THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Genetic Testing for Dyslipidemias

Dyslipidemias are a clinically and genetically heterogenous group of disorders associated with abnormal levels of lipids and lipoproteins, including increased or decreased levels of LDL or HDL cholesterol or increased levels of triglycerides [1]. Dyslipidemias can have a monogenic cause, or may be associated with other conditions such as diabetes and thyroid disease, or lifestyle factors. The most common subset of monogenic dyslipidemia is familial hypercholesterolemia (FH), which has an estimated prevalence of 1 in 200 in the Caucasian population [2].

Our Dyslipidemia Panes includes analysis of all 23 genes listed below.

Dyslipidemia Panel Genes					
ABCA1	APOA1	CETP	LDLR	LMF1	SAR1B
ABCG5	APOA5	GPD1	LDLRAP1	LPL	SCARB1
ABCG8	APOB	GPIHBP1	LIPA	MTTP	STAP1
ANGPTL3	APOC2	LCAT	LIPC	PCSK9	

Gene	OMIM#	Associated disorders	Dyslipidemia phenotype	Inheritance	References
ABCA1	600046	Tangier disease; High density lipoprotein (HDL) deficiency	Low HDL-C	Recessive; Dominant	[3, 4]
ABCG5	605459	Sitosterolemia	Hypercholesterolemia, hypersitosterolemia	Recessive	[5]
ABCG8	605460	Sitosterolemia	Hypercholesterolemia, hypersitosterolemia	Recessive	[5]
ANGPTL3	605019	Familial hypobetalipoproteinemia-2	Low LDL-C	Recessive	[6]
APOA1	107680	Apolipoprotein A-I deficiency; HDL deficiency	Low HDL-C	Recessive; Dominant	[7, 8]
APOA5	606368	Hyperchylomicronemia; Hypertriglyceridemia	Hypertriglyceridemia	Dominant/Recessive; Dominant	[9, 10]
APOB	107730	Familial hypercholesterolemia; hypobetalipoproteinemia	High LDL-C; Low LDL-C	Co-dominant	[1, 11]
APOC2	608083	Apolipoprotein C-II deficiency	Hypertriglyceridemia	Recessive	[12]
CETP	118470	Hyperalphalipoproteinemia	High HDL-C	Dominant/Recessive	[13, 14]
GPD1	138420	Transient infantile hypertriglyceridemia	Hypertriglyceridemia	Recessive	[15]
GPIHBP1	612757	Hyperlipoproteinemia 1D	Hypertriglyceridemia	Recessive	[16]
LCAT	606967	Familial LCAT deficiency	Low HDL-C	Recessive	[17]
LDLR	606945	Familial hypercholesterolemia	High LDL-C	Co-dominant	[1]
LDLRAP1	605747	Familial hypercholesterolemia	High LDL-C	Recessive	[1]

LIPA	613497	Cholesterol ester storage disease / Wolman disease	High LDL-C	Recessive	[18, 19]
LIPC	151670	Hepatic lipase deficiency	High HDL-C	Dominant/Recessive	[20, 21]
LMF1	611761	Combined lipase deficiency	Hypertriglyceridemia	Recessive	[22, 23]

LPL	609708	Lipoprotein lipase deficiency; Familial combined hyperlipidemia	Hypertriglyceridemia	Recessive; Dominant	[24, 25]
MTTP	157147	Abetalipoproteinemia	Low LDL-C	Recessive	[26]
PCSK9	607786	Familial hypercholesterolemia; Hypobetalipoproteinemia	High LDL-C; Low LDL-C	Dominant	[1]
SAR1B	607690	Chylomicron retention disease	Low LDL-C	Recessive	[27]
SCARB1	601040	Scavenger receptor B1 deficiency	High HDL-C	Dominant/Recessive	[28, 29]
STAP1	604298	Familial hypercholesterolemia	High LDL-C	Dominant	[30]

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Dyslipidemia Panel (23 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3000
CPT codes:	81406 81407
Turn-around time:	8 weeks

