Genomics Education Programme

NHS Health Education England

Familial hypercholesterolaemia

Key facts

- Familial hypercholesterolaemia (FH) is an autosomal dominant hyperlipidaemia disorder.
- Untreated FH results in premature coronary artery disease (typically fourth decade in men, up to 10 years later in women).
- Clinical management, involving statin therapy, is usually provided through specialist lipid clinics.
- FH is underdiagnosed, with an estimated prevalence in the UK of 1 in 500.

Clinical features

- Serum cholesterol concentrations are elevated from birth and are usually at least double the normal values.
- Premature coronary artery disease is a key feature: >50% risk in men by age 50; at least 30% risk in women by age 60.
- Tendon xanthomata (virtually diagnostic); premature corneal arcus and xanthelasmas may also be present.

Genetic basis

- FH is an autosomal dominant condition, which means that each child of someone with FH has a 50%, or 1-in-2, chance of inheriting the gene alteration that causes the condition.
- As FH is common, sometimes both parents can have the condition. In this case each child has a:
  - 50% chance of inheriting the gene alteration from only one parent, resulting in the usual form of FH;
  - 25% chance of inheriting the gene alteration from both parents. This is called homozygous FH and is a more severe life-threatening condition with the risk of coronary heart disease in childhood; or
  - 25% chance of not having FH, as they have not inherited the gene alteration from either parent.
- FH results from a gene alteration in one of three genes: *LDLR; APOB* and *PCSK9*.
- Alterations in the *LDLR* gene account for 80%-95% of cases, with over 200 different gene alterations documented in the UK.
- Alterations in the *APOB* gene and *PCSK9* gene occur in 5% and 2% of UK patients respectively

Clinical management

- NICE guidelines, published in 2008, recommend the use of the Simon Broome criteria (see overleaf) for the identification of patients with FH.
- Secondary causes of hypercholesterolaemia (for example, diabetes, hypothyroidism, hepatic or renal disease) should be excluded before considering a diagnosis of FH.
- Family history of coronary artery disease at an earlier age than expected should be evaluated with a lipid screen.
- For a person with definite or possible FH, refer to a specialist lipid clinic for ongoing management.

Genetic testing

Genetic testing can be used to:

- confirm the diagnosis in someone with possible FH (diagnostic testing); and
- provide information about the genetic status of relatives of someone with FH through cascade testing.

The availability of genetic testing in the UK is region specific, and usually provided through specialist lipid clinics (diagnostic testing/cascade testing) or regional genetic centres (cascade testing).

NICE guidelines, published in 2008, recommend the use of the Simon Broome criteria for the identification of patients with familial hypercholesterolaemia

Simon Broome diagnostic criteria for index individuals*

Diagnose a person with **definate FH** if they have:

- cholesterol concentrations as defined in table 1 and tendon xanthomas, or evidence of these signs in first or second-degree relative; or
- DNA-based evidence of an *LDL*-receptor mutation, familial defective apo B-100, or a *PCSK9* mutation.

Diagnose a person with **possible FH** if they have cholesterol concentrations as defined in table 1 and at least one of the following:

- family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative
- family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative, or greater than 6.7 mmol/l in child, brother or sister aged younger than 16 years.

Table 1. Cholesterol levels to be used as diagnositc criteria for the index individual[1]

	Total cholesterol	LDL-C
Child/young person	>6.7 mmol/l	>4.0 mmol/l
Adult	>7.5 mmol/l	>4.9 mmol/l

[1]Levels either pre-treatment or highest on treatment
LDL-C, low-density lipoprotein cholesterol

*Marks D, Thorogood M, Neil HA, Humphries SE (2003) A review on the diagnosis, natural history and treatment of familial hypercholesterolaemia. Atherosclerosis 168 (1): 1-14v

This information is intended for educational use and was current in March 2015. For clinical management, it is recommended that local guidelines and protocols are used.