SUPPLEMENTAL MATERIAL

Appendix

List of CASCADE FH® sites and personnel

SITE	INVESTIGATOR	RESEARCH TEAM
Massachusetts General Hospital	Linda Hemphill, MD	Dianne Brennan, Amy Jewell, Shriie Ganesh
Baylor College of Medicine	Christie Ballantyne, MD	TerryTechmanski, Mini Grace Varughese, MD, Xiaoming Jia, MD, Aliza Hussain, MD, Ali Agha, MD, Matthew Deshotels, MD
The Rogosin Institute	Lisa Hudgins, MD	Nelson Chen, Betty Jane Sloan
The University of Kansas Medical Center	Patrick Moriarty, MD	Julie-Ann Dutton, Mark McClellan
University of Pennsylvania	Marina Cuchel, MD,PhD	Daniel J. Rader, MD, Archna Bajaj, MD, Daniel Soffer, MD, Douglas Jacoby, MD, Paull C. Lee, Benjamin Thieu
Oregon Health & Science University	P. Barton Duell, MD	Jill Rose, Tina Kaufman, Jonathon Purnell, MD, Michael Shapiro, MD
Vanderbilt Medical Center	MacRae Linton, MD	Barbara Carranza Leon, MD, Jennifer Kelley, MD, Beth Meader,ANP, Sherry Bowman, Anca Ifrim
Duke University Medical Center	John Guyton, MD	Shubi Khan
Preventive Cardiology Inc	Seth Baum, MD	Johanna Lore, Ashlee Mattone Murray
UT Southwestern Medical Center	Zahid Ahmad, MD	Chandna Vasandani, PhD
Lancaster General Hospital - Research Institute	Rolf Andersen, MD	Rebekah Nevin, Kate Clipman
NYU Langone Center	James Underberg, MD	Eugenia Gianos, MD, Vanessa Milne Hurta
The Ohio State University Medical Center	John Larry, MD	Matthew Jindra
Children's Hospital Corporation, dba Boston Children's Hospital	Sarah DeFerranti, MD	Jacob Hartz, MD, Heather Harker Ryan
Johns Hopkins University	Seth Martin, MD	Kathleen Byrne, ANP, Emily Brown
University of California, San Francisco	John Kane, MD	Eveline Stock, MD, Mary Malloy, MD, Dorothy Wallder
Thomas Jefferson University	David J. Whellan, MD	Melissa McCarey
Ann and Robert Lurie Children's Hospital of Chicago	Irwin Benuck, MD	Kathleen Van'T Hof
Nemours Cardiac Center	Samuel Gidding, MD (formerly at Nemours Cardiac Center)	Kristi Fitzgerald, Frances Zappalla, DO, J.Alitio Canas, MD, Matthew Benson, MD, Carol Prospero
Hartford Hospital	Paul Thompson, MD	Antonio Fernandez, MD, Karen Knight, William Roman

Data S1. Severe FH

Seven severe FH individuals with TC and LDL-Cs ranging from 467-543 mg/dL and 368-476 mg/dL, respectively, and no known secondary causes of hypercholesterolemia (e.g. untreated hypothyroidism, nephrotic syndrome, and cholestasis) were considered to possibly have HoFH. Their cases were carefully reviewed and ultimately excluded from the analysis. While there was considerable overlap between their lipid levels and those of genetically confirmed HoFH, these patients either did not have physical findings, family history, or personal history to meet the criteria for a diagnosis of HoFH. Their characteristics are summarized in **Table S1**. Two of these subjects underwent genetic testing. One of them was found to be heterozygous for a known *LDLR* pathogenic variant, but no other pathogenic variant was found; this finding combined with the absence of CAD history in the family and hypercholesterolemia only identified later in life in the father precluded the diagnosis of HoFH. The second patient was found to carry 3 *LDLR* variants: a benign variant (p.Ala391Thr), a pathogenic variant (p.Cys75Ser) and a VUS (p.Cys116Ser). With an untreated LDL-C level of 368 mg/dL and a poorly defined family history, the diagnosis of HoFH could not be made.

Data S2. Family Heart Database Query.

