Genomic Diagnostics
LEADING THE WAY TO IMPROVE HEALTH

Familial hypercholesterolaemia

What is Familial Hypercholesterolaemia?

Familial hypercholesterolaemia (FH) is a genetic disorder characterised by very high levels of low-density lipoprotein (LDL) cholesterol, usually >4.9 mmol/L (>190 mg/dL) in untreated adults. This leads to an increased risk for coronary heart disease (CHD) at an early age.

- **Men with untreated FH have a 50% risk for a coronary event by age 50.**
- **Women with untreated FH have a 30% risk for a coronary event by age 60.**

Early and aggressive treatment with high doses of potent statins or statin combination therapy to lower LDL cholesterol significantly reduces CHD morbidity and mortality for people with FH.

Because there is considerable overlap between the LDL levels of those with FH and common multifactorial hypercholesterolaemia, FH often goes undiagnosed until middle age, when much of the preventive value of cholesterol-lowering therapy is lost.

Prevalence

According to the FH Australasia network (athero.org.au), it is estimated that 1 in 300 people in Australia have FH, equating to 77,000 people. Importantly, 80% (61,000) of these individuals have not been diagnosed.

Genetics of FH

Most cases of FH are caused by heterozygous pathogenic variants in the *LDLR, APOB* and *PCSK9* genes. More than 1200 different pathogenic variants have been identified in the *LDLR* gene, which encodes the LDL receptor that binds LDL, the major cholesterol-carrying lipoprotein of plasma, and transports LDL into cells by endocytosis. Pathogenic variants 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. Pathogenic variants in *APOB* disrupt the binding of LDL particles to the LDL receptor, while pathogenic variants in *PCSK9* cause increased degradation of the receptor. All these mechanisms lead to elevated LDL levels and consequent premature development of atherosclerotic plaque (Figure 1).

Rarely, FH can be caused by homozygous pathogenic variants. Individuals with this type of FH typically have severe coronary heart disease by their mid-20s; the rate of death or the need for surgical treatment of heart problems by the teenage years is high.

Both heterozygous and homozygous FH are inherited in an autosomal dominant manner. A person with heterozygous FH (HeFH) has a 1 in 2 (50%) chance of passing on the pathogenic variant to their children, while all children of a person with homozygous FH will inherit a pathogenic variant.

Genetic Testing is the Gold Standard

While a diagnosis of FH can be made using a combination of family history and clinical and biochemical findings, genetic testing is considered as the gold standard.

In addition to providing a conclusive diagnosis through detection of a pathogenic variant, genetic testing may also provide insight into clinical phenotype, as some pathogenic variants (referred to as *LDLR* null) are associated with higher LDL-C levels and higher cardiovascular risk. Moreover, patients with severe heterozygous FH can have LDL-C concentrations that overlap with those of patients who have homozygous FH, and vice versa, leading to alternative therapeutic approaches. Polygenic factors, gene-environment interactions, and gene-gene interactions can modify the effect of pathogenic variants on LDL-C levels, making genetic testing even more important for risk stratification. Rarely, genetic testing can also help in guiding therapy, as particular pathogenic variants (i.e. null pathogenic variants of *LDLR* in homozygous patients) can make certain therapies ineffective.

Most of the known pathogenic variants are in *LDLR*, *APOB* and *PCSK9*, but potentially other genes involved in LDL-C catabolism can be implicated. Several pathogenic variants remain unknown, and not finding a pathogenic variant on genetic testing does not exclude the diagnosis, especially if there is strong phenotypic evidence.

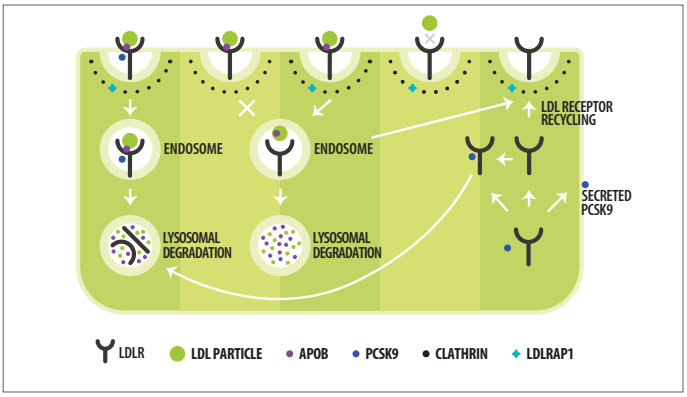

Figure 1: LDL Cholesterol catabolism

How will genetic testing help you and your patient?

