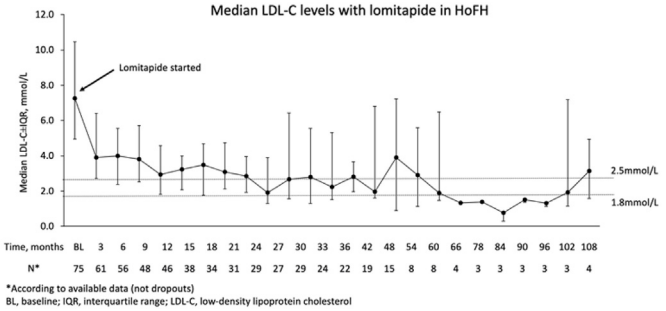
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Figure.



Conclusion: Lomitapide is an effective long-term treatment for reducing LDL-C in HoFH. Hepatic fat increases were modest and hepatic stiffness remained normal. Additional data are needed to determine the impact of LDL-C reduction with lomitapide on major adverse cardiovascular events in HoFH.

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Posttranscriptional regulation of the LDL Receptor in humans by the U2-spliceosome and its interactors

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Aims: The low-density lipoprotein receptor (LDLR) in the liver is the major determinant of LDL-cholesterol levels in human plasma. The discovery of genes that regulate the activity of LDLR helps to identify pathomechanisms of hypercholesterolemia and novel therapeutic targets against atherosclerotic cardiovascular disease.
Methods and results: In a genome-wide RNAi screen, the knock-down of 54 genes led to a significant inhibition of LDL uptake. Fifteen of these genes encode for proteins involved in splicing, especially components or interactors of the U2-spliceosome. Knocking down 11 out of 15 genes resulted in the selective retention of intron 3 of LDLR. The transcript is translated into an LDLR fragment, which lacks 88% of the full length LDLR and is detectable in cells and their medium upon overexpression, but neither in non-transfected cells nor in human plasma. The intron 3 retention transcript is expressed in considerable amounts in human liver and in blood cells. Its expression correlates with plasma LDL-cholesterol and age. Single nucleotide polymorphisms and rare variants of one spliceosome gene, RBM25, are associated with LDL-cholesterol in the population and familial hypercholesterolemia, respectively. Single nucleotide polymorphisms and three rare variants of one spliceosome gene, RBM25, are associated with LDL-cholesterol in the population and familial hypercholesterolemia, respectively. Compared to overexpression of wild type RBM25, overexpression of the three rare RBM25 mutants led to lower LDL uptake by Huh7 cells.
Conclusions: In conclusion, we here identified a novel post-transcriptional mechanism for the regulation of LDLR activity in humans.

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The effect of adjusting LDL-cholesterol for Lipoprotein(a)-cholesterol on the diagnosis of Familial Hypercholesterolaemia

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Background: Familial Hypercholesterolaemia (FH) is a common (1:250) low-density-lipoprotein cholesterol (LDL-c) disorder associated with premature cardiovascular disease. Current clinical diagnostic tools for FH include the Simon Broome (SB) and Dutch Lipid Clinic Network (DLCN) criteria, which are used to prioritise patients for molecular genetic testing. In practice LDL-c is commonly estimated using the Friedewald equation. However, the cholesterol content of lipoprotein(a) (Lp(a)) can lead to overestimation of 'true' LDL-c and potentially inappropriate FH clinical diagnosis. We assessed how adjusting LDL-c for Lp(a) affects FH diagnoses using SB and DLCN criteria.
Methods: Adults referred to a tertiary lipid clinic were included if they met a diagnosis of at least 'possible' FH by SB or DLCN criteria and had undergone FH genetic testing. LDL-c was adjusted for Lp(a) using estimated cholesterol contents of 30% and 45%. Patients were assessed by DLCN and SB (LDL-c only) criteria before and after LDL-c adjustment. Reclassification rates to 'unlikely' FH and diagnostic tool accuracy, using molecular genetic results as the gold standard, were compared.
Results: 513 patients met inclusion criteria. Median age was 49 (IQR 40-57) with 57% female, 48% white and 79% mutation negative (M-). Median LDL-c and Lp(a) were 5.9 mmol/L (IQR 5.4-6.6) and 288 mg/L (IQR 108-755) respectively. After LDL-c adjustment, more M- than M+ patients were reclassified as 'unlikely' FH (Table 1). Reclassification rates varied with LDL-c adjustment and Lp(a) subgroup (<300, 300-500, >500-1000 and >1000 mg/L); greater Lp(a) and LDL-c adjustments lead to greater reclassification rates. Importantly, M+ reclassification was not restricted to higher Lp(a) levels and was seen in isolated cases with Lp(a) levels <500 mg/L for SB and <300 mg/L for DLCN at ≥30% and 45% adjustment respectively. Despite this, the accuracy of diagnostic tools increased (Table 1).