The Family Heart Database was queried in order to identify individuals who may have HoFH in the "real world". The following criteria were utilized for our query:

1. Maximum recorded LDL-C levels greater than or equal to 400 mg/dL, OR, if LDL-C results was not available, maximum recorded TC levels greater than or equal to 500 mg/dL. These cutoffs were selected as an approximation of the lowest LDL-C and TC levels observed in a HoFH patient of the CASCADE-FH registry carrying two pathogenic *LDLR* variants.
2. Maximum recorded triglyceride levels lower than or equal 350 mg/dL, the highest triglyceride level observed in observed in a HoFH patient of the CASCADE-FH registry carrying two pathogenic *LDLR* variants.
3. Exclusion of individuals with 1) ICD codes indicating a diagnosis for diabetes, hypothyroidism, hypertriglyceridemia, nephrotic syndrome, primary biliary cirrhosis, or sclerosing cholangitis or 2) no recorded diagnosis code at any timepoint. These criteria were used to exclude patients with known secondary causes of dyslipidemia.
4. Exclusion of individuals older than 37 years, unless:
    a. Records indicated treatment at any time with lomitapide, a LLT approved only for HoFH
    b. Records included a diagnosis of FH (as indicated by the presence of the specific ICD10 diagnosis code, E78.0) in the context of the lipid criteria listed above.

The age cutoff criterium was based on the oldest age at diagnosis of the genetically confirmed HoFH patients and was adopted as an arbitrary filter to exclude those individuals with uncoded

secondary cause of hypercholesterolemia. The rationale for this choice lay on the assumption that by that age most of these patients are either identified and treated or are deceased.

Information on lipid lowering treatment was extracted from the database using paid prescription data, as previously reported.[1] The lipid-lowering treatments for these patients were classified as follows. Every patient was represented only once in the analysis, using the most effective therapy recorded and grouped based on potency of LDL-C therapy: no LLT > ezetimibe >low or moderate intensity statin > high intensity statin > statin + ezetimibe > PCSK9 inhibitors > HoFH medications. Using our prior approach for determining the "statin + ezetimibe" category, we considered medications that include both in one pill (Vytorin, Liptruzet) and any paid prescription for a statin that was within 30 days of a paid prescription for ezetimibe. Finally, we also extracted the presence of lipoprotein apheresis treatment.

Data S3. Liver transplant.

Illustrative of the severity of HoFH, six individuals (5 children and one 18-year-old) in the registry have undergone liver transplantation (one underwent a combined liver/renal transplant), with five of them receiving their transplant before enrollment in the registry. At the time of transplantation, these individuals were aged 4, 6, 8, 15, 17, and 18 years. Because their lipid values improved dramatically with transplantation (see **Table S2**), we have excluded them from the main lipid analysis but discuss their cases below. Some of these cases have been previously described.[46] Overall, the lipid profiles of all 6 patients responded extremely well to liver transplantation. Only one patient experienced a serious adverse event linked to nonadherence with immunosuppression therapy, which resolved.

Patient LT1: This Hispanic female was retrospectively enrolled in the registry at age 19. She was diagnosed at the age of 5 on the basis of lipid levels, xanthomas, known high cholesterol in both parents, and eventually, genetic testing. Her LDL-C was still unacceptably high despite 30% reduction while on statin, ezetimibe. An echocardiogram, stress test and chest magnetic resonance angiography (MRA) at ages 8 and 9 were negative. However, a chest computed tomography angiography (CCTA) at age 11 showed mild calcified stenosis of the LM ostium (with motion artifact) and large amount of calcified plaque in the aortic root. At age 12, she began biweekly lipoprotein apheresis. At age 13, a CCTA followed by coronary angiography showed >70% occlusion of the RCA and nearly complete occlusion of the LM ostia that was treated with percutaneous coronary intervention (PCI with stent). She also had mild aortic stenosis and insufficiency as well as soft plaque in the aortic root. A carotid ultrasound was normal. At age 15, she underwent a liver transplant. Complications included hospitalizations for

acute liver rejection due to noncompliance with immunosuppressants and acute pyelonephritis with septic shock. At age 17, a CT angiogram showed a patent coronary stent and <50% occlusion of the RCA.