If pathogenic variants are identified

- Appropriate surveillance, management and lifestyle counselling can be initiated as soon as possible to dramatically reduce CVD risk. Refer to the FH Australasia management webpage (athero.org.au) for detailed information.
- Genetic testing can be offered to family members, including children, to facilitate timely identification of at-risk individuals.
- Consider enrolling patients with FH in the FH registry in your state.

If no pathogenic variants are identified

- If your patient was tested because they met clinical criteria, a negative test result does not rule out a FH diagnosis.
- Management and treatment should be based on clinical findings.
- Screening of family members by LDL-C levels should still be considered.
- If your patient was tested because of a known family pathogenic variant, they are not at increased risk for elevated LDL-C levels related to FH.

Extended FH gene panel testing with Genomic Diagnostics

Up to 80% of FH cases are attributed to pathogenic variants in the *LDLR, PCSK9* and *APOB* genes. Extending testing to include *ABCG5, ABCG8, APOE, CYP27A1, LDLRAP1* and *LIPA* genes improves the diagnostic efficiency by almost 15%. Inclusion of copy number changes in the *LDLR* gene further improves detection by 5% (Figure 2).

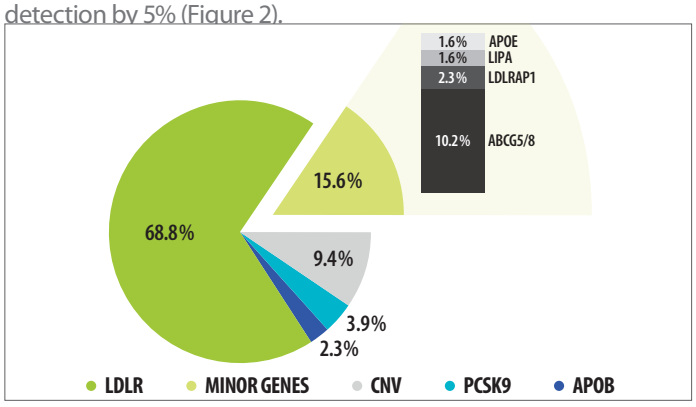

Figure 2: The Distribution of Pathogenic/Likely Pathogenic FH-causing variants in index cases. (Ye-Xuan Cao et al)

Testing for additional genes also helps for clinical characterisation of hyperlipidaemia. FH associated with *LDLRAP1* is clinically similar to HeFH. Sitosterolemia, which is caused by *ABCG5* and *ABCG8* pathogenic variants, is a specific form of hyperlipidaemia that manifests as hypercholesterolaemia and high levels (30-100x normal) of plant sterols (phytosterols) in blood and other tissues. Several studies have reported that a specific pathogenic variant (p.Leu167del) in *APOE* gene causes autosomal dominant FH.

Genomic Diagnostics FH Offerings:

Genes Included	Method	Turnaround Time
FH extended panel – *LDLR, PCSK9, APOB, ABCG5, ABCG8, APOE, CYP27A1, LDLRAP1* and *LIPA* genes	Massively Parallel Sequencing (MPS) to detect sequence variants in all coding exons and splice sites. MLPA to detect copy number variants in the LDLR gene.	4 - 6 weeks
Targeted pathogenic variant testing	Single gene testing for known familial variant by MPS	2 - 3 weeks

Medicare Item Numbers for FH - MBS 73352: Diagnostic Testing

Item Descriptor:

Characterisation of germline variants causing familial hypercholesterolaemia (which must include the *LDLR, PCSK9* and *APOB* genes), requested by a specialist or consultant physician, for a patient:

(a) for whom no familial pathogenic variant has been identified; and

(b) who has any of the following:
(i) a Dutch Lipid Clinic Network (DLCNS)* score of at least 6;
(ii) an LDL-cholesterol level of at least 6.5 mmol/L in the absence of secondary causes;
(iii) an LDL-cholesterol level of between 5.0 and 6.5 mmol/L with signs of premature or accelerated atherogenesis

MBS 73353: Familial Testing

Item Descriptor:

Detection of a familial mutation for a patient who has a first- or second-degree relative with a documented pathogenic germline gene variant for familial hypercholesterolaemia.

*The DLCNS is a validated set of criteria based on the patient's family history of premature CVD in their first degree relatives, their own CVD history, their untreated lipid levels and specific physical signs. The score categorises patients by the likelihood of FH diagnosis (athero.org.au).

1. PMID: 18753174, 2. PMID: 15177124, 3. Youngblom E, Pariani M, Knowles JW. Familial Hypercholesterolaemia: GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK174884/ 4. Ye-Xuan Cao et. al Improvement of Definite Diagnosis of Familial Hypercholesterolaemia Using an Expanding Genetic Analysis, JACC: Asia, Volume 1, Issue 1;2021, 82-89.

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