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AMPATHCHAT

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Detection of Familial Hypercholesterolaemia using Next Generation Sequencing (NGS)

Background

Familial hypercholesterolaemia (FH) is the most common autosomal-dominant inherited disorder of lipid metabolism.[1]

Worldwide, the prevalence of FH is between 1:250 and 1:500 whereas in South Africa, it is thought to be as common as 1:70.[1,2] This high prevalence is attributed to separate founder effects in several South African populations: the Afrikaner, Ashkenazi Jewish and Indian populations. The prevalence of FH in the black populations of South Africa is currently unknown. Pathogenic sequence variants (previously known as mutations) in certain genes have resulted in abnormalities of the low-density lipoprotein (LDL) receptor causing a raised LDL-cholesterol (LDL-C) concentration.[3]

Pathogenic sequence variants in the *LDLR* gene are the most common cause of FH, while the variants in the *APOB* and *PCSK9* genes are less frequent causes of FH[1].

Clinical Significance

FH is characterised by chronically elevated LDL-C levels, which lead to atherosclerotic plaque deposition in the skin, tendons, coronary arteries and proximal aorta. This results in the typical clinical phenotype of skin and tendon xanthomata, arcus corneae and generalised premature atherosclerosis, including coronary artery disease (CAD).[1,4,5]

Heterozygous familial hypercholesterolaemia (HeFH) is common, and tends to present in early adulthood.[1,2,5] HeFH is characterised by elevated LDL-C levels, double the normal levels, with tendon xanthoma and premature CAD. If left untreated, the cumulative risk of CAD is >50% in males and 30% in females by the age of 60 years.[5]

Homozygous familial hypercholesterolaemia (HoFH) is very rare, characterised by LDL-C levels ≥13 mmol/l, tendon and skin xanthomas, and generally presents with severe CAD in early childhood. If left untreated,there is a 100-fold relative risk of atherosclerotic cardiovascular disease (ASCVD) when compared with individuals with normal lipograms.[5]

Diagnostic Guidelines

Several formal diagnostic criteria exist for FH, including the Dutch Lipid Clinic criteria, the Med Ped criteria and the Simon Broome criteria (used in the United Kingdom). The Wits FIND-FH programme has recently demonstrated that utilising Next Generation Sequencing (NGS) as part of cascade testing is a useful tool, as it has enabled the identification of a growing number of cases of FH in black individuals, as well as assisting in the follow up of family members of known FH patients[5] (see Figure 1). NGS testing allows early diagnosis of at-risk family members, ensuring that they are offered prophylactic treatment, thereby decreasing severe FH-associated morbidity and mortality.

FH NGS test is now available:

Ampath Genetics is proud to announce the implementation of NGS genetic testing for FH. Our panel includes complete genetic sequencing of the three main genes, *LDLR, APOB* and *PCSK9*.

FH genetic testing using NGS is found to be an effective sequence variant detection method, which not only identifies the founder, known or targeted familial variants, but also allows identification of multiple and novel variants in the three genes in a single approach. The **FHNGS test** is available with a turnaround time of four weeks. For more information or assistance, please contact Dr Jessica Trusler at truslerj@ampath.co.za, the clinical genetic counsellors or the NGS lab at 012 678 0645.

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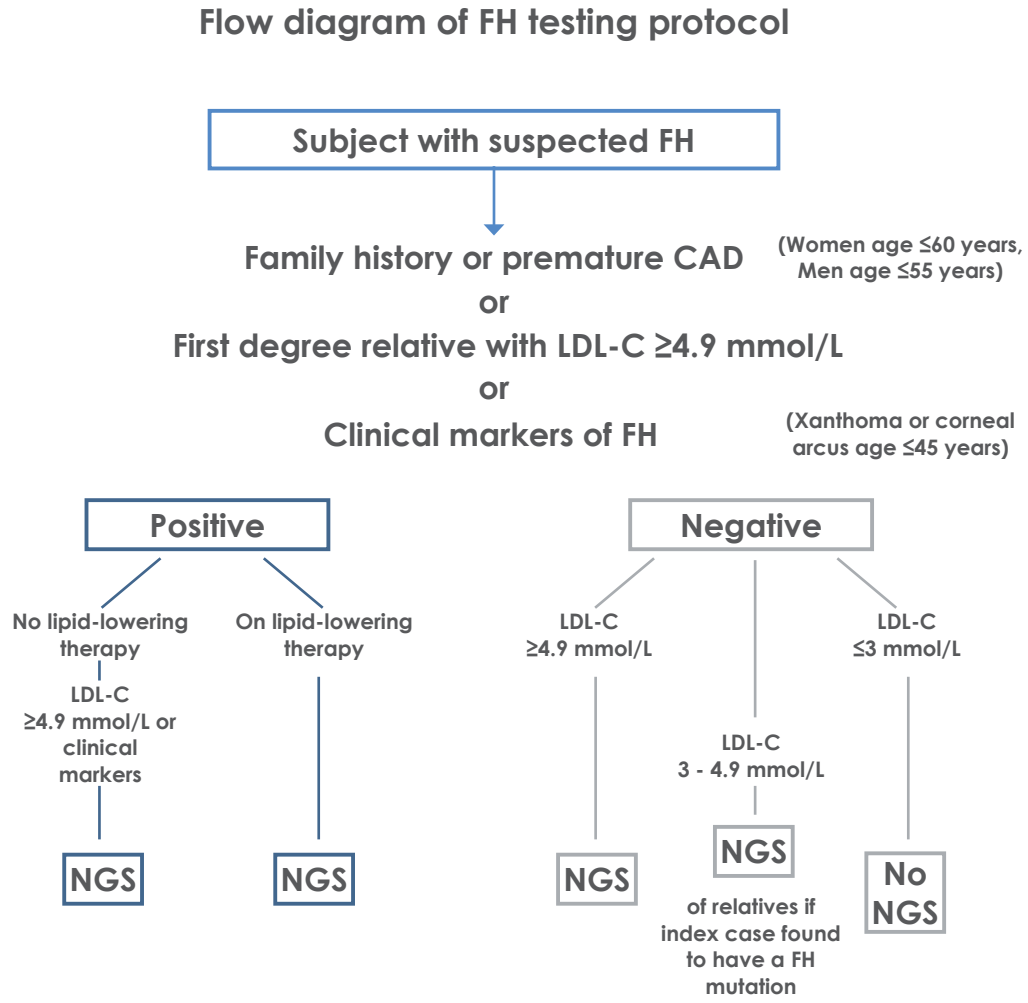
Figure 1. Flow chart of the familial hypercholesterolaemia (FH) testing protocol used in the Wits FIND-FH programe CAD indicates coronary artery disease; LDL-C indicates low-density lipoprotein cholesterol; and NGS indicates next generation sequencing.



NGS = Next-generation sequencing for variants in the LDLR, APOB, PCSK9 and LDLRAP1 genes

References:

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