Results:
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Dron, J.S. and R.A. Hegele, *Genetics of Lipid and Lipoprotein Disorders and Traits.* Curr Genet Med Rep, 2016. **4**(3): p. 130-141.
2. Benn, M., et al., *Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication.* J Clin Endocrinol Metab, 2012. **97**(11): p. 3956-64.
3. Bodzioch, M., et al., *The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease.* Nat Genet, 1999. **22**(4): p. 347-51.
4. Brooks-Wilson, A., et al., *Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency.* Nat Genet, 1999. **22**(4): p. 336-45.
5. Berge, K.E., et al., *Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters.* Science, 2000. **290**(5497): p. 1771-5.
6. Minicocci, I., et al., *Mutations in the ANGPTL3 gene and familial combined hypolipidemia: a clinical and biochemical characterization.* J Clin Endocrinol Metab, 2012. **97**(7): p. E1266-75.
7. Yokota, H., et al., *Apolipoprotein A-I deficiency with accumulated risk for CHD but no symptoms of CHD.* Atherosclerosis, 2002. **162**(2): p. 399-407.
8. Kiss, R.S., et al., *Genetic etiology of isolated low HDL syndrome: incidence and heterogeneity of efflux defects.* Arterioscler Thromb Vasc Biol, 2007. **27**(5): p. 1139-45.
9. Charrière, S., et al., *Modulation of phenotypic expression of APOA5 Q97X and L242P mutations.* Atherosclerosis, 2009. **207**(1): p. 150-6.
10. Johansen, C.T., et al., *Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridemia.* Nat Genet, 2010. **42**(8): p. 684-7.
11. Whitfield, A.J., et al., *Lipid disorders and mutations in the APOB gene.* Clin Chem, 2004. **50**(10): p. 1725-32.
12. Cox, D.W., W.C. Breckenridge, and J.A. Little, *Inheritance of apolipoprotein C-II deficiency with hypertriglyceridemia and pancreatitis.* N Engl J Med, 1978. **299**(26): p. 1421-4.
13. Ohtani, R., et al., *Novel mutations of cholesteryl ester transfer protein (CETP) gene in Japanese hyperalphalipoproteinemic subjects.* Clin Chim Acta, 2012. **413**(5-6): p. 537-43.
14. Rhyne, J., et al., *The two novel CETP mutations Gln87X and Gln165X in a compound heterozygous state are associated with marked hyperalphalipoproteinemia and absence of significant coronary artery disease.* J Mol Med (Berl), 2006. **84**(8): p. 647-50.
15. Basel-Vanagaite, L., et al., *Transient infantile hypertriglyceridemia, fatty liver, and hepatic fibrosis caused by mutated GPD1, encoding glycerol-3-phosphate dehydrogenase 1.* Am J Hum Genet, 2012. **90**(1): p. 49-60.

16. Surendran, R.P., et al., *Mutations in LPL, APOC2, APOA5, GPIHBP1 and LMF1 in patients with severe hypertriglyceridaemia.* J Intern Med, 2012. **272**(2): p. 185-96.
17. Funke, H., et al., *A molecular defect causing fish eye disease: an amino acid exchange in lecithin-cholesterol acyltransferase (LCAT) leads to the selective loss of alpha-LCAT activity.* Proc Natl Acad Sci U S A, 1991. **88**(11): p. 4855-9.
18. Klima, H., et al., *A splice junction mutation causes deletion of a 72-base exon from the mRNA for lysosomal acid lipase in a patient with cholesteryl ester storage disease.* J Clin Invest, 1993. **92**(6): p. 2713-8.
19. Lee, T.M., et al., *Intragenic deletion as a novel type of mutation in Wolman disease.* Mol Genet Metab, 2011. **104**(4): p. 703-5.
20. Hegele, R.A., et al., *A hepatic lipase gene mutation associated with heritable lipolytic deficiency.* J Clin Endocrinol Metab, 1991. **72**(3): p. 730-2.
21. Ruel, I.L., et al., *Characterization of a novel mutation causing hepatic lipase deficiency among French Canadians.* J Lipid Res, 2003. **44**(8): p. 1508-14.
22. Cefalù, A.B., et al., *Novel LMF1 nonsense mutation in a patient with severe hypertriglyceridemia.* J Clin Endocrinol Metab, 2009. **94**(11): p. 4584-90.
23. Cefalù, A.B., et al., *Identification of a novel LMF1 nonsense mutation responsible for severe hypertriglyceridemia by targeted next-generation sequencing.* J Clin Lipidol, 2017. **11**(1): p. 272-281.e8.
24. Gilbert, B., et al., *Lipoprotein lipase (LPL) deficiency: a new patient homozygote for the preponderant mutation Gly188Glu in the human LPL gene and review of reported mutations: 75 % are clustered in exons 5 and 6.* Ann Genet, 2001. **44**(1): p. 25-32.
25. Yang, W.S., et al., *A mutation in the promoter of the lipoprotein lipase (LPL) gene in a patient with familial combined hyperlipidemia and low LPL activity.* Proc Natl Acad Sci U S A, 1995. **92**(10): p. 4462-6.
26. Benayoun, L., et al., *Abetalipoproteinemia in Israel: evidence for a founder mutation in the Ashkenazi Jewish population and a contiguous gene deletion in an Arab patient.* Mol Genet Metab, 2007. **90**(4): p. 453-7.
27. Jones, B., et al., *Mutations in a Sar1 GTPase of COPII vesicles are associated with lipid absorption disorders.* Nat Genet, 2003. **34**(1): p. 29-31.
28. Yang, X., et al., *SCARB1 Gene Variants Are Associated With the Phenotype of Combined High High-Density Lipoprotein Cholesterol and High Lipoprotein (a).* Circ Cardiovasc Genet, 2016. **9**(5): p. 408-418.
29. Zanoni, P., et al., *Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease.* Science, 2016. **351**(6278): p. 1166-71.
30. Fouchier, S.W., et al., *Mutations in STAP1 are associated with autosomal dominant hypercholesterolemia.* Circ Res, 2014. **115**(6): p. 552-5.

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS' NEEDS