Table 1. Reclassification rates and accuracy.

Adjustment factor	M-	M+	P-value	Accuracy
	SB			0.46
30%	50/292 (17.1%)	7/85 (8.2%)	0.06	0.53
45%	76/292 (26.0%)	10/85 (11.8%)	0.01*	0.57
	DLCN			0.32
30%	51/399 (12.8%)	4/108 (3.7%)	0.01*	0.40
45%	78/399 (19.5%)	7/108 (6.5%)	<0.01*	0.44

Conclusion: LDL-c adjustment for Lp(a) improves the diagnostic accuracy of SB and DLCN criteria using LDL-c thresholds with potential cost-savings from reduced genetic testing. However, adjustment can also lead to inappropriate reclassification of M+ patients and therefore potentially missed diagnoses.

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Lipoprotein apheresis reduces SARS-CoV-2 S protein antibody levels in patients with familial hypercholesterolaemia after vaccination with BNT162b2

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Introduction: In patients with familial hypercholesterolaemia (FH), lipoprotein apheresis (LA) is an extracorporeal modality allowing removal of apolipoprotein-B-containing lipoproteins. However, other serum proteins have also been found to be reduced after LA [1]. After SARS-CoV-2 vaccination, S protein antibody titres are increased, although waning humoral immune response over 6 months after receiving 2 doses of BNT162b2 (Pfizer/BioNTech) vaccine has been shown to occur naturally [2]. The effect of LA on antibody titres of S protein IgG antibodies obtained from vaccination are unknown.

Methods: We retrospectively reviewed 15 LA procedures in 4 patients (50% male, mean age 49 years, mean BMI 23.3 kg/m^2) with FH (3 with homozygous FH and 1 with heterozygous FH) between February and June 2021 with measurement of pre- and post-apheresis SARS-CoV-2 S protein (IgG) antibody levels. Both KANEKA (Lipo-adsorber) and INFOMED (double filtration) machines were used. All patients received at least 2 doses of BNT162b2 vaccine.
Results: 93% (14/15) of LA procedures saw a reduction in SARS-CoV-2 S protein antibody levels. Mean percentage drop with KANEKA and INFOMED machines were 18.6% (standard deviation (SD) 8.43, N=13) and 34.6% (SD 3.16, N=2), respectively. Unless patients received SARS-CoV-2 vaccination prior, all antibody titres dropped naturally between LA sessions (mean percentage drop 30% (SD 20.6, N=7)). There were no significant differences of reduction in antibody levels between males and females in this study.
Conclusion: Universally, we observed a reduction in SARS-CoV-2 S protein antibody levels post-apheresis. Given that KANEKA is a Lipo-adsorber, we would not have expected such a significant drop in antibody levels although a larger cohort is needed to further quantify this finding. One study reported a natural decrease in IgG SARS-CoV-2 antibodies by a factor of 18.3 over 6 months [2]. Notable reduction of S protein IgG antibodies is found here both between and after LA sessions. This poses the question as to whether patients undergoing apheresis need extra vaccine doses sooner to confer adequate protection against SARS-CoV-2.
References
1. Julius U, Siegert G, Kostka H, Schatz U, Hohenstein B. Effects of different lipoprotein apheresis methods on serum protein levels. Atheroscler Suppl. 2015 May;18:95-102. doi: 10.1016/j.atherosclerosissup.2015.02.018
2. Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, Doolman R, Asraf K, Mendelson E, Ziv A, Rubin C, Freedman L, Kreiss Y, Regev-Yochay G. Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. N Engl J Med. 2021 Dec 9;385(24):e84. doi: 10.1056/NEJMoa2114583. Epub 2021 Oct 6.