Patient LT2: This Hispanic female enrolled in the registry at age 14. She was diagnosed at age 2 after the appearance of xanthomas; the diagnosis was confirmed with genetic testing. She had a family history of both HeFH and premature CAD. Her initial cardiac evaluation at age 3 showed mild aortic insufficiency and diffuse intimal thickening with some mild, nonobstructive plaque in the LAD, LM by intravascular ultrasound (IVUS), not seen on the angiogram (RCA not evaluated because of spasm). This regressed after 1.5 years of statin, ezetimibe and biweekly lipoprotein apheresis. However, 5 years later, there were new aortic plaques adjacent to the right and left coronary ostium as well as in the iliac artery, and her xanthomas were quickly enlarging. At age 8, she underwent a liver transplant. Post-transplant complications included bile duct obstruction and pancreatitis 8 weeks after surgery. CCTA at age 15 showed minimal CAD and unchanged mild aortic insufficiency.

Patient LT3: This Asian male enrolled in the registry at age 23. He was diagnosed at the age of 1 after the sudden death of his brother, who also had HoFH. Genetic testing confirmed the presence of two identical known *LDLR* variants and the diagnosis of HoFH. At age 4, he was treated with statin with minimal response, then portacaval shunt surgery followed by biweekly lipoprotein apheresis. His aortic valve remained disease-free, and his first coronary catheterization at age 10 was normal. At age 14, however, he developed severe nephrotic syndrome and progressive renal failure, poorly controlled hypertension, and severe

hypothyroidism. His LDL-C increased into the 600s despite statin, ezetimibe and lipoprotein apheresis. Coronary angiography showed narrowing of the proximal RCA and multiple plaques in the first diagonal off the LAD that progressed by age 18 to severe ostial/proximal stenosis of the RCA, 60% stenosis of the mid LAD and 60% stenosis of the 1st septal perforator. An echocardiogram showed mild aortic and annular sclerosis and ventricular hypertrophy. He underwent a combined renal/liver transplantation without surgical complications or signs of rejection. Repeat catheterization showed regression of disease in the main coronaries evident at 1.5 years and 4.5 years after transplant. However, at 4.5 years, a new asymptomatic 30% to 49% stenosis of the minor ramus artery was detected. An exercise stress test was negative. His highest pre-treatment and most recent post-transplant lab values were obtained in 2017 (age 26) while on ezetimibe 10 mg per day and simvastatin 20 mg per day can be seen below. He continues on tacrolimus and antihypertensives and levothyroxine and has developed Stage 3 renal failure. At age 30, he is asymptomatic for CVD and is a 4th year medical student.

Patient LT4: This Asian male was retrospectively enrolled in the registry at age 9. He was diagnosed at the age of 2 based high LDL-C, xanthomas, parents with HeFH and the presence of two identical known *LDLR* variants. He did not have aortic valve disease, but CCTA showed mild focal narrowing of the RCA and moderate plaque in the thoracic aorta. He had minimal response to lipid-lowering medications and did not have adequate venous access for lipoprotein apheresis. His parents elected to have liver transplantation. At the age of 4 he underwent a liver transplant. Coronary CTA at age 7 showed no plaque in the RCA and LAD; he also had mild+ aortic insufficiency.

Patient LT5: This Hispanic male enrolled in the registry at age 9. He was diagnosed at age 4 due to elevated LDL-C, xanthomas, family history of HeFH and premature CAD and the presence of two identical known *LDLR* variants. He had little response to statin therapy. At age 5 he was found to have mild aortic stenosis. At age 6, he underwent 2 vessel coronary artery bypass procedure. He was subsequently treated with lipid apheresis which was aborted due to recurrent clotting of his intravenous lines. Ultimately, at age 6 he underwent a liver transplantation. Post-transplant, statin was discontinued. At age 8, an allograph aortic valve conduit was successfully placed without complications.

Patient LT6 This Hispanic female enrolled in the registry at age 17. She was diagnosed clinically at the age of one due to elevated LDL-C, xanthomas, and a family history of both HeFH and premature CAD. She had a minimal response to atorvastatin, ezetimibe and bile acid sequestrants. She began biweekly lipoprotein apheresis at age 5. Her first catheterization at age 6 showed mild plaque in the proximal LM artery and aortic calcification adjacent to the RCA ostium. IVUS showed additional plaque in the LCX. An echocardiogram showed mild Aortic. Insufficiency (AI). This progressed to mild Aortic Stenosis (AS) with continued AI one year later. A repeat catheterization at age 8 showed normal coronaries (narrowed RCA ostium felt due to vasospasm), but IVUS showed mild plaque in the LAD and LCX. A CCTA at age 10 done because of intermittent chest pain showed mild plaque in the proximal LAD and RCA, possible obstructive plaque in the RCA ostium and diffuse aortic plaque at the sinuses of Valsalva, ascending and thoracic aorta. An echo showed progression to moderate calcified AS and AI with mild LVH. A carotid ultrasound at age 13 showed moderate plaque in both internal and common carotid arteries. At age 14, CCTAs showed normal coronaries but with motion artifact. At age

