R134 Familial Hypercholesterolemia (FH) – OMIM 143890
R325 Lysosomal acid lipase deficiency – OMIM 278000
R323 Sitosterolemia – OMIM 210250/618666

Background

Familial Hypercholesterolemia (FH) is caused by a pathogenic variant in one of the genes involved in LDL cholesterol metabolism, *LDLR* (OMIM 606945), *APOB* (OMIM 107730) and *PCSK9* (OMIM 607786). In the heterozygous state, FH affects about 1 in 500 people and typically leads to LDL cholesterol concentrations approximately twice as high as normal. In the rare homozygous condition (1 in 1 million) LDL cholesterol is greatly elevated (approximately five times normal levels). A recessive form of hypercholesterolemia is caused by biallelic pathogenic variants in LDLRAP1 (OMIM 605747).

Individuals with FH have a high risk of premature coronary heart disease if left untreated. Early detection of this condition is important as the right treatment (the use of cholesterol-lowering drugs combined with a healthy lifestyle) can prevent heart attacks with life expectancy being restored to normal. Hence proactive diagnosis for individuals and families is recommended. Clinical suspicion of a diagnosis of FH is based on demonstration of raised LDL cholesterol, and a family history of raised cholesterol and/or premature coronary heart disease. Some patients have physical signs; fatty lumps on the Achilles tendon, knuckles or knees (Tendon Xanthomas); small yellow lumps on the inner corner of the eyelid (Xanthelasmas); a white ring around the iris (Corneal Arcus). However, these clinical signs are often not present, particularly in younger patients.

The inheritance pattern in most cases is autosomal dominant so there is a 50% chance of first-degree relatives having FH. Therefore, family cascade testing is recommended for families with FH. For NICE guidance on FH see https://www.nice.org.uk/guidance/cg71?unlid=7376144720162911388
For details of the clinical FH service in Wales please click on the following link: www.fhwales.co.uk.

Identification of families with a likely polygenic form of hyperlipidemia is also useful as, although genetic cascade testing would not be indicated, biochemical screening using lipid profiles may be considered. The presence of a number of SNPs has been shown to be associated with an effect on LDL-C levels, either increasing or decreasing. Each SNP's effect on LDL-C levels is weighted and the cumulative score is assigned to a decile group according to Talmud *et al*., (2013), that predicts the overall affect.

Differential diagnoses: Lysosomal acid lipase deficiency is an inherited condition characterized by the accumulation of harmful amounts of lipids in cells and tissues throughout the body caused by biallelic pathogenic variants in LIPA (OMIM 613497). Sitosterolemia is an inherited condition characterized by the accumulation of plant sterols in the blood and is caused by biallelic pathogenic variants in ABCG5 (OMIM 605459) and ABCG8 (OMIM 605460). Hyperlipidemia characterized by raised triglyceride and cholesterol levels is inherited in an autosomal recessive trait and is associated with variants in APOE (OMIM 107741).

Talmud PJ *et al*. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolemia: a case-control study. The Lancet; 381: 1293-301 (2013)

Recommended Clinical Referral Criteria

- Increased levels of Low Density Lipoprotein Cholesterol (LDL-C) in blood
- Family history of high cholesterol or premature coronary heart disease
- Clinical scoring criteria may be applied (Simon Broome or Modified Dutch Criteria)

Molecular Analysis

Mutation screen: OGT SureSeq Custom Cardiff Familial Hypercholesterolemia NGS panel (LDLR NM_00527.4; LDLRAP1 NM_015627.2; APOB NM_000384.2; PCSK9 NM_174936.3; APOE NM_000041.2; ABCG5 NM_022436.2; ABCG8 NM_022437.3; LIPA NM_000235.2). Includes 12 SNPs associated with polygenic FH and LDL-C concentration.

Family follow-up: Testing for known familial mutations identified in any gene on the FH NGS panel.

Test (Price available on request)	**TAT**
Test for known familial mutations	42cd
Mutation screening and dosage analysis by NGS panel	42cd

This NGS assay aims to cover 100% of the promoter, coding sequence and 20bp of flanking intron (to a minimum vertical depth of 20X) of the targeted genes.

The bioinformatic analysis pipeline also returns details of copy number variation (CNV) for the 5'UTR and coding sequences of the LDLR gene at the single exon level of resolution. All LDLR gene CNVs detected at NGS analysis are confirmed by Multiplex Ligation-dependent Probe Amplification (MLPA), prior to reporting using the MRC Holland SALSA P062-D2 LDLR gene kit.

Sample Requirements
Blood – 5ml in EDTA (1ml neonates/infants);
Please contact lab prior to sending a prenatal sample.
Please label samples with three identifiers and date of collection
All samples must be accompanied by request form
Consent for testing & DNA storage is assumed when request for test received

Contact Details
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Accredited to ISO 15189:2012
(8988)

Links

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