

# Familial Hypercholesterolaemia (FH)

## Contact details:

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**Clinical Advice:** Available from Dr G Bayly, Bristol Royal Infirmary, Bristol (Tel: 0117 342 3245) or your local lipid specialist.

## Sample Required:

Adult: 5mls blood in EDTA  
Paediatric: at least 1ml EDTA (preferably >2ml)

Samples should be accompanied by a FULLY completed request form (available as download at [www.nbt.nhs.uk/genetics](http://www.nbt.nhs.uk/genetics) or from the laboratory).

Please include details of test, family history, address and POSTCODE, NHS number, referring clinician and unit/hospital.

## Consent and DNA Storage:

All genetic testing requires consent. It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.

DNA is stored from **all** patients unless consent for this is specifically denied.

Stored samples may be used for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

## Clinical Background and Genetics

- FH (MIM 143890) is a dominant disorder with a UK incidence of approx 1 in 300-500. Severe homozygous FH affects 1 in 160,000-300,000. FH is characterised by increased serum cholesterol (LDL-C), tendon xanthoma, and premature coronary heart disease.
- In mutation positive patients with a clinical diagnosis of FH, approx. 93 % have a mutation in the low-density lipoprotein receptor gene (*LDLR*), with 5% of these being a copy number variant. Around 5% have a single mutation in the apolipoprotein B-100 gene (*APOB*) and around 2% a mutation in Proprotein convertase subtilisin/kexin type 9 (*PCSK9*)<sup>(1)</sup>. A substantial proportion of clinically FH patients have no mutation, and in the majority (up to 80-90%) of these, their raised cholesterol is likely to have a polygenic aetiology, as determined using the 12-SNP score<sup>(4,5)</sup>. In <10% of patients with the clinical phenotype of FH and with a low SNP score (ie no evidence for a polygenic explanation for their high cholesterol phenotype) the genetic cause of their high cholesterol remains unknown. For mutation negative FH subjects who meet the Simon Broome Diagnostic criteria of Definite FH with a clear autosomal dominant pattern of the disorder and with a low SNP score, the referring clinician should consider recruiting to the 100,000 Genomes project.

## Service Offered

Assay	Gene and Transcript	Region Analysed	Reporting Time	
Level 1 NGS Diagnostic Screen V3 assay	<i>LDLR</i> NM_000527.4	All 18 exons + promoter	56 days	
	<i>APOB</i> NM_000384.2	29 exons + promoter		
	<i>PCSK9</i> NM_174936.3	12 exons + promoter		
	<i>LDLRAP1</i> NM_015627.2	9 exons + promoter		
	<i>SLCO1B1</i> (ref 3)	<i>rs2306283 rs4149056</i>		
	12 LDL-C raising SNPs (ref 5)	<i>rs2479409, rs629301, rs1367117, rs4299376, rs1564348, rs1800562, rs3757354, rs11220462, rs8017377, rs6511720, rs429358, rs7412</i>		
Level 2	MLPA	<i>LDLR</i>	<i>LDLR</i> 18 exons	28 days
Level 3	Familial (Cascade or Segregation)	As required	As required	28 days

## NGS Diagnostic Screen

- NGS v3 assay validation has 99.99% sensitivity for point mutations and 99.73% for indels in all genes. The assay will detect *LDLR* copy number mutations (5% cases). Due to issues of data quality, copy number analysis may be inconclusive in a proportion of cases. MLPA is available as an additional request.
- Bioinformatic analysis uses a bespoke validated pipeline based on the Broad Institute GATK best practice pipeline with variant pathogenicity analysis using Alamut following CMGS national best practice guidelines.
- The genotype is reported for *SLCO1B1* SNPs<sup>(2)</sup>. The LDL-C SNP score is reported for negative and VUS (variants of uncertain significance) cases.

## Referrals:

- Diagnostic Testing:** Available to patients meeting Simon Broome criteria with the involvement of a specialist lipid clinician<sup>(3)</sup>.
- Familial Testing (Cascade / Segregation):**  
**Cascade:** Offered where a known pathogenic mutation identified in the proband.  
**Segregation:** To ascertain whether a VUS is associated with disease in a family.

## Quality and Cost

- BGL participates in EMQN/NEQAS for sequencing/variant analysis and NEQAS for FH.
- Please contact the laboratory for current prices or for further service information

## References

- Graham, C. A. *et al.* (2005) Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detection rate. *Atherosclerosis* (182) 331-340.
- Romaine SPR *et al* The influence of *SLCO1B1* (OATP1B1) gene polymorphisms on response to statin therapy *The Pharmacogenomics Journal* (2010) 10, 1–11
- Identification and management of Familial Hypercholesterolaemia, NICE Clinical Guideline (2008).
- Talmud *et al* (2013) *Lancet* 381 (9874): 1293-301. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study.
- Futema *et al* *Clinical Chemistry* 61:1 231-238 2015