17, the echocardiogram showed severe AS and moderate AI, and she developed SOB on exertion. Cath showed 50% stenosis of the proximal RCA. She underwent a Ross procedure to replace her aortic valve with her pulmonary artery valve. She was unable to adhere to the very low-fat diet required to tolerate lomitapide. One year later at age 18, she underwent liver transplantation complicated only by transient T wave inversions shortly after surgery. However, 1 year after surgery, she was noncompliant with tacrolimus and had an episode of acute liver rejection. During steroid immunosuppression, she developed insulin-requiring diabetes that has persisted after the discontinuation of steroids. She is a college student.

Data S4. Lipoprotein(a) levels.

At least one lipoprotein (a) result was available for 49/67 (73%) of HoFH patients in the CASCADE FH Registry including 41 (80%) of adults and 8 (50%) of children, however the relationship to LLT was not reported. Of the 49 patients with an available Lp(a), 36 (73%) and 9 (18%) had a history of ASCVD and aortic stenosis respectively at the time of registry enrollment. During prospective follow-up, 5 individuals experienced 7 ASCVD events with one being fatal.

An elevated Lp(a), defined as > 50 mg/dL or >125 nmol/L, was noted in 14/49 (29%) of patients. Of those with an elevated Lp(a), all (100%) had ASCVD at the time of registry enrollment and 1(7%) had known aortic stenosis, but none of them experienced an ASCVD event during the prospective follow-up period. Four were receiving lipoprotein apheresis.

Of the 35 with an Lp(a) in the normal range, 20 (57%) were receiving lipoprotein apheresis. Given that lipoprotein apheresis is known to acutely lower Lp(a) and that time of testing in relation to apheresis was not collected in the registry, it is possible that we are underestimating the percentage of individuals with elevated Lp(a).

Table S1. Untreated TC and LDL-C and other characteristics of Severe FH patients.

	TC	LDL-C	FamFH+	FamCVD+	Tendon xanthomas	genetics	
SevFH1	467	368			N	Y	p.A391T (B) p.C116S (VUS) p.C75S (LP/P)
SevFH2	499	409	S	N	Y	N	
SevFH3	543	476	UNK	UNK	Y	N	
SevFH4	503	402	M, S	M	UNK	N	
SevFH5	500	412	M, S	M, S, MGM	Y	N	
SevFH6	512	419	M	M	N	UNK	
SevFH7	529	420	F	N	N	Y	c.313+2T>C

SevFH, severe familial hypercholesterolemia; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; FamFH+, family history positive for familial hypercholesterolemia; Fam CVD+, family history positive for cardiovascular disease; F, Father; M, mother; MGM, maternal grandmother; N, negative; S, sibling; UNK, Unknown; B, benign; VUS, variant of unknown significance; LP/P, likely pathogenic/pathogenic

Table S2. Laboratory results of patients that underwent liver transplant.

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Lipid panel (mg/dl)												
TC	758	147	674	171	864	195	967	134	1019	160	866	110
LDL-C	720	87	573	110	697	132	887	82	946	67	692	53
TG		30		50		65		50	171	53		155
HDL-C		54		50		50		42	38	82		26
Lp(a)		19				37		18			62	14
Transaminases (IU/L)												
AST		23		8		22		38		37		19
ALT		28		16		28		21		47		26

Pre, before liver transplant; Post, after liver transplant; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; Lp(a), lipoprotein (a); AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table S3. Lipid Levels Among Adults and Children with Homozygous FH: Data (mg/dl) are expressed as median (IQR) and min/max range. Patients that underwent liver transplant and 2 patients with evidence of non-compliance are not included.

