diagnosis have an identifiable mutation in an FH-causing gene[13]. Evidence suggests that in most of the individuals with a negative result (~80%) hypercholesterolemia is the result of multiple small effect LDL-C raising alleles[14].

A **negative genetic test** for a known familial mutation in an FH gene is a true negative result and that individual would not be at increased lifetime risk for elevated LDL-C.

HOW DO I ORDER THE GENETIC TEST?

Access to clinical genetic testing for FH in Canada is limited and arranging for genetic testing may require preapproval from your Provincial Ministry of Health Care for out-of-province or out-of-country testing. Consider referral to a lipid specialist for consultation about further testing and management.

In Quebec, health care providers can order FH testing focused on the most common gene mutations found in French Canadian individuals from CHU Sainte Justine Molecular Laboratory (Requisition here). This test is of limited utility in other ethnic groups as it only looks for French Canadian founder mutations (mutation commonly found in a particular ethnic group) and not the hundreds of gene mutations seen in different ethnicities residing in Canada.[1]

Connect with your local genetics centre for more information.

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.

HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?

If mutations are identified

- Appropriate surveillance, management and lifestyle counselling can be initiated as soon as possible to dramatically reduce CVD [See Surveillance and Management for more]
- Genetic testing can be offered to family members, including children, to facilitate timely identification of at-risk individuals.[1,3]
- Consider enrolling patients with FH in the Canadian FH Registry by referring them to a participating clinician or centre.[1,9]

If no mutations are identified

- If your patient was tested because s/he met clinical criteria (Table 2 or 3), a negative test result does not rule out an FH diagnosis
  - Management and treatment should be based on clinical findings
  - Screening of family members by LDL-C levels or using Table 2 or 3 should still be considered
- If your patient was tested because of a known family mutation, s/he is not at increased risk for elevated LDL-C levels related to FH.

ARE THERE HARMS OR LIMITATIONS OF GENETIC TESTING?

Sensitivity

- A negative genetic test result does not rule out an FH diagnosis in an individual who otherwise meets clinical criteria (Tables 2 and 3)

Insurance discrimination

- Genetic testing in an asymptomatic individual may challenge his/her ability to obtain life, disability, critical illness, long-term care and/or extended health insurance

Non-Paternity

- Non-paternity could be revealed, for example, in the case where a father is HoFH and genetic testing of his offspring does not reveal one FH causing gene mutation

SURVEILLANCE AND MANAGEMENT

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 FH[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[1].** 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. [1-3,12]

LIFESTYLE

Families with FH should be counselled about the importance of lifestyle modification such as: [1-3,12]

- ✓ 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 here 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 FH[1] and referral to a specialist for treatment decisions is recommended. For recent recommendations on screening, management and treatment of individuals with HoFH please see Cuchel *et al.* 2014 European Heart Journal.

RESOURCES FOR HEALTH PROFESSIONALS

Familial Hypercholesterolemia (FH) Canada

RESOURCES FOR THE PUBLIC

Familial Hypercholesterolemia (FH) Canada Registry information - Patient brochure

REFERENCES:

[1] Genest J, Hegele RA, Bergeron J, et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. Can J Cardiol 2014; 30(12): 1471-81.

[2] Bouhairie VE and Goldberg AC. Familial Hypercholesterolemia. Cardiol Clin 2015; 33(2): 169-179.

[3] Vogt A. The genetics of familial hypercholesterolemia and emerging therapies. Appl Clin Genet 2015; 8: 27-36.

[4] Yuan G, Wang J, Hegele RA. Heterozygous familial hypercholesterolemia: an under-recognized cause of early cardiovascular disease. CMAJ 2006; 174(8):1124-9.

[5] Norgestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013; 34(45): 3478-90a.

[6] Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014; 35(32):2146-57.

[7] Anderson TJ, Grégoire J, Pearson GJ, et al. Canadian Cardiovascular Society Guidelines for the management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol 2016.

[8] Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol 2004;160(5): 407-20.

[9] Turgeon RD, Barry AR, Pearson GJ. Familial hypercholesterolemia: Review of diagnosis, screening, and treatment. Can Fam Physician 2016; 62(1): 32-7.

[10] Watts GF, Sullivan DR, Poplawski N, et al. Familial hypercholesterolaemia: a model of care for Australasia. Atheroscler Suppl 2011; 12(2): 221-63.

[11] Ned RM, Sijbrands EJ. Cascade Screening for Familial Hypercholesterolemia (FH). PLoS Curr 2011; 3: RRN1238.

[12] Feldman DI, Blaha MJ, Santos RD, et al. Recommendations for the management of patients with familial hypercholesterolemia. Curr Atheroscler Rep 2015; 17(1): 473.

[13] Kassner U, Wühle-Demuth M, Missala I, et al. Clinical utility gene card for: hyperlipoproteinemia, TYPE II. Eur J Hum Genet 2014; 22(7): e1-e4.

[14] Pears R, Griffin M, Futema M, Humphries SE. Improving the cost-effectiveness equation of cascade testing for familial hypercholesterolaemia. Curr Opin Lipidol 2015; 26(3): 162-8.

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