Familial Chylomicronaemia (FCS) genetic testing request form

Patient details:

Name: _____

Date of birth: _____

Patient number: _____

Clinician details:

Name: _____

Hospital: _____

Email: _____

Clinical signs and symptoms can be supportive for right diagnosing. Therefore please complete this section as fully as possible for all cases.

DEMOGRAPHICS

Ethnicity: _____

BMI kg/M2: _____

LIPIDS

Full lipid profile (Pre-treatment) in mmol/L

Total cholesterol: _____

Triglycerides: _____

HDL-cholesterol: _____

LDL-cholesterol: _____

Non-HDL-cholesterol: _____

Peak triglyceride concentration (mmol/L): _____

Lowest triglyceride concentration (mmol/L): _____

Apolipoprotein B (pre-treatment, if known) in g/L: _____

Evidence of chylomicron layer (fridge test): ☐ Yes ☐ No

PANCREATITIS

Any history of pancreatitis? ☐ Yes ☐ No

If yes, how many episodes? _____

Any family history of hypertriglyceridaemia or pancreatitis? ☐ Yes ☐ No

Details (if known) _____

FCS Score[1] _____

(Above 7: genetic testing should be considered[2])

Familial Chylomicronaemia (FCS) genetic testing request form

Please use the following FCS Scoring Tool[1] to mark which of the following points apply and generate a score for your patient

TRIGLYCERIDES

Has the patient had fasting TGs of >10 mmol/L for three consecutive blood analyses?	(+5)	☐
Has the patient had fasting TGs of >20 mmol/L at least once?	(+1)	☐
Has the patient had fasting TGs of <2 mmol/L at least once?	(-5)	☐

MEDICAL HISTORY

Does the patient have a history of pancreatitis?	(+1)	☐
Does the patient have unexplained recurrent abdominal pain?	(+1)	☐
Does the patient have a family history of familial combined hyperlipidaemia?	(+1)	☐

DIFFERENTIAL DIAGNOSIS

Have you excluded secondary factors (except pregnancy and ethinylestradiol)?	(+2)	☐
Has the patient failed to respond to hypolipidaemic treatment (TG decrease <20%)?	(+1)	☐

How old was the patient when their symptoms first appeared?

<40 years	(+1)	☐
<20 years	(+2)	☐
<10 years	(+3)	☐

Score interpretation

Total score: ☐

≥10 FCS very likely **9** FCS unlikely **≤8** FCS very unlikely

Relevant proteins for FCS

PROTEIN	FUNCTIONS AND REGULATION
Lipoprotein lipase (LPL)[3-7]	Hydrolysis of triglycerides in chylomicrons and VLDL and peripheral uptake of FFS; is activated by ApoC2 and ApoA5; is inhibited by ApoC1, ApoC3 and ANGPTL 3, 4 and 8
Glycosyl-phosphatidylinositol cored high density lipoprotein binding protein (GPIHBP1)[8-11]	Endothelial LPL transport protein; stabilises the binding of chylomicrons; supports lipolysis
ApoC2[3,12]	Co-factor of the LPL; activates LPL
ApoA5[7,13]	Cofactor for the interaction of APOC2 and LPL; amplifier of the LPL activity
Lipase Maturation Factor - 1 (LMF1)[14,15]	Chaperone, mediates folding of LPL in adipocytes and myocytes
Glycerol-3-phosphate dehydrogenase 1 (GPD-1)[16]	Degradation of glycerol-3-phosphate, the starting product of TG synthesis
cAMP-responsive element-binding protein H (CREBH)[17,18]	Transcription factor in the liver that regulates triglycerides and cholesterol
Glucokinase regulatory protein (GCKR)[17,19]	Regulation of the activity of the enzyme glucokinase in the liver

Other genetic defects may be identified in the future.

Reference: 1. Moulin P, et al. Atherosclerosis. 2018;275:265-72. **2.** Bashir et al. Atherosclerosis 391 (2024) 117476, https://doi.org/10.1016/j.atherosclerosis.2024.117476. **3.** Gotoda T, et al. Diagnosis and management of type I and type V hyperlipoproteinemia. J Atheroscler Thromb. 19: 1–12 (2012). **4.** Murthy V, et al. Molecular pathobiology of the human lipoprotein lipase gene. Pharmacol Ther; 70: 101–135 (1996) **5.** Sukonina V, et al. Angiopoietin-like protein 4 converts lipoprotein lipase to inactive monomers and modulates lipase activity in adipose tissue. Proc Natl Acad Sci USA 2006;103(46):17450–17455. **6.** Wen Y, et al. Angiopoietin-like protein 8: a multifaceted protein instrumental in regulating triglyceride metabolism. Current Opinion in Lipidology 35(2):p 58-65, April 2024. **7.** Nilsson, S. K., et al. Apolipoprotein A- V; a potent triglyceride reducer. Atherosclerosis 219, 15–21 (2011). **8.** Beigneux A P, et al. Chylomicronemia with a mutant GPIHBP1 (Q115P) that cannot bind lipoprotein lipase. Arterioscler. Thromb. Vasc. Biol. 29, 956–962 (2009). **9.** Beigneux A. P. GPIHBP1 and the processing of triglyceride-rich lipoproteins. Clin. Lipidol. 5, 575–582 (2010). **10.** Gin P, et al. Chylomicronemia mutations yield new insights into interactions between lipoprotein lipase and GPIHBP1. Hum. Mol. Genet. 21, 2961–2972 (2012). **11.** Rios J, et al. Deletion of GPIHBP1 causing severe chylomicronemia. J. Inherit. Metab. Dis. 35, 531–540 (2012). **12.** Okubo M, et al. Apolipoprotein C- II: a novel large deletion in APOC2 caused by Alu–Alu homologous recombination in an infant with apolipoprotein C- II deficiency. Clin. Chim. Acta 438, 148–153 (2014). **13.** Albers K, et al. Homozygosity for a partial deletion of apoprotein A- V signal peptide results in intracellular missorting of the protein and chylomicronemia in a breast-fed infant. Atherosclerosis 233, 97–103 (2014). **14.** Peterfy, M. Lipase maturation factor 1: a lipase chaperone involved in lipid metabolism. Biochim. Biophys. Acta 1821, 790–794 (2012). **15.** Doolittle MH, et al. Lipase maturation factor 1: structure and role in lipase folding and assembly. Curr Opin Lipidol. 21(3):198-203 (2010). **16.** Matarazzo L, et al. Successful fenofibrate therapy for severe and persistent hypertriglyceridemia in a boy with cirrhosis and glycerol-3-phosphate dehydrogenase 1 deficiency. JIMD Rep. 54:25–31 (2010). **17.** Hegele RA, et al. Rare dyslipidaemias, from phenotype to genotype to management: a European Atherosclerosis Society task force consensus statementLancet Diabetes & Endocrinology. 8:50-67 (2020). **18.** Dron JS, et al. Loss-of-Function CREB3L3 Variants in Patients With Severe Hypertriglyceridemia. Arterioscler Thromb Vasc Biol. 40(8):1935-1941 (2020). **19.** Hadarits F, et al. Mol Biol Rep. 39(2):1949-55 (2012).

PP-22378