	Adult				Children			
	n	**Enrollment**	**Follow-up**	**% Reduction**	**n**	**Enrollment**	**Follow-up**	**% Reduction**
TC	36	274 (215/414) 75/772	186 (126/256) 63/521	38 (-8/59) -92/80	7	464 (397/772) 281/845	326 (147/400) 103/480	32 (-0.4/74) -16/88
LDL-C	36	187 (146/345) 38/711	127 (59/213) 18/422	50 (-11/71) -105/93	7	406 (342/712) 211/769	256 (112/337) 65/430	36 (3/77) -21/92
HDL-C	33	37 (29/52) 17/74	44 (32/56) 17/75	-4.5 (-36/8) -88/53	7	39 (27/47) 23/55	37 (23/41) 20/57	19 (-32/35) -70/51
TG	34	98 (60/157) 34/315	74 (55/129) 23/291	19 (-25/34) -228/91	7	96 (73/143) 27.0/204.0	65 (44/109) 19/176	-19 (-28/45) -141/91
	n	**Pre-Treatment**	**Follow-up**	**% Reduction**	**n**	**Pre-Treatment**	**Follow-up**	**% Reduction**
TC	31	604 (579/800) 358/983	192 (127/249) 63/521	70 (61/78) 29/92	7	792 (754/855) 581/961	326 (147/400) 103/480	56 (47/82) 38/88
LDL-C	27	511 (459/673) 318/939	147 (71/196) 18.0/422	73 (62/86) 36/96	7	721 (695/776) 511/907	256 (112/337) 65/430	61 (51/86) 42/91
HDL-C	9	34 (32/43) 20/55	38 (32/58) 17/62	-13 (-43/24) -190/47	2	35 (32/37) 30/39	32 (29/36) 25/39	3 (-14/20) -30/20
TG	9	116 (85/124) 50/420	75 (66/78) 46/191	33 (17/37) -125/84	2	212 (142/283) 71/353	62 (40/83) 19/104	25 (-11/60) -46/95

TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol.

Table S4. LDL-C levels and LLT of HoFH patient treated with Evinacumab at last follow-up visit. LDL-C levels are reported in mg/dL.

	Untreated	Before evinacumab		During evinacumab (15mg/kg/mo)		
Pt #	LDL-C	LDL-C	LLT	LDL-C	% Change	LLT
E-1	707	304	R 40mg/day, EZ 10mg/day, L 5 mg /2x/wk A q week	211	31%	R 40mg/day, EZ 10mg/day, A q week
E-2	530	260	Ator 80mg/day, EZ 10mg/day, Evol 420mg/mo, A q 2 week	82	68%	Ator 80mg/day, EZ 10mg/day, A q 2 week,
E-3	869	839	R 40mg/day, EZ 10mg/day, A q 2 week	404	52%	R 40mg/day, EZ 10mg/day, Evol 420mg/mo, PE q mo
E-4	642	102	Ator 5 mg qod, EZ 10mg/day, Evol 140 mg q2wk, A q 2 wk	58	43%	Ator 5 mg qod, EZ 10mg/day, Evol 140 mg q2wk, A q 2 wk,
E-5	400	195	R 40mg/day, EZ 10mg/day, A q 2 week, Evol 140 mg q2wk, L 5 mg/day, Fen 135 mg/day	100	49%	R 40mg/day, EZ 10mg/day, A q 2 week, Evol 140 mg q2 wk, L 5 mg/day, Fen 135 mg/day
E-6	n/a	189	Ator 80mg/day, EZ 10mg/day, Evol 140mg/2wk, A q 2 week, N 2000 mg/day	86	54%	Ator 80mg/day, EZ 10mg/day, Evol 140mg/2wk, A q 2 week, N 2000 mg/day
Median (IQR)	642 (530/707)	228 (191/293)		93 (83/183)	51% (45,54%)	

LDL-C, low density lipoprotein cholesterol; LLT, lipid lowering treatment; IQR, interquartile range; R, rosuvastatin; EZ, ezetimibe; L,lomitapide; A, apheresis; Ator, atorvastatin; Evol, evolocumab; PE, plasma exchange; Fen, fenofibrate; N, niacin. LDL-C levels are reported as untreated, at the last visit before starting evinacumab and at last follow-up while treated with evinacumab. For patients undergoing apheresis, LDL-C levels reported are pre-apheresis.