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Low-density lipoprotein receptor-negative compound heterozygous familial hypercholesterolaemia: case study with follow-up over 23 years

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Introduction: Homozygous familial hypercholesterolaemia may be classified as low density lipoprotein (LDL) receptor defective or negative and as a true homozygous or compound/combined heterozygous disorder [1]. This report describes long term medical and surgical treatment for a patient with compound heterozygous LDL-receptor negative familial hypercholesterolaemia. Informed consent was obtained.
Case report: A 7-year-old girl presented with lack of energy and a heart murmur. Her serum total cholesterol was 18.7 mmol/L and apolipoprotein-B 3.56 g/L (reference range 0.75 – 1.25 g/L). Cutaneous xanthomata were found on her buttocks and knees. Her parents had cholesterol levels of 9.6 and 8.6 mmol/L. During cardiac surgery extensive atheroma was found in the ascending aorta.
Despite diet and probucol her serum total cholesterol remained high at 14.8 mmol/L. LDL apheresis reduced her total cholesterol to 4 mmol/L. At age 14 years she underwent aortic valve replacement and coronary artery bypass grafting. Over the next few years she developed impaired exercise tolerance. At age 17, she was given a combined heart and liver transplant followed by immunosuppression. Following the liver transplant total cholesterol was well controlled at 5 mmol/L on a statin. Thirteen years later she developed liver disease due to autoimmune rejection and symptoms of ischaemic heart disease. She hence underwent a second liver transplant and insertion of coronary artery stents, twenty-three years after initial presentation. Her daughter has heterozygous familial Hypercholesterolaemia.
Genome analysis showed two LDL receptor gene mutations, a single base substitution and a base pair duplication. Complete loss of LDL receptor function was demonstrated by cultured skin fibroblast bioassay. New LDL-receptor-independent drugs are promising therapeutic options in this condition [2]. Statin with Lomitapide therapy has been shown to lower LDL cholesterol by more than 60% [3].

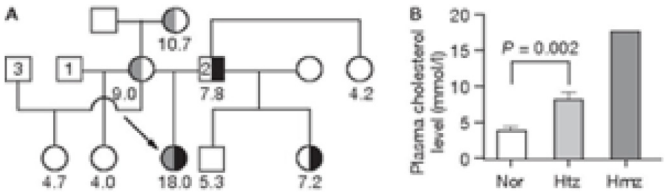

Figure. Pedigree and total cholesterol levels in unaffected, heterozygous and homozygous family members.

Conclusion: This report illustrates the challenges faced in managing compound heterozygous receptor negative familial hypercholesterolaemia which requires early diagnosis and intensive combination treatment.
References
1. https://www.heartuk.org.uk/news/latest/post/8-heart-uk-statement-on-the-management-of-homozygous-familial-hypercholesterolaemia-in-the-united-kingdom.
2. Brandts J, et.al. Familial Hypercholesterolaemia. JACC Focus seminar 4/4, J American College Cardiology 2021;78(18):1831-43.
3. Yahya R, et.al. Low-density lipoprotein receptor-negative compound heterozygous familial hypercholesterolemia: Two lifetime journeys of lipid-lowering therapy. J Clinical Lipidology 2017;11(1):301-5.

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Cardiovascular disease morbidity is associated with social deprivation in subjects with familial hypercholesterolaemia (FH): a study comparing FH individuals in UK primary care and the UK Simon Broome register linked with secondary care records

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Background: Measures of social deprivation are associated with higher cardiovascular diseases (CVD) morbidity and mortality. To determine if this is also seen in subjects with Familial Hypercholesterolaemia (FH), CVD morbidity has been examined in participants in the UK primary care database (CPRD) and in the UK Simon Broome (SB) register using linkage to the UK secondary care Hospital Episodes Statistics (HES).
Methods: A composite CVD outcome was analysed (first HES outcome of coronary heart disease, myocardial infarction, stable or unstable angina, stroke, TIA, PVD, heart failure, PCI and CABG). The measure of socio-economic status/deprivation used was the English index of multiple deprivation (IMD). Cox proportional hazards regression estimated hazards ratios (HR) for incident CVD and mortality [95% CI] in each IMD quintile.
Results: We identified 4,309 patients with FH in UK CPRD primary care database (followed from 1988 to 2020), free from CVD, and 2988 SB register participants, with linked secondary care HES records. In both groups, the prevalence of FH was considerably lower in the most deprived quintile (60% in CPRD and 52% in SB). CPRD patients in the most deprived