Table S5. Molecular Characterization of Variants Found in True Homozygotes

Nucleotide change	Protein Effect	Variant Classification*	Functionality	N
LDLR				
c.304C>T	p.Gln102Ter	P	Null	1
c.590G>A	p.Cys197Tyr	LP	Predicted Defective	3
c.2043C>A	p.Cys681Ter	P	Null	3
c.249delTinsGG	p.Ile83fs	P	Predicted Null	2
c.1055G>A	p.Cys352Tyr	LP	Predicted Defective	1
c.191-512_940+631del	-	P	Predicted Null	1
c.530C>T	p.Ser177Leu	P	Null	2
c.1090T>C	p.Cys364Arg	LP	Predicted Defective	1
c.654_656del	p.Gly219del	P	Null	1
LDLRAP1				
Homozygous deletion of exons 5-9 of LDLRAP1 gene	-	P	Predicted Null	1
c.460-1G>A (intron 4)	-	P	Predicted Null	1
APOB				
c.10580G>A	p.(Arg3527Gln)	P	Defective	1

* Variant Classification for *LDLR* according to ClinGen FH VCEP Guidelines (DOI 10.1016/j.gim.2021.09.012), for *APOB* and *LDLRAP1* according to the ClinGen general guidelines (DOI 10.1038/gim.2015.30). LP, likely pathogenic; P, pathogenic.

Table S6. Molecular Characterization of – Variants found in compound heterozygotes.

Nucleotide change 1	Protein Effect	Variant Class*	Functionality	Nucleotide change 2	Protein Effect	Variant Class*	Functionality	N
LDLR								
c.590G>A	p.Cys197Tyr	LP	Pred Def	c.1016T>C	p.Leu339Pro	VUS	NA	1
c.1A>T	p.Met1Leu	P	Null	c.418G>A	p.Glu140Lys	P	Def	1
c.261_262delinsAG	p.Trp87Ter	P	Pred Null	c.1056_1060+3del	-	LP	Pred Def/Null	1
c.302A>G	p.Glu101Gly	VUS	Pred Def	c.1216C>A	p.Arg406Arg	LP	Def/Null	1
c.1382del	p.Gly461fs	P	Pred Null	c.1238C>T	p.Thr413Met	LP	Pred Def	1
c.1878del	p.Ala627fs	P	Pred Null	c.314-?_940+?del	-	P	Def/Null	1
c.1118_1121dup	p.Tyr375fs	P	Null	c.2113G>C	p.Ala705Pro	VUS	NA	1
c.501C>A	p.Cys167Ter	P	Pred Null	c. 798T>A	p.Asp266Glu	P	Def	1
c.680_681del	p.Asp227fs	P	Pred Null	c.2389+1G>T	p.Ala771Ile796del	P	Def/Null	1
c.269A>C	p.Asp90Ala	LP	Pred Def	c.2390-?_2583+?del	-	P	Pred Null	1
c.681C>G	p.Asp227Glu	P	Def	c.1775G>A	p.Gly592Glu	P	Def	1

c.301G>A	p.Glu101Lys	P	Def	c.1898G>A	p.Arg633His	LP	Pred Def	1
c.1775G>A	p.Gly592Glu	P	Def	c.519C>G	p.Cys173Trp	LP	Pred Def	1
c.682G>T	p.Glu228Ter	P	Null	c.191-?_1845+?dup	-	P	Pred Null	1
c.337G>T	p.Glu113Ter	P	Pred Null	c.1246C>T	p.Arg416Trp	P	Def	1

* Variant Classification for *LDLR* according to ClinGen FH VCEP Guidelines (DOI 10.1016/j.gim.2021.09.012). Def, defective; Pred, predicted; LP, likely pathogenic; P, pathogenic; VUS, variant of unknown significance.

Table S7. Molecular Characterization of – variants found in double heterozygotes.

LDLR	Protein Effect	Variant Class	Functionality	APOB	Protein Effect	Variant Class	Functionality	N
c.314-?_940+?del	-	P	Def/Null	c.7976C>T	p.Pro2659Leu	VUS	NA	1

* Variant Classification for *LDLR* according to ClinGen FH VCEP Guidelines (DOI 10.1016/j.gim.2021.09.012), for *APOB* according to the ClinGen general guidelines (DOI 10.1038/gim.2015.30). P, pathogenic; VUS, variant of